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| <b>Sponsor:</b> Sanofi Pasteur<br><br><b>Drug substance:</b> Quadrivalent Meningococcal ACYW Conjugate Vaccine   | <b>Study Identifiers:</b> U1111-1143-8912, NCT03205358,<br>2014-004367-20<br><br><b>Study code:</b> MET54 |
| <b>Title of the study:</b> A Phase II Study of the Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Healthy Toddlers  |   |
| <b>Study centers:</b> This was a multi-center trial in Finland involving 8 centers.  |   |
| <b>Study period:</b><br>Date first subject enrolled: 31/Mar/2015<br>Date last subject completed: 19/Aug/2015   |   |
| <b>Phase of development:</b> II  |   |
| <b>Objectives:</b><br>1) To evaluate the antibody responses to the antigens (serogroups A, C, Y, and W) present in MenACYW conjugate vaccine and Nimenrix® measured by serum bactericidal assay using baby rabbit complement (rSBA) and by serum bactericidal assay using human complement (hSBA)<br>2) To evaluate the antibody responses against tetanus in subjects who received MenACYW conjugate vaccine or Nimenrix®<br>3) To evaluate the safety profile of MenACYW conjugate vaccine and Nimenrix®                             |   |
| <b>Methodology:</b><br>This was a Phase II, randomized, parallel active-controlled, open-label study in toddlers in Finland 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 Nimenrix®.<br>Healthy, meningococcal-vaccine naïve toddlers aged 12 to 23 months were randomized to the following 2 groups: <ul style="list-style-type: none"> <li>• Group 1: MenACYW conjugate vaccine</li> <li>• Group 2: Nimenrix®</li> </ul> |   |
| <b>Number of subjects:</b> Planned: 200<br>Randomized: 188<br>Vaccinated: 188<br><br><b>Evaluated:</b><br>Immunogenicity: 177<br>Safety: 188   |   |

**Diagnosis and criteria for inclusion:**

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

- 1) Aged 12 to 23 months on the day of the first study visit
- 2) Born at full term of pregnancy ( $\geq 37$  weeks) or with a birth weight  $\geq 2.5$  kg (5.5 pounds)
- 3) Informed consent form (ICF) has been signed and dated by the parent(s) or other legally acceptable representative (and by an independent witness if required by local regulations)
- 4) Subject and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures
- 5) Covered by health insurance where applicable

**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 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 ( $\mu\text{g}$ )

Serogroup C ----- 10  $\mu\text{g}$

Serogroup Y ----- 10  $\mu\text{g}$

Serogroup W135 ----- 10  $\mu\text{g}$

Tetanus toxoid protein carrier ----- approximately 65  $\mu\text{g}$

Route of administration: Intramuscular (IM)

**Control product: Nimenrix®:** Meningococcal group A, C, W-135 and Y conjugate vaccine

Form: Powder and solvent for solution for injection. The powder is white. The solvent is clear and colorless.

Composition:

After reconstitution, 1 dose (0.5 mL) of Nimenrix® contained the following:

Neisseria meningitidis polysaccharides:

Serogroup A ----- 5  $\mu\text{g}$

Serogroup C ----- 5  $\mu\text{g}$

Serogroup W-135 ----- 5  $\mu\text{g}$

Serogroup Y ----- 5  $\mu\text{g}$

Tetanus toxoid protein carrier ----- approximately 44  $\mu\text{g}$

Excipients:

In the powder: Sucrose, Trometamol

In the solvent: Sodium chloride, Water for injection

Route of administration: IM

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

**Criteria for evaluation:**

**Immunogenicity:**

The following serological endpoints were assessed immediately before and 30 days after vaccination:

- Antibody titers against meningococcal serogroups A, C, Y, and W measured by rSBA and hSBA for Group 1 and Group 2.

Tetanus toxoid is contained in both the investigational and control vaccines as a carrier protein. Therefore, blood samples were also tested for anti-tetanus antibodies by enzyme-linked immunosorbent assay (ELISA). The following parameters were assessed:

- At both pre- and post-vaccination time point, geometric mean concentrations (GMCs)
- At both pre- and post-vaccination time points, the proportion of subjects achieving seroprotective levels  $\geq 0.01$  international units (IU)/milliliters (mL) and  $\geq 0.1$  IU/mL of antibody concentrations to tetanus toxoid

**Safety:**

- 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.
- 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.
- 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.
- 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.
- 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. Descriptive statistics and reverse cumulative distribution curve (RCDC) figures were provided for the antibody concentrations or titers against the meningococcal serogroups (A, C, Y, W) and anti-tetanus antibodies contained in MenACYW conjugate vaccine and Nimenrix®.

