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<b>Sponsor:</b> Sanofi Pasteur	<b>Study Identifiers:</b> U1111-1161-2787, NCT03205371, 2018-001472-38
<b>Drug substance:</b> Quadrivalent Meningococcal ACYW Conjugate Vaccine	<b>Study code:</b> MET57
<b>Title of the study:</b> Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Other Pediatric Vaccines in Healthy Toddlers	
<b>Study centers:</b> This was a multi-center, multi-national study involving 30 centers over 4 countries.	
<b>Study period:</b> Date first subject enrolled: 07/Nov/2016 Date last subject completed: 19/Jul/2018	
<b>Phase of development:</b> III	
<b>Objectives:</b> <b>Primary objective:</b> To describe the immunogenicity profile of MenACYW conjugate vaccine administered alone or concomitantly with licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13). <b>Secondary objective:</b> To describe the immunogenicity profile of licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) when administered alone or concomitantly with MenACYW conjugate vaccine.	
<b>Methodology:</b> This was a Phase III, open-label (immunology laboratory technicians were blinded to group assignment), randomized, parallel-group, active-controlled, multi-center study to describe the immunogenicity and safety of a single dose of MenACYW conjugate vaccine when administered alone and when administered concomitantly with other pediatric vaccine(s) in healthy toddlers in South Korea, and Thailand (measles-mumps-rubella [MMR] vaccine + varicella [V] vaccine), Mexico (diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and <i>Haemophilus influenzae</i> type-b [DTaP-IPV-HB-Hib] conjugate vaccine), and the Russian Federation (pneumococcal conjugate vaccine [PCV13]). In South Korea and Mexico, healthy, meningococcal-vaccine naïve toddlers aged 12 to 23 months on the day of enrollment were randomized in a 2:1:1 ratio (by country) to the following groups: <u>South Korea:</u> Group 1: MenACYW conjugate vaccine + MMR + V on Day (D) 0 Group 2: MenACYW conjugate vaccine on D0 Group 3: MMR + V on D0 <u>Mexico:</u> Group 4: MenACYW conjugate vaccine + DTaP-IPV-HB-Hib on D0 Group 5: MenACYW conjugate vaccine on D0	

Group 6: DTaP-IPV-HB-Hib on D0

In the Russian Federation, healthy, meningococcal-vaccine naïve toddlers aged 12 to 14 months or 16 to 23 months on the day of enrollment were assigned to Group 8 with a balanced population distribution of half of the subjects aged 12 to 14 months and half of the subjects aged 16 to 23 months. Healthy, meningococcal-vaccine naïve toddlers, who had not received the 3rd dose of PCV13, aged 15 to 23 months on the day of enrollment were randomized in a 2:1 ratio to Groups 7 and 9, in order to comply with the National Immunization Calendar of the Russian Federation:

The Russian Federation:

Group 7: MenACYW conjugate vaccine + PCV13 on D0

Group 8: MenACYW conjugate vaccine on D0

Group 9: PCV13 on D0 (Visit 1)

Note about Visits:

Visit 0=Screening visit for subjects in the Russian Federation only

Visit 1=D0, vaccination visit (all countries)

Visit 2=D30 (+14 days), 30 to 44 days after D0 (all countries)

In the Russian Federation, Visit 0 and Visit 1 may have taken place on the same day, or Visit 1 may have taken place up to 5 days after Visit 0.

In Thailand, healthy, meningococcal-vaccine naïve toddlers aged 12 to 23 months on the day of enrollment were randomized in a 2:1:1 ratio to the following groups:

Thailand:

Group 10: MenACYW conjugate vaccine + MMR + V on D0

Group 11: MenACYW conjugate vaccine on D0

Group 12: MMR + V on D0

All Subjects:

All subjects were to provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at Visit 2 (30 to 44 days after vaccination[s]). Solicited adverse event (AE) information was collected for 7 days after vaccination(s); unsolicited AE information was collected from Visit 1 (D0) to Visit 2, and serious adverse event (SAE) information was collected throughout the study period from Visit 1 through Visit 2.

