NCT Number: NCT03205371

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Other Pediatric Vaccines in Healthy Toddlers

Phase III, open-label (immunology laboratory technicians will be 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 vaccines in healthy toddlers in South Korea, Thailand, the Russian Federation, and Mexico

Clinical Trial Protocol, Amendment 3

Health Authority File Numbers:	Korea, Republic of (or South Korea): 20160036536 The Russian Federation: Not available The United Mexican States (Mexico): 163300410A0093 Thailand Not available
WHO Universal Trial Number (UTN):	U1111-1161-2787
Trial Code:	MET57
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid Solution / Intramuscular
Indication For This Study:	MenACYW conjugate vaccine as a single dose in toddlers 12 to 23 months old
Manufacturer:	Same as Sponsor
Coordinating Investigators:	Korea: [redacted] The Russian Federation: [redacted] Mexico: [redacted]

Principal Investigators:

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Version and Date of the Protocol: Version 4.0 dated 11 September 2017

This protocol version 4.0 is the third amendment to the initial trial protocol version 1.0, dated 15 January 2016. It is preceded by Amendment 1 (protocol version 2.0, dated 11 July 2016) and Amendment 2 (protocol version 3.0, dated 05 May 2017).

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	MenACYW conjugate vaccine
Active Substances:	Capsular polysaccharide from meningococcal serogroups A, C, Y, and W conjugated to tetanus toxoid

Title of the Trial:	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Other Pediatric Vaccines in Healthy Toddlers
Development Phase:	Phase III
Coordinating Investigators:	Korea: [redacted] The Russian Federation: [redacted] Mexico: [redacted]
Principal Investigators:	Thailand: [redacted]
Trial Centers:	This will be a multi-center, multinational trial conducted at approximately 29 sites: approximately 13 in South Korea, 2 in Thailand, 3 in Mexico, and 11 in the Russian Federation. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	4Q 2016 to 2Q 2018
Trial Design and Methodology:	This will be a Phase III, open-label (immunology laboratory technicians will be 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 vaccine [MMR] + varicella vaccine [V]), Mexico (diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type-b conjugate vaccine [DTaP-IPV-HB-Hib]), 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 will be randomized in a 2:1:1 ratio (by country) to the following groups:

	South Korea: Group 1: MenACYW conjugate vaccine + MMR + V on Day (D) 0 Group 2: MenACYW conjugate vaccine on D0 Group 3: MMR + V on D0 Mexico: 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 will be 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 have not received the 3rd dose of PCV13, aged 15 to 23 months on the day of enrollment will be 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 ***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 take place on the same day, or Visit 1 may take 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 will be randomized in a 2:1:1 ratio to the following groups: Thailand: Group 10: MenACYW conjugate vaccine + MMR + V on Day (D) 0 Group 11: MenACYW conjugate vaccine on D0 Group 12: MMR + V on D0 *All Subjects:* All subjects will 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 will be collected for 7 days after vaccination(s); unsolicited AE information will be collected from Visit 1 (D0) to Visit 2, and serious adverse event (SAE) information will be 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 should receive the remainder of the recommended toddler vaccines, which are 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 will also be tested for complete blood count (CBC) and blood chemistry. These subjects will also provide a urine sample for urinalysis. Samples will 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 will be examined by a neurologist at Visit 0 and at Visit 2. The examinations by a neurologist and additional biological analyses have been 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.
Early Safety Data Review:	This trial will not include an early review of safety data (i.e., no early safety review[s] of preliminary safety data occurring at pre-determined milestones defined in the protocol, with pause in enrollment). However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), or the governing regulatory authorities in the countries where the trial is taking place. If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs / IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the subjects' parent(s) / guardian and should assure appropriate therapy and follow-up.
Primary Objective:	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).
Primary Endpoints:	Antibody (Ab) titers against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (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 Objective:	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.
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 (pertussis toxoid [PT] and filamentous hemagglutinin [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
Observational Objectives:	***Immunogenicity*** To describe the Ab responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine measured by serum bactericidal assay using baby rabbit complement (rSBA) in all subjects in Group 1 and Group 2 and in a subset of subjects in Group 4, Group 5, Group 7, and Group 8 (100 subjects per group in Groups 1, 4, and 7; 50 subjects per group in Groups 2, 5, and 8) (South Korea, Mexico, and the Russian Federation only). ***Safety*** • To describe the safety profile of MenACYW conjugate vaccine when administered alone or concomitantly with licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) • To describe the safety profile of licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) when administered alone or concomitantly with MenACYW conjugate vaccine
Observational Endpoints:	***Immunogenicity*** Ab titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine in 100 subjects from each of Groups 1, 4, and 7, and in 50 subjects from each of Groups 2, 5, and 8. ***Safety*** • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination(s) of any unsolicited systemic AEs reported in the 30 minutes after vaccination(s) • 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(s) • 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(s) • 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 Visit 2 after vaccination(s) • Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the trial