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

**Summary:**

**Population characteristics:**

Subject Disposition:

A total of 188 subjects were enrolled in this study and randomly allocated to either Group 1 (94 subjects) or Group 2 (94 subjects). All 188 subjects (100.0%) completed the trial; there were no early terminations due to an SAE or AE.

Demographics:

There were a total of 98 (52.1%) male subjects and 90 (47.9%) female subjects in the SafAS; the overall ratio of male/female subjects was 1.09. There were more males than females in Group 1 (male/female ratio was 1.54). There were more females than males in Group 2 (male/female ratio was 0.77).

Subjects' ages were comparable across the 2 groups. The mean age of the subjects at enrollment was  $1.44 \pm 0.302$  years in Group 1 and  $1.47 \pm 0.314$  years in Group 2.

#### **Immunogenicity results:**

##### **Meningococcal Antibody Responses Measured by rSBA**

###### *GMTs of Antibodies against Meningococcal Serogroups A, C, Y, and W*

At baseline, meningococcal rSBA GMTs were comparable or similar in both groups for serogroups C, Y, and W and were numerically higher for serogroup A in Group 1 (12.4) than in Group 2 (5.6).

Thirty days after vaccination, meningococcal rSBA GMTs for all 4 serogroups were higher than at baseline in both groups. For serogroup A, the rSBA GMT for Group 1 (3137.5) was lower compared to Group 2 (7377.0). For serogroup C, the rSBA GMT for Group 1 (2440.1) was higher compared to Group 2 (418.6). For serogroups Y and W, the rSBA GMTs for Group 1 (2633.3 and 5306.8, respectively) were comparable to Group 2 (2759.6 and 4333.7, respectively).

###### *Fold Rise in rSBA Antibody Titers*

Most subjects in both groups had a  $\geq 4$ -fold rise in rSBA antibody titers 30 days after vaccination. For serogroup A, the percentage of subjects with a  $\geq 4$ -fold rise in rSBA antibody titers 30 days after vaccination was numerically lower in Group 1 than in Group 2; for serogroups C, Y, and W, the percentages of subjects with a  $\geq 4$ -fold rise in rSBA antibody titers 30 days after vaccination were comparable or similar between the 2 groups:

- 91.2% (83/91) in Group 1 and 98.8% (85/86) in Group 2 for serogroup A
- 100.0% (91/91) in Group 1 and 96.5% (83/86) in Group 2 for serogroup C
- 98.9% (90/91) in Group 1 and 98.8% (85/86) in Group 2 for serogroup Y
- 100.0% (91/91) in Group 1 and 100.0% (86/86) in Group 2 for serogroup W

###### *Meningococcal rSBA Antibody Titers $\geq 1:8$ and $\geq 1:128$*

###### rSBA Titers $\geq 1:8$

At baseline, the percentage of subjects with meningococcal rSBA titers  $\geq 1:8$  for serogroup A was numerically higher in Group 1 (33.0% [30/91]) than Group 2 (17.4% [15/86]). At baseline, comparable percentages of subjects in Group 1 and Group 2 had meningococcal rSBA titers  $\geq 1:8$  for serogroups C, Y, and W.

Thirty days after vaccination, the percentages of subjects with rSBA titers  $\geq 1:8$  were increased from baseline for all serogroups in both groups. For serogroups A, Y, and W, the percentages were similar (100.0%) between the 2 groups. For serogroup C, the percentage of subjects with rSBA titers  $\geq 1:8$  was comparable in Group 1 (100.0% [91/91]) and Group 2 (98.8% [85/86]).

###### rSBA Titers $\geq 1:128$

At baseline, the percentage of subjects with meningococcal rSBA titers  $\geq 1:128$  for serogroup A was numerically higher in Group 1 (31.9% [29/91]) than Group 2 (17.4% [15/86]). At baseline, comparable percentages of subjects in Group 1 and Group 2 had meningococcal rSBA titers  $\geq 1:128$  for serogroups C, Y, and W.

Thirty days after vaccination, the percentages of subjects with rSBA titers  $\geq 1:128$  were increased from baseline for all serogroups in both groups. For serogroups A, Y, and W, the percentages were similar (100.0%) between the 2 groups. For serogroup C, the percentage of subjects with rSBA titers  $\geq 1:128$  was numerically higher in Group 1 (100.0% [91/91]) than in Group 2 (94.2% [81/86]).