Upon completion of all study procedures and termination from the trial at Visit 2, study participants were to receive the remainder of the recommended toddler vaccines, which were part of the respective National Immunization Programs (NIP) for each country, from their health care provider.

Note: In this document, “days” refers to calendar days.

For the Russian Federation only:

Per Guideline for the conduct of clinical trials of the Russian Federation Health Authorities and in accordance with local practices, in addition to study vaccine immunogenicity assessment, the blood of subjects enrolled at sites in the Russian Federation was also to be tested for complete blood count (CBC) and blood chemistry. These subjects were also to provide a urine sample for urinalysis. Samples were to be provided at Visit 0 (screening visit, baseline) and at Visit 2 (30 days [+14 days] after the vaccination[s] at Visit 1). According to recommendations of Russian Health Authorities, the subjects were to be examined by a neurologist at Visit 0 and at Visit 2. The examinations by a neurologist and additional biological analyses were implemented for subjects enrolled at sites in the Russian Federation per Guideline of the Russian Federation Health Authorities only and not to address any concern of the Sponsor regarding safety issues.

### Blood sampling

All subjects were to provide a pre-vaccination blood sample at Visit 0 (screening visit in the Russian Federation only) or at Visit 1 (in South Korea, Mexico, and Thailand) and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination[s] on D0).

**Table S1: Schedules for blood sampling and antigen testing**

Blood Sampling/Antigen Testing*		
Group	Visit 0/Visit 1 <sup>†</sup> (pre-vaccination)	D30 (+14 days)
1	MenACYW conjugate vaccine <sup>‡</sup> MMR+V vaccines <sup>§</sup>	MenACYW conjugate vaccine <sup>‡</sup> MMR+V vaccines <sup>§</sup>
2	MenACYW conjugate vaccine <sup>‡</sup>	MenACYW conjugate vaccine <sup>‡</sup>
3	MMR+V vaccines <sup>§</sup>	MMR+V vaccines <sup>§</sup>
4	MenACYW conjugate vaccine <sup>‡</sup> DTaP-IPV-HB-Hib vaccine <sup>**</sup>	MenACYW conjugate vaccine <sup>‡</sup> DTaP-IPV-HB-Hib vaccine <sup>**</sup> , <sup>††</sup>
5	MenACYW conjugate vaccine <sup>‡</sup>	MenACYW conjugate vaccine <sup>‡</sup>
6	DTaP-IPV-HB-Hib vaccine <sup>**</sup>	DTaP-IPV-HB-Hib vaccine <sup>**</sup> , <sup>††</sup>
7	MenACYW conjugate vaccine <sup>‡</sup> PCV13 vaccine <sup>‡‡</sup>	MenACYW conjugate vaccine <sup>‡</sup> PCV13 vaccine <sup>‡‡</sup>
8	MenACYW conjugate vaccine <sup>‡</sup>	MenACYW conjugate vaccine <sup>‡</sup>
9	PCV13 vaccine <sup>‡‡</sup>	PCV13 vaccine <sup>‡‡</sup>
10	MenACYW conjugate vaccine <sup>‡</sup> MMR+V vaccines <sup>§</sup>	MenACYW conjugate vaccine <sup>‡</sup> MMR+V vaccines <sup>§</sup>
11	MenACYW conjugate vaccine <sup>‡</sup>	MenACYW conjugate vaccine <sup>‡</sup>
12	MMR+V vaccines <sup>§</sup>	MMR+V vaccines <sup>§</sup>

\*Sera were tested for antibodies (Abs) elicited by the antigens contained in the respective vaccines.