Planned Sample Size:	A total of approximately 1200 subjects are planned to be enrolled; South Korea (approximate numbers)*: Group 1 (MenACYW conjugate vaccine + MMR + V): n=100 Group 2 (MenACYW conjugate vaccine): n=50 Group 3 (MMR + V): n=50 Mexico: Group 4 (MenACYW conjugate vaccine + DTaP-IPV-HB-Hib): n=200 Group 5 (MenACYW conjugate vaccine): n=100 Group 6 (DTaP-IPV-HB-Hib): n=100 The Russian Federation: Group 7 (MenACYW conjugate vaccine + PCV13): n=200 Group 8 (MenACYW conjugate vaccine): n=100 Group 9 (PCV13): n=100 Thailand (approximate numbers)*: Group 10 (MenACYW conjugate vaccine + MMR + V): n=100 Group 11 (MenACYW conjugate vaccine): n=50 Group 12 (MMR + V): n=50 *A total of 400 subjects are planned to be enrolled in South Korea and Thailand (in Groups 1, 2, 3, 10, 11, and 12). Approximately 200 subjects will be enrolled in South Korea and the remaining subjects will be enrolled in Thailand.
Schedule of Study Procedures:	***Vaccination*** South Korea: • Subjects in Group 1 will receive 1 dose of MenACYW conjugate vaccine, 1 dose of MMR vaccine, and 1 dose of V vaccine on D0 • Subjects in Group 2 will receive 1 dose of MenACYW conjugate vaccine on D0 • Subjects in Group 3 will receive 1 dose of MMR vaccine and 1 dose of V vaccine on D0 Mexico: • Subjects in Group 4 will receive 1 dose of MenACYW conjugate vaccine and 1 dose of DTaP-IPV-HB-Hib vaccine on D0 • Subjects in Group 5 will receive 1 dose of MenACYW conjugate vaccine on D0 • Subjects in Group 6 will receive 1 dose of DTaP-IPV-HB-Hib vaccine on D0 The Russian Federation: • Subjects in Group 7 will receive 1 dose of MenACYW conjugate vaccine and 1 dose of PCV13 vaccine on D0 (Visit 1) • Subjects in Group 8 will receive 1 dose of MenACYW conjugate vaccine on D0 (Visit 1) • Subjects in Group 9 will receive 1 dose of PCV13 vaccine on D0 (Visit 1)

Thailand:

- Subjects in Group 10 will receive 1 dose of MenACYW conjugate vaccine, 1 dose of MMR vaccine, and 1 dose of V vaccine on D0
- Subjects in Group 11 will receive 1 dose of MenACYW conjugate vaccine on D0
- Subjects in Group 12 will receive 1 dose of MMR vaccine and 1 dose of V vaccine on D0