###### *Meningococcal Vaccine Seroresponse as Defined in the SAP*

An additional vaccine seroresponse definition, to the one present in the protocol, was presented in the SAP as follows: post-vaccination titers  $\geq 1:32$  for subjects with pre-vaccination titers  $< 1:8$  or at least a 4-fold increase in titers from pre- to post-vaccination for subjects with pre-vaccination titers  $\geq 1:8$

Most subjects in both groups demonstrated an rSBA vaccine seroresponse using this second definition at D30. The percentage of subjects with any rSBA vaccine seroresponse for serogroup A was numerically lower in Group 1 than Group 2 and the percentages of subjects with any rSBA vaccine seroresponse were similar or comparable between the 2 groups for serogroups C, Y, and W:

- 91.2% (83/91) in Group 1 and 98.8% (85/86) in Group 2 for serogroup A
- 100.0% (91/91) in Group 1 and 96.5% (83/86) in Group 2 for serogroup C
- 98.9% (90/91) in Group 1 and 98.8% (85/86) in Group 2 for serogroup Y
- 100.0% (91/91) in Group 1 and 100.0% (86/86) in Group 2 for serogroup W

#### *Meningococcal Vaccine Seroresponse as Defined in the Protocol SAP*

Vaccine seroresponse was defined in the protocol and SAP as post-vaccination titers  $\geq 1:8$  for subjects with pre-vaccination titers  $< 1:8$  or at least a 4-fold increase in titers from pre- to post-vaccination for subjects with pre-vaccination titers  $\geq 1:8$ .

Most subjects in both groups demonstrated rSBA vaccine seroresponse using this first definition at D30. The percentage of subjects with any rSBA vaccine seroresponse for serogroup A was numerically lower in Group 1 than Group 2 and the percentages of subjects with any rSBA vaccine seroresponse were similar or comparable between the 2 groups for serogroups C, Y, and W:

- 91.2% (83/91) in Group 1 and 98.8% (85/86) in Group 2 for serogroup A
- 100.0% (91/91) in Group 1 and 96.5% (83/86) in Group 2 for serogroup C
- 98.9% (90/91) in Group 1 and 98.8% (85/86) in Group 2 for serogroup Y
- 100.0% (91/91) in Group 1 and 100.0% (86/86) in Group 2 for serogroup W

#### **Meningococcal Antibody Responses Measured by hSBA**

##### *GMTs of Antibodies Against Meningococcal Serogroups A, C, Y, and W*

At baseline, meningococcal hSBA GMTs were comparable in both groups.

Thirty days after vaccination, meningococcal hSBA GMTs for all 4 serogroups were higher than at baseline in both groups. For serogroups A and Y, the hSBA GMTs for Group 1 (76.8 and 96.6, respectively) were comparable to the hSBA GMTs for Group 2 (61.5 and 76.4, respectively) and CIs were overlapping. For serogroups C and W, the hSBA GMTs for Group 1 (492.9 and 71.7, respectively) were higher than those in Group 2 (28.4 and 44.5, respectively) with non-overlapping CIs.

##### *Fold Rise in hSBA Antibody Titers*

Most subjects ( $> 93\%$  in Group 1 and  $> 73\%$  in Group 2) had a 4-fold rise in hSBA antibody titers 30 days after vaccination. The percentage of subjects with a  $\geq 4$ -fold rise in hSBA antibody titers 30 days after vaccination was comparable in both groups for serogroups A, Y, and W and was higher in Group 1 than in Group 2 for serogroup C:

- 94.4% (85/90) in Group 1 and 87.2% (75/86) in Group 2 for serogroup A
- 100.0% (91/91) in Group 1 and 74.4% (64/86) in Group 2 for serogroup C
- 96.7% (88/91) in Group 1 and 96.5% (83/86) in Group 2 for serogroup Y
- 96.7% (88/91) in Group 1 and 94.2% (81/86) in Group 2 for serogroup W

##### *Meningococcal hSBA Antibody Titers $\geq 1:4$ and $\geq 1:8$*

###### hSBA Titers $\geq 1:4$

At baseline, generally comparable percentages of subjects in Group 1 and Group 2 had meningococcal hSBA titers  $\geq 1:4$  for serogroups A, C, Y, and W.

Thirty days after vaccination, the percentages of subjects with hSBA titers  $\geq 1:4$  were increased from baseline for all serogroups in both groups. In Group 1, 100.0% (91/91) of subjects had hSBA titers  $\geq 1:4$  after MenACYW conjugate vaccine administration. In Group 2, the percentage of subjects with hSBA titers  $\geq 1:4$  ranged from 94.2% (81/86) to 100.0% (86/86) after Nimenrix®.