<sup>†</sup>At Visit 0 for subjects in the Russian Federation; at Visit 1 for subjects in Mexico, South Korea, and Thailand

<sup>‡</sup> Ab titers against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) (in 100% of subjects) and by serum bactericidal assay using baby rabbit complement (rSBA) (in 50 subjects per group in Groups 2, 5, and 8; and in 100 subjects per group in Groups 1, 4, and 7)

<sup>§</sup> Anti-measles, anti-mumps, anti-rubella, and anti-varicella Ab concentrations

<sup>\*\*</sup> Anti- tetanus and anti-pertussis (pertussis toxoid [PT] and filamentous hemagglutinin [FHA]) Ab concentrations measured at Visit 1 and D30

<sup>††</sup> Anti-diphtheria, anti-polyribosyl-ribitol phosphate (PRP), anti-hepatitis B surface antigen (HBsAg) Ab concentrations and anti-poliovirus types 1, 2, and 3 Ab titers measured at D30

<sup>‡‡</sup> Anti-pneumococcal Ab concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

### Additional blood sampling – for the Russian Federation only:

Subjects enrolled at sites in the Russian Federation were also to provide approximately 2 milliliters (mL) of additional blood sample, (depending on local laboratory needs) for CBC and blood chemistry testing at Visit 0 (screening visit) and at Visit 2 (30 days [+14 days] after Visit 1) per Health Authority guidelines and in accordance with local regulations (total blood volume collected was approximately 7 mL per blood draw).

### Urine sampling – for the Russian Federation only

Subjects enrolled at sites in the Russian Federation were also to provide an approximately 8 mL urine sample (depending on local laboratory needs) for urinalysis at Visit 0 and at Visit 2 (30 days [+14 days] after Visit 1) per Health Authority request and in accordance with local regulations.

Collection of safety data

- All subjects were observed for 30 minutes after vaccination under the supervision of a responsible healthcare professional at each study site and any unsolicited systemic AEs occurring during that time were recorded as immediate unsolicited systemic AEs in the electronic case report form (CRF).
- The subject's parent/guardian was to record information in a diary card about solicited reactions from D0 to D07 after vaccination(s) and unsolicited AEs from D0 to Visit 2. SAEs were to be reported throughout the duration of the trial.
- In addition, the subject's parent/guardian was asked to notify the site immediately about potential SAEs at any time during the trial.
- Staff were to contact subject's parent/guardian by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the diary card up to Visit 2 and to bring it back at Visit 2.
- The completed diary card was to be reviewed with the subject's parent/guardian at Visit 2.

For the Russian Federation only:

Any clinically significant abnormal results of CBC, blood chemistry, urinalysis, or neurological examination (according to Investigator judgment) were to be reported as medical history (for Visit 0 results) or as AEs (for Visit 2 results). All laboratory tests were to be sampled and analyzed locally. Results of lab tests were to be assessed by the Investigator. The laboratory values for CBC, blood chemistry, and urinalysis, and results of neurological examinations were only to be collected in the CRF if they were clinically significant.

Laboratory tests were to be considered clinically significant in the following circumstances:

- Symptomatic
- Requiring corrective treatment or additional consultation by relevant specialist
- Leading to study vaccine discontinuation or postponing vaccination
- Meet SAE criteria

**Number of subjects:**  
 Planned: 1200  
 Randomized: 1183  
 Vaccinated: 1177

**Evaluated:**  
 Immunogenicity: 1156  
 Safety: 1177

**Diagnosis and criteria for inclusion:**

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

1) For South Korea: Korean males and females aged 12 to 23 months on the day of the 1st study visit

For Mexico: Males and females aged 12 to 23 months on the day of the 1st study visit

For the Russian Federation: Males and females aged 12 to 14 months or 16 to 23 months on the day of the 1st study visit (eligible for enrollment to Group 8) or 15 to 23 months on the day of the 1st study visit (eligible for enrollment to Group 7 or 9)

For Thailand: Thai males and females aged 12 to 23 months on the day of the 1st study visit

2) Subject had received all recommended standard of care vaccinations according to his/her age as per local regulations.\*

For the Russian Federation only, subjects aged 15 to 23 months on the day of the 1st study visit (eligible for enrollment to Group 7 or 9) must not have received the 3rd PCV13 vaccination corresponding to his or her age as per the country's NIP. The 2nd dose of PCV13 must have been administered at least 4 weeks before the 3rd dose of PCV13 is administered in the study.

For South Korea, subjects must not have received the MMR or V vaccination corresponding to his or her age at inclusion.

For Mexico, subjects must not have received the DTaP-IPV-HB-Hib vaccination corresponding to his or her age at inclusion.