Blood sampling

All subjects will 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† (pre-vaccination)	Day 30 (+14 days)
1	MenACYW conjugate vaccine‡ MMR+V vaccines§	MenACYW conjugate vaccine‡ MMR+V vaccines§
2	MenACYW conjugate vaccine‡	MenACYW conjugate vaccine‡
3	MMR+V vaccines§	MMR+V vaccines§
4	MenACYW conjugate vaccine‡ DTaP-IPV-HB-Hib vaccine**	MenACYW conjugate vaccine‡ DTaP-IPV-HB-Hib vaccine**,††
5	MenACYW conjugate vaccine‡	MenACYW conjugate vaccine‡
6	DTaP-IPV-HB-Hib vaccine**	DTaP-IPV-HB-Hib vaccine**,††
7	MenACYW conjugate vaccine‡ PCV13 vaccine‡‡	MenACYW conjugate vaccine‡ PCV13 vaccine‡‡
8	MenACYW conjugate vaccine‡	MenACYW conjugate vaccine‡
9	PCV13 vaccine‡‡	PCV13 vaccine‡‡
10	MenACYW conjugate vaccine‡ MMR+V vaccines§	MenACYW conjugate vaccine‡ MMR+V vaccines§
11	MenACYW conjugate vaccine‡	MenACYW conjugate vaccine‡
12	MMR+V vaccines§	MMR+V vaccines§

*Sera will be tested for antibodies elicited by the antigens contained in the respective vaccines.

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

‡Ab titers against meningococcal serogroups A, C, Y, and W measured by hSBA (in 100% of subjects) and by rSBA (in 50 subjects per group in Groups 2, 5, and 8; and in 100 subjects per group in Groups 1, 4, and 7)

§ Anti-measles, anti-mumps, anti-rubella, and anti-varicella Ab concentrations

** Anti- tetanus and anti-pertussis (pertussis toxoid [PT] and filamentous hemagglutinin [FHA]) Ab concentrations measured at Visit 1 and Day 30

††Anti-diphtheria, anti-polyribosyl-ribitol phosphate (PRP), anti-hepatitis B surface antigen Ab concentrations and anti-poliovirus types 1, 2, and 3 Ab titers measured at Day 30

‡‡ 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 will also 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 will be approximately 7 mL per blood draw). *Urine sample – for the Russian Federation only* Subjects enrolled at sites in the Russian Federation will also 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 will be 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 will be recorded as immediate unsolicited systemic AEs in the CRF. • The subject's parent / guardian will 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 will be reported throughout the duration of the trial. • In addition, the subject's parent / guardian will be asked to notify the site immediately about potential SAEs at any time during the trial. • Staff will 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 will 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) will be reported as medical history (for Visit 0 results) or as AEs (for Visit 2 results). All laboratory tests will be sampled and analyzed locally. Results of lab tests will be assessed by the Investigator. The laboratory values for CBC, blood chemistry, and urinalysis, and results of neurological examinations will only be collected in the CRF if they are clinically significant. Laboratory tests are 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
Duration of Participation in the Trial:	The duration of each subject's participation in the trial will be approximately 30 to 44 days.

Investigational Products	
Trial Product 1:	**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 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:	Intramuscular (IM)
Batch Number:	To be determined
Trial 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 is formulated to contain the following components: Measles virus: not less than 1000 tissue culture infectious doses ($TCID_{50}$) Mumps virus: not less than 12,500 $TCID_{50}$ Rubella virus: not less than 1000 $TCID_{50}$ Each 0.5 mL dose is 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 (≤ 0.3 mg), fetal bovine serum (< 1 part per million [ppm]), other buffer and media ingredients, and approximately 25 µg of neomycin. The product contains no preservative.
Route:	Subcutaneous (SC)
Batch Number:	To be determined
Trial 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 is formulated to contain a minimum of 1350 plaque-forming units (PFU) of Oka/Merck varicella virus. Each 0.5 mL dose also contains 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 contains 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, ethylenediaminetetraacetic acid (EDTA), neomycin, and fetal bovine serum. The product contains no preservative.
Route:	SC
Batch Number:	To be determined
Trial 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 is formulated to contain the following components: Diphtheria Toxoid..... ≥ 20 international units (IU) Tetanus Toxoid .....≥ 40 IU *Bordetella pertussis* antigens Pertussis Toxoid .....25 µg Filamentous Haemagglutinin.....25 µg Poliovirus (Inactivated) Type 1 (Mahoney) .....40 D antigen units Type 2 (MEF-1).....8 D antigen units Type 3 (Saukett) .....32 D antigen units Hepatitis B surface antigen.....10 µg *Haemophilus influenzae* type b polysaccharide.....12 µg (Polyribosylribitol Phosphate) conjugated to Tetanus Protein..... 22-36 µg The vaccine also contains the excipients: disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, water for injections The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin, and polymyxin B, which are used during the manufacturing process.
Route:	IM
Batch Number:	To be determined