#### hSBA Titers $\geq 1:8$

At baseline, generally comparable percentages of subjects in Group 1 and Group 2 had meningococcal hSBA titers  $\geq 1:8$  for serogroups A, C, Y, and W.

Thirty days after vaccination, the percentages of subjects with hSBA titers  $\geq 1:8$  were increased from baseline for all serogroups in both groups. The percentages of subjects with hSBA titers  $\geq 1:8$  after MenACYW conjugate vaccine administration for serogroups A, Y, and W were comparable to those after Nimenrix® (ranging from 97.8% [89/91] to 98.9% [90/91] in Group 1 and from 91.9% [79/86] to 100.0% [86/86] in Group 2). The percentage of subjects with hSBA titers  $\geq 1:8$  for serogroup C was higher in Group 1 (100.0% [91/91]) than in Group 2 (89.5% [77/86]).

#### *Meningococcal Vaccine Seroreponse*

Most subjects in both groups demonstrated hSBA vaccine seroreponse at D30. The percentage of subjects with an hSBA vaccine seroreponse was comparable in both groups for serogroups A, Y, and W (ranging from 96.7% [87/90] to 98.9% [90/91] in Group 1 and from 91.9% [79/86] to 98.8% [85/86] in Group 2). The percentage of subjects with an hSBA vaccine seroreponse for serogroup C was higher in Group 1 (100.0% [91/91]) than in Group 2 (86.0% [74/86]).

#### **Anti-tetanus Toxoid Antibody Concentrations**

##### *GMTs of Antibodies against Tetanus Toxoid*

At baseline, GMCs of anti-tetanus antibodies measured by ELISA were comparable in Group 1 and Group 2.

Thirty days after vaccination, GMCs were higher for both study groups and were comparable in Group 1 (11.5 IU/mL) and Group 2 (9.5 IU/mL).

##### *Seroprotective Levels of Tetanus Toxoid Antibody Concentrations*

#### Seroprotective Levels $\geq 0.01$ IU/mL

At baseline, all subjects had seroprotective concentrations  $\geq 0.01$  IU/mL in both groups.

Thirty days after vaccination, all subjects had seroprotective concentrations  $\geq 0.01$  IU/mL in both groups: 100.0% (90/90) in Group 1 and 100.0% (86/86) in Group 2.

#### Seroprotective Levels $\geq 0.1$ IU/mL

At baseline, all subjects had seroprotective concentrations  $\geq 0.1$  IU/mL in both groups.

Thirty days after vaccination, all subjects had seroprotective concentrations  $\geq 0.1$  IU/mL in both groups: 100.0% (90/90) in Group 1 and 100.0% (86/86) in Group 2.

#### **Safety Results:**

##### **Solicited Reactions Between D0 and D07**

Overall, the percentages of subjects reporting at least 1 solicited reaction were comparable between Group 1 and Group 2 (79.8% [75/94] and 83.0% [78/94], respectively). The percentages of subjects reporting at least 1 Grade 3 solicited reaction were comparable between Group 1 (6.4% [6/94]) and Group 2 (7.4% [7/94]).

##### *Solicited Injection Site Reactions*

The percentages of subjects reporting at least 1 solicited injection site reaction were comparable between Group 1 (48.9% [46/94]) and Group 2 (53.2% [50/94]).

The most frequently reported solicited injection site reaction was redness (preferred term: erythema) reported by 30.9% (29/94) of subjects in Group 1 and 35.1% (33/94) of subjects in Group 2, followed by tenderness, which was reported by 29.8% (28/94) of subjects in Group 1 and 33.0% (31/94) of subjects in Group 2. Injection site swelling was reported less frequently, by 14.9% (14/94) of subjects in Group 1 and 18.1% (17/94) of subjects in Group 2.

The majority of reactions at the MenACYW conjugate vaccine or Nimenrix® injection sites were of Grade 1 or 2 intensity, all started between D0 and D03, and most lasted 1 to 3 days.

Few subjects reported Grade 3 solicited injection site reactions: 3.2% of subjects (3/94) in Group 1 and 4.3% of subjects (4/94) in Group 2.

#### *Solicited Systemic Reactions*

The percentage of subjects who reported at least 1 solicited systemic reaction was 61.7% (58/94) in Group 1 and 69.1% (65/94) in Group 2. Irritability was the most frequently reported solicited systemic reaction, reported by 52.1% (49/94) of subjects in Group 1 and 56.4% (53/94) of subjects in Group 2. Abnormal crying was reported by 33.0% (31/94) of subjects in Group 1 and 39.4% (37/94) of subjects in Group 2. Drowsiness was reported by 34.0% (32/94) of subjects in Group 1 and 27.7% (26/94) of subjects in Group 2. Loss of appetite was reported by 23.4% (22/94) of subjects in Group 1 and 36.2% (34/94) of subjects in Group 2. Less frequently reported were fever (7.4% [7/94] and 4.4% [4/94] of subjects in Groups 1 and 2, respectively) and vomiting (4.3% [4/94] and 5.3% [5/94] of subjects in Groups 1 and 2, respectively).