For Thailand, subjects must not have received the any dose of MMR or V vaccination.

3) Informed consent form (ICF) has been signed and dated by the parent(s) or guardian if allowed by local regulations (and by independent witnesses if required by local regulations)†

4) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures

\*Subjects must have received the total number of doses expected for each vaccine recommended for his/her age in the respective NIPs, but inclusion of subjects with variations in the vaccine administration timeframes is considered acceptable if the total number of doses for the corresponding vaccines have been completed (eg, in Mexico, 3 infant doses of the pentavalent vaccine must have been administered but the 4th dose due in the 2nd year of life should not have been administered for subjects to be included in the trial). For the Russian Federation only, subjects that have not received a seasonal flu vaccination from 6 months of age according to the Russian NIP are still eligible to participate in this study. For Thailand only, subjects who may have received a vaccine ahead of the schedule can still be included in the study provided the 1st doses of MMR and V vaccines have not been administered prior to inclusion.

†In the Russian Federation, as per local regulations, only the subject's parent(s) are entitled to sign an ICF. A child under the responsibility of a guardian will not be included in the study.

#### Study treatments

**Study product 1: MenACYW conjugate vaccine:** Meningococcal PS (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)

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 (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)

**Study product 2: M-M-R®II (MMR):** Measles, Mumps, and Rubella Virus Vaccine Live (Merck & Co., Inc., Whitehouse Station, NJ, USA); (licensed in South Korea and Thailand)

Form: Solution for injection supplied as lyophilized vaccine and diluent for reconstitution

Composition:

Each 0.5 mL dose of reconstituted vaccine was formulated to contain the following components:

Measles virus: not less than 1000 tissue culture infectious doses (TCID50)

Mumps virus: not less than 12 500 TCID50

Rubella virus: not less than 1000 TCID50

Each 0.5 mL dose was also formulated to contain the following inactive ingredients: sorbitol (14.5 milligrams [mg]), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin ( $\leq$  0.3 mg), fetal bovine serum ( $<$  1 part per million [ppm]), other buffer and media ingredients, and approximately 25  $\mu$ g of neomycin. The product contained no preservative.

Route of administration: Subcutaneous (SC)

**Study product 3: VARIVAX® (V):** Varicella Virus Vaccine Live (Merck, Sharp & Dohme, Haarlem, The Netherlands); (licensed in South Korea and Thailand)

Form: Suspension for injection supplied as lyophilized vaccine to be reconstituted using the accompanying sterile diluent

Composition:

Each 0.5 mL dose of vaccine was formulated to contain a minimum of 1350 plaque-forming units (PFU) of Oka/Merck varicella virus.

Each 0.5 mL dose also contained approximately 25 mg of sucrose, 12.5 mg hydrolyzed gelatin, 3.2 mg of sodium chloride, 0.5 mg of monosodium L-glutamate, 0.45 mg of sodium phosphate dibasic, 0.08 mg of potassium phosphate monobasic, and 0.08 mg of potassium chloride. The product also contained residual components of Medical Research Council cell strain 5 (MRC-5) cells including deoxyribonucleic acid (DNA) and protein and trace quantities of sodium phosphate monobasic, ethylenediamine tetraacetic acid (EDTA), neomycin, and fetal bovine serum. The product contained no preservative.

Route of administration: SC

**Study product 4: Hexaxim®(DTaP-IPV-HB-Hib):** Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (recombinant deoxyribonucleic acid [rDNA]), poliomyelitis (inactivated), and *Haemophilus influenzae* type b conjugate vaccine (adsorbed); (Sanofi Pasteur SA, Marcy l'Etoile, France); (licensed in Mexico as Hexacima)

Form: Suspension for injection

Composition:

Each 0.5 mL dose was formulated to contain the following components:

Diphtheria Toxoid .....  $\geq$  20 international units (IU)  
Tetanus Toxoid .....  $\geq$  40 IU

Bordetella pertussis antigens:

PT ..... 25  $\mu$ g  
FHA ..... 25  $\mu$ g

Poliovirus (Inactivated):

Type 1 (Mahoney) ..... 40 D antigen units  
Type 2 (MEF-1) ..... 8 D antigen units  
Type 3 (Saukett) ..... 32 D antigen units

HBsAg ..... 10  $\mu$ g

*Haemophilus influenzae* type b PS (PRP) ..... 12  $\mu$ g  
conjugated to Tetanus Protein ..... 22-36  $\mu$ g

The vaccine also contained the excipients: disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, water for injections. The vaccine may have contained traces of glutaraldehyde, formaldehyde, neomycin, streptomycin, and polymyxin B, which were used during the manufacturing process.