Trial Product 5:	**Prevenar 13® (PCV13)**: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Pfizer Ireland Pharmaceuticals, Ireland) (licensed in the Russian Federation)
Form:	Suspension for IM injection
Composition:	Each 0.5 mL vaccine dose is 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 CRM_{197} carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer, and 125 µg aluminum as aluminum phosphate adjuvant.
Route:	IM
Batch Number:	To be determined
Screening Criteria:	For subjects in South Korea, Mexico, and Thailand, there are no screening criteria other than the inclusion and exclusion criteria. For the Russian Federation, as per Guideline for the conduct of clinical trials of the Russian Federation Health Authorities and in accordance with local practices, in addition to being tested for study vaccine immunogenicity assessment, the blood of subjects enrolled at sites in the Russian Federation will be tested for complete blood count (CBC) and blood chemistry. These subjects will also provide a urine sample for urinalysis. According to recommendations of Russian Health Authorities, the subjects will be examined by a neurologist. The examination by a neurologist and additional biological analyses have been implemented for subjects enrolled at sites in the Russian Federation per the request of the Russian Federation Health Authorities only and not to address any concern of the Sponsor regarding safety issues.
Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order to be eligible for trial enrollment: 1) **For South Korea**: Korean males and females aged 12 to 23 months on the day of the first study visit **For Mexico**: Males and females aged 12 to 23 months on the day of the first study visit **For the Russian Federation**: Males and females aged 12 to 14 months or 16 to 23 months on the day of the first study visit (eligible for enrollment to Group 8) or 15 to 23 months on the day of the first 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 first 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 first study visit (eligible for enrollment to Group 7 or 9) must not have received the third 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 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 (e.g., 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 first 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.*
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment: 1) Participation in the 4 weeks preceding the first trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure 2) Receipt of any vaccine in the 4 weeks (28 days) preceding the first trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after the study investigational vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. 3) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B vaccine)

	4) **For subjects enrolled at sites in the Russian Federation**: previous vaccination with the third dose of PCV13 in subjects 15 to 23 months of age (eligible for Group 7 or 9) 5) **For subjects enrolled at sites in Mexico**: known history of seizures, or uncontrolled neurologic disorder (including epilepsy); or encephalopathy of unknown etiology occurring within 7 days following previous vaccination with pertussis containing vaccine; previous vaccination with DTaP-IPV-HB-Hib or DTaP-containing vaccine at 12 to 23 months of age 6) **For subjects enrolled at sites in South Korea and Thailand**: known history of seizures, cerebral injury, or encephalopathy; previous vaccination with MMR or V at or before 12 to 23 months of age 7) Receipt of immune globulins, blood or blood-derived products in the past 3 months 8) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months) 9) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically 10) At high risk for meningococcal infection during the trial, according to the Investigator's judgment (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease) 11) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine(s) used in the trial or to a vaccine containing any of the same substances 12) Verbal report of thrombocytopenia, as reported by the parent/guardian, contraindicating intramuscular vaccination by the Investigator's judgment 13) Known bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination by the Investigator's judgment 14) Personal history of Guillain-Barré syndrome (GBS) 15) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine 16) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion 17) **For subjects enrolled at sites in South Korea, Mexico, and Thailand:** Moderate or severe acute illness/infection (according to investigator's judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