Overall, most solicited systemic reactions were of Grade 1 or Grade 2 intensity, started between D0 and D030, and lasted 1 to 3 days.

#### **Unsolicited AEs Between D0 and D30**

The percentages of subjects reporting at least 1 unsolicited non-serious AE were comparable between Group 1 (58.5% [55/94]) and Group 2 (60.6% [57/94]). The number of unsolicited non-serious AEs was numerically lower in Group 1 (n=77 AEs) compared to Group 2 (n=90 AEs).

A small percentage of unsolicited non-serious AEs were considered by the Investigators as being related to the vaccine given on D0: 5.3% of subjects (5/94) in Group 1 and 6.4% of subjects (6/94) in Group 2. Most of these events were of Grade 1 or Grade 2 intensity.

#### *Immediate AEs*

There were no immediate unsolicited AEs reported in either of the groups. There were no immediate SAEs, including any anaphylactic or life-threatening events.

#### *Unsolicited Non-Serious Injection Site ARs*

There were no subjects who reported at least 1 unsolicited non-serious injection site reaction after vaccination in Group 1. A total of 3 subjects (3.2%) in Group 2 reported at least 1 unsolicited non-serious injection site AR: injection site induration was reported in 2 subjects (2.1%) and injection site urticaria was reported in 1 subject (1.1%).

No subjects reported Grade 3 unsolicited non-serious injection site reactions.

#### *Unsolicited Non-Serious AEs*

Unsolicited non-serious systemic AEs were most frequently reported in the SOC of Infections and infestations (39.4% [37/94] of subjects in Group 1 and 40.4% [38/94] of subjects in Group 2). The most frequently reported unsolicited non-serious systemic AEs in this SOC were upper respiratory tract infection reported by 8.5% (8/94) of subjects in Group 1 and 17.0% (16/94) of subjects in Group 2; nasopharyngitis reported by 9.6% (9/94) of subjects in Group 1 and 5.3% (5/94) of subjects in Group 2; followed by rhinitis reported by 7.4% (7/94) of subjects in Group 1 and 5.3% (5/94) of subjects in Group 2.

Other frequently reported unsolicited non-serious systemic AEs were reported in the SOC of Gastrointestinal disorders: 14.9% (14/94) of subjects in Group 1 and 10.6% (10/94) of subjects in Group 2. The most commonly reported unsolicited non-serious AEs in this SOC were diarrhea reported by 8.5% (8/94) of subjects in Group 1 and 4.3% (4/94) of subjects in Group 2 and teething reported by 4.3% (4/94) of subjects in Group 1 and 3.2% (3/94) of subjects in Group 2.

Most unsolicited non-serious AEs within 30 days of Visit 1 were of Grade 1 or Grade 2 intensity. The percentages of subjects who reported at least 1 Grade 3 unsolicited non-serious systemic AE were similar between Group 1 (3.2% [3/94]) and Group 2 (3.2% [3/94]).

#### *Unsolicited Non-Serious Systemic ARs*

Few subjects reported unsolicited non-serious systemic ARs. The percentages of subjects who reported at least 1 unsolicited, non-serious systemic AR were comparable between Group 1 (5.3% [5/94]) and Group 2 (4.3% [4/94]).

Unsolicited non-serious systemic ARs were most frequently reported in the SOC of Gastrointestinal disorders, reported by 5.3% (5/94) of subjects in Group 1 and 2.1% (2/94) of subjects in Group 2. The most frequently reported unsolicited non-serious systemic AR in this SOC was diarrhea reported by 4.3% (4/94) of subjects in Group 1 and 2.1% (2/94) of subjects in Group 2.

No subjects reported Grade 3 unsolicited non-serious systemic ARs.

#### *Discontinuations Due to an AE*

No subject discontinued the study due to an SAE or other AE.

#### *SAEs*

No SAEs occurred within 7 days after vaccination at Visit 1.

One subject experienced 2 SAEs after D07 through the 30-day follow-up after vaccination at Visit 1. None of these SAEs were considered as related to the vaccine by the Investigator and none led to discontinuation from the study.

#### *Deaths*

No cases of death were reported during the study.

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