Route of administration: IM

**Study product 5: Prevenar 13® (PCV13):** Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein) (Pfizer Ireland Pharmaceuticals, Ireland) (licensed in the Russian Federation)

Form: Suspension for IM injection

Composition:

Each 0.5 mL vaccine dose was formulated to contain approximately 2.2 µg of each of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F saccharides, 4.4 µg of 6B saccharides; 34 µg CRM197 carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer, and 125 µg aluminum as aluminum phosphate adjuvant.

Route of administration: IM

**Duration of participation:** The duration of each subject's participation in the study was approximately 30 to 44 days.

**Criteria for evaluation:**

**Primary endpoint:**

Ab titers against meningococcal serogroups A, C, Y, and W measured by hSBA for Groups 1, 2, 4, 5, 7, 8, 10, and 11 at Visit 0 (for subjects in the Russian Federation) or Visit 1 (for subjects in Mexico, South Korea, or Thailand) (before vaccination[s]) and 30 days (+14 days) after vaccination(s) (all subjects).

**Secondary endpoints:**

- Abs to the antigens contained in MMR vaccine measured before and 30 days (+14 days) after vaccination with MMR vaccine for Groups 1, 3, 10, and 12
- Anti-varicella Ab concentrations measured before and 30 days (+14 days) after vaccination with V vaccine for Groups 1, 3, 10, and 12
- Abs to the tetanus and acellular pertussis antigens (PT and FHA) contained in DTaP-IPV-HB-Hib vaccine measured before and 30 days (+14 days) after vaccination with DTaP-IPV-HB-Hib vaccine for Groups 4 and 6
- Abs to the diphtheria, inactivated polio, hepatitis B, and *Haemophilus influenzae* antigens contained in DTaP-IPV-HB-Hib vaccine measured 30 days (+14 days) after vaccination with DTaP-IPV-HB-Hib vaccine for Groups 4 and 6
- Anti-pneumococcal Ab concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F measured before and 30 days (+14 days) after vaccination with PCV13 vaccine for Groups 7 and 9

**Statistical methods:**

All analyses were descriptive. No hypotheses were tested. 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).

**Immunogenicity**

Descriptive statistics were provided for the Ab titers against meningococcal serogroups contained in MenACYW conjugate vaccine and for the antigens contained in the licensed vaccines. In general, categorical variables were summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages.

For GMTs or geometric mean concentrations (GMCs), 95% CIs of point estimates were calculated using normal approximation assuming they are log-normally distributed.

For the Primary Objective:

The blood collection and Ab testing schedule are presented in Table S1.

The immunogenicity descriptive analyses at least included the following:

Ab titers against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenACYW conjugate vaccine:

- GMT and 95% CI
- Titer distribution and RCDCs
- Percentage of subjects with titer  $\geq 1:4$  and  $\geq 1:8$  and 95% CI
- Percentage of subjects with titer  $\geq 4$ -fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse\*

\* 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.

For the Secondary Objective:

The analyses on the concomitant vaccines included GMTs and titer distribution or GMCs, and RCDCs, as well as percentage of subjects with:

- Abs to the antigens contained in MMR vaccine measured before and 30 days after vaccination with MMR vaccine:
  - Anti-measles Ab concentrations  $\geq 255$  mIU/mL
  - Anti-mumps Ab concentrations  $\geq 10$  Mumps Ab units/mL
  - Anti-rubella Ab concentrations  $\geq 10$  IU/mL
- Anti-varicella Ab concentrations before and 30 days after vaccination with V vaccine  $\geq 5$  glycoprotein (gp) enzyme-linked immunosorbent assay [ELISA] Ab units/mL
- Abs to the antigens contained in DTaP-IPV-HB-Hib vaccine measured before and 30 days after vaccination with DTaP-IPV-HB-Hib vaccine:
  - Anti-tetanus Ab concentrations  $\geq 0.01$  and  $0.1$  IU/mL at D0 and  $\geq 0.1$  and  $1.0$  IU/mL at D30
  - Anti-pertussis (PT and FHA) Ab concentrations and pertussis vaccine response<sup>†</sup>
- Abs to the antigens contained in DTaP-IPV-HB-Hib vaccine measured 30 days after vaccination with DTaP-IPV-HB-Hib vaccine:
  - Anti-diphtheria Ab concentrations  $\geq 0.1$  and  $1.0$  IU/mL
  - Anti-PRP Ab concentrations  $\geq 0.15$  and  $1.0$   $\mu\text{g/mL}$
  - Anti-poliovirus types 1, 2, and 3 Ab titers  $\geq 1:8$
  - Anti-HBsAg Ab concentrations  $\geq 10$  and  $100$  milli-international units (mIU)/mL
- Anti-pneumococcal Ab concentrations  $\geq 0.35$   $\mu\text{g/mL}$  and  $1.0$   $\mu\text{g/mL}$  and 95% CI for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F measured before and 30 days after vaccination with PCV13 vaccine

<sup>†</sup> Pertussis vaccine response:

- If the pre-booster vaccination concentration is  $< 4$  x lower limit of quantification (LLOQ), then the post-booster vaccination concentration is  $\geq 4$  x the pre-booster concentration;
- If the pre-booster vaccination concentration is  $\geq 4$  x LLOQ, then the post-booster vaccination concentration is  $\geq 2$  x the pre-booster concentration.



**Summary:**

**Population characteristics:**

Subject Disposition:

A total of 1183 subjects were enrolled in this study and randomly allocated to one of the following groups depending on the country: Group 1 (107 subjects), Group 2 (53 subjects), and Group 3 (53 subjects) in South Korea, Group 4 (200 subjects), Group 5 (100 subjects), and Group 6 (100 subjects) in Mexico, Group 7 (200 subjects), Group 8 (100 subjects), and Group 9 (100 subjects) in the Russian Federation, and Group 10 (86 subjects), Group 11 (42 subjects), and Group 12 (42 subjects) in Thailand.

There were no early terminations due to an SAE (there was a single instance of early termination due to a non-serious AE of gastroenteritis). A total of 1177 (99.5%) subjects received vaccine and all of these subjects received the vaccine as randomized. A total of 1159 (98.0%) subjects completed the trial.

Demographics:

Among all randomized subjects, there were 633 (53.5%) male subjects and 550 (46.5%) female subjects: the overall ratio of male/female subjects was 1.15. There were more males than females in Groups 1, 2, 4, 5, 6, 7, and 9 (male/female ratio ranging from 1.08 to 1.94). In Groups 3, 8, 10, 11, and 12, the male/female ratio ranged from 0.83 to 0.96.

The mean age ( $\pm$  SD) of the subjects at enrollment was  $15.2 \pm 2.97$  months for all randomized subjects. The mean age ( $\pm$  SD) of the subjects enrolled in South Korea (Groups 1 to 3) and Thailand (Groups 10 to 12) ranged from  $12.3 \pm 0.96$  to  $12.8 \pm 1.76$  months. The mean age ( $\pm$  SD) of the subjects enrolled in Mexico (Groups 4 to 6) and the Russian Federation (Groups 7 to 9) ranged from  $16.0 \pm 3.10$  to  $16.8 \pm 2.99$  months. In South Korea, racial origin and ethnicity were not collected due to local regulation. In Thailand, all the subjects enrolled were Asian. In Mexico, all the subjects enrolled but 1 (Asian) were White. All the subjects enrolled but 2 were Hispanic or Latino. In the Russian Federation, all the subjects enrolled but 7 (Asian) were White.

**Immunogenicity:**

Primary Objective: Immunogenicity Profile of MenACYW Conjugate Vaccine Administered Alone or Concomitantly with Licensed Pediatric Vaccine(s)

Overall, the immunogenicity profile of MenACYW conjugate vaccine administered alone was comparable to the one of MenACYW conjugate vaccine administered concomitantly with licensed pediatric vaccines (MMR+V, DTaP-IPV-HB-Hib, or PCV13).

The percentages of subjects with hSBA titers  $\geq 1:4$  and  $\geq 1:8$  were high and comparable in all the groups for all serogroups (ranging from 93.3% to 100% for hSBA titers  $\geq 1:4$  and from 83.7% to 100% for hSBA titers  $\geq 1:8$ ).

The post-vaccination hSBA GMTs were comparable in all the groups for all serogroups except for the serogroup A. The clinical relevance of the difference in GMTs observed was minimal and corresponding differences were not observed with other immune endpoints.

- The post-vaccination hSBA GMTs were lower when MenACYW conjugate vaccine was administered alone (Group 11) compared to when MenACYW conjugate vaccine was administered concomitantly with MMR+V (Group 10) for the serogroup A: 32.0 vs 58.0, respectively
- The post-vaccination hSBA GMTs were higher when MenACYW conjugate vaccine was administered alone (Group 8) compared to when MenACYW conjugate vaccine was administered concomitantly with PCV13 (Group 7) for the serogroup A: 49.0 vs 24.6, respectively

The percentages of subjects with an hSBA vaccine seroresponse at D30 were comparable in all the groups for all serogroups (ranging from 56.1% to 100%).

The percentages of subjects with at least a 4-fold rise in hSBA titers from baseline to D30 were comparable in all the groups for all serogroups (ranging from 57.1% to 100%) except for the serogroup A:

- The percentage of subjects with at least a 4-fold rise in hSBA titers was lower when MenACYW conjugate vaccine was administered alone (Groups 2&11) compared to when MenACYW conjugate vaccine was administered concomitantly with MMR+V (Groups 1&10) for the serogroup A: 64.4% vs 82.5%, respectively

Secondary Objective: Immunogenicity Profile of Licensed Pediatric Vaccine(s) When Administered Alone or Concomitantly with MenACYW Conjugate Vaccine

Overall, the immunogenicity profile of licensed pediatric vaccines (MMR+V, DTaP-IPV-HB-Hib, or PCV13) administered alone was comparable to the one of licensed pediatric vaccines administered concomitantly with MenACYW conjugate vaccine.

The post-vaccination GMTs and response rates were high and comparable in all the groups who received MMR+V vaccines. The GMTs ranged from 1998 to 2923 for anti-measles Abs, from 80.4 to 108 for anti-mumps Abs, from 73.4 to 111 for anti-rubella Abs, and from 11.5 to 19.0 for anti-varicella Abs. The response rates ranged from 95.3% to 98.0% for anti-measles Abs concentrations  $\geq 255$  mIU/mL, from 97.6% to 100% for anti-mumps Abs concentrations  $\geq 10$  Mumps Ab units/mL, was 100% for anti-rubella Abs concentrations  $\geq 10$  IU/mL, and from 90.2% to 100% for anti-varicella Abs concentrations  $\geq 5$  gpELISA Ab units/mL.

The response rates and post-vaccination GMTs were high and comparable in both groups who received DTaP-IPV-HB-Hib vaccine.

The post-vaccination GMTs were high and comparable in both groups who received PCV13 vaccine (ranging from 0.802 [serotype 3] to 7.62 [serotype 14] in Group 7 and from 0.773 [serotype 3] to 6.30 [serotype 14] in Group 9). The response rates were high and comparable in both groups for all the serotypes except for the serotype 4:

- The percentage of subjects with anti-pneumococcal Abs concentrations  $\geq 1.0$   $\mu\text{g/mL}$  was lower when PCV13 vaccine was administered alone (Group 9) compared to when PCV13 vaccine was administered concomitantly with MenACYW conjugate vaccine (Group 7) for the serotype 4: 62.0% vs 80.1%, respectively

**Issue date:** 09-Feb-2021