	18) **For subjects enrolled at sites in the Russian Federation:** Acute disease of any severity on the day of vaccination or febrile illness (axillary temperature ≥ 37.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided. 19) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw 20) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study
Statistical Methods:	All analyses will be descriptive. No hypotheses will be tested. All immunogenicity analyses will be performed on the Per-Protocol Analysis Set (PPAS). Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set (FAS) according to randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS). ***Immunogenicity*** Descriptive statistics will be provided for the antibody titers against meningococcal serogroups contained in MenACYW conjugate vaccine and for the antigens contained in the licensed vaccines. In general, categorical variables will be summarized and presented by frequency counts, percentages, and confidence intervals (CIs). The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For geometric mean titers (GMTs) or geometric mean concentrations (GMCs) 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed. **For the Primary Objective** The blood collection and antibody testing schedule are presented in Table S1. The immunogenicity descriptive analyses will at least include 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 reverse cumulative distribution curves (RCDCs) • Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI • Percentage of subjects with titer ≥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 is defined as: • 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.

	For the Secondary Objective
	The analyses on the concomitant vaccines will include GMTs and titer distribution or GMCs, and RCDCs, as well as % 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 (serostatus cutoff: 120 mIU/mL)
	  • anti-mumps Ab concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
	  • anti-rubella Ab concentrations (serostatus cutoff: 10 IU/mL)
	• Anti-varicella Ab concentrations before and 30 days after vaccination with V vaccine (serostatus cutoff: 1.25 glycoprotein enzyme-linked immunosorbent assay (gpELISA) 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 ≥ 0.1 and 1.0 IU/mL
	  • anti-pertussis (PT and FHA) Ab concentrations and pertussis vaccine response[†]
	• 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 ≥ 0.1 and 1.0 IU/mL
	  • anti-PRP Ab concentrations and ≥ 0.15 and 1.0 µg/mL
	  • anti-poliovirus types 1, 2, and 3 Ab titers ≥ 1:8
	  • anti-hepatitis B surface antigen Ab concentrations ≥ 10 and 100 milli-international units (mIU)/mL
	• Anti-pneumococcal Ab concentrations ≥ 0.35 µg/mL and 1.0 µg/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
	[†]Pertussis vaccine response:
	• If the pre-booster vaccination concentration is < 4 x lower limit of quantitation (LLOQ), then the post-booster vaccination concentration is ≥ 4 x the pre-booster concentration;
	• If the pre-booster vaccination concentration is ≥ 4 x LLOQ, then the post-booster vaccination concentration is ≥ 2 x the pre-booster concentration.
	For the Observational Objective
	Immunogenicity
	The immunogenicity descriptive analyses will at least include the following:
	Ab titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days after vaccination with MenACYW conjugate vaccine:
	  • GMT and 95% CI
	  • Titer distribution and RCDCs
	  • Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI

	• Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI • Percentage of subjects with rSBA vaccine seroresponse* * rSBA vaccine seroresponse is defined as a post-vaccination titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8, or a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8. ***Safety*** Safety results will be described for subjects in all study groups. The main parameters for the safety endpoints will be described by 95% CIs (based on the Clopper-Pearson method). [redacted]

Table of Study Procedures - Subjects in South Korea, Mexico, and Thailand

Phase III Trial, 2 Visits, 1 Vaccination Visit (1, 2, or 3 Vaccinations), 1 Telephone Call, 2 Blood Samples, 30 Days Duration Per Subject

Visit/Contact	Visit 1	Telephone Call	Visit 2
Trial timelines (days)	Day 0	Day 8	Day 30
Time windows (days)	--	+2 days	+14 days
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Medical history	X		
Physical examination*	X		
Review of temporary contraindications for blood sampling†			X
Randomization/allocation of subject number	X		
Blood sampling (BL), 5 mL‡	BL1		BL2
Vaccination§	X		
Immediate surveillance under supervision by a responsible healthcare professional at each study site (30 minutes)	X		
Diary card provided	X		
Telephone call**		X	
Recording of solicited injection site & systemic reactions	D0 to D07		
Recording of unsolicited AEs	D0 to Visit 2		
Reporting of SAEs	To be reported throughout the study period		
Diary card reviewed and collected			X
Collection of reportable concomitant medications	X		X
Termination of the trial			X

*Temperature needs to be measured and recorded in source documents.

†Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

‡Blood sample at Visit 1 will be drawn before administration of vaccine(s)

§Subjects in **Groups 2, 5, and 11** will receive 1 dose of MenACYW conjugate vaccine. Subjects in **Groups 1 and 10** will receive 1 dose each of MenACYW conjugate vaccine, MMR, and V. Subjects in **Groups 3 and 12** will receive 1 dose each of MMR and V. Subjects in **Group 4** will receive 1 dose each of MenACYW conjugate vaccine and DTaP-IPV-HB-Hib vaccine. Subjects in **Group 6** will receive 1 dose of DTaP-IPV-HB-Hib vaccine.

**This call is made 8 to 10 days after the vaccination at Visit 1. If D08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported, and will remind the subject's parent/guardian to continue using the diary card up to Visit 2, to bring the diary card to the study center at Visit 2, and confirm the date and time of Visit 2

Table of Study Procedures - Subjects in the Russian Federation Only

Phase III Trial, 3 Visits, 1 Vaccination Visit (1 or 2 Vaccinations), 1 Telephone Call, 2 Blood Samples, 2 Urine Samples, 30 Days Duration Per Subject

Visit/Contact	Visit 0	Visit 1*	Telephone Call	Visit 2
Trial timelines (days)	Day -5	Day 0	Day 8	Day 30
Time windows (days)	+ 5 days	--	+2 days	+14 days
Informed consent	X			
Inclusion/exclusion criteria	X	X†		
Collection of demographic data	X			
Medical history	X			
Physical examination‡	X	X†		
Neurological examination by a neurologist	X§			X
Review of temporary contraindications for blood sampling**				X
Allocation of subject number	X			
Blood sampling (BL) (complete blood count, blood chemistry, and immunogenicity) approximately 7 mL	BL1††			BL2
Urine sample, approximately 8 mL	X‡‡			X
Randomization of subject		X		
Vaccination§§		X		
Immediate surveillance under supervision by a responsible healthcare professional at each study site (30 minutes)		X		
Diary card provided		X		
Telephone call***			X	
Recording of solicited injection site & systemic reactions		D0 to D07		
Recording of unsolicited AEs		D0 to Visit 2		
Reporting of SAEs		To be reported throughout the study period		
Diary card reviewed and collected				X
Collection of reportable concomitant medications	X	X†		X
Termination of the trial				X

*Visit 0 and Visit 1 are separate visits that may take place on the same day. However, Visit 1 can be performed up to 5 days after Visit 0.

†Only performed when activities planned for Visit 1 are not conducted on the same day as Visit 0

‡Temperature needs to be measured and recorded in source documents. When Visit 0 and Visit 1 take place on different days, temperature needs to be measured and recorded at both Visits. Temperature must be measured on the day of vaccination, before administration of vaccine(s).

§ The results (discharge summary) of the neurologist's examination, performed for the subject in terms of routine practice, can be used, if the examination was done within 7 days before Visit 0.

**Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

††The results of CBC and biochemistry laboratory tests, performed for the subject in terms of routine practice, can be used, if the tests were done within 7 days before Visit 0. In this case, the blood sample volume collected at Visit 0 will be 5 mL.

‡‡The results of urine laboratory tests, performed for the subject in terms of routine practice, can be used, if the tests were done within 7 days before Visit 0. In this case, no urine sample will be collected at Visit 0.

§§Subjects in **Group 8** will receive 1 dose of MenACYW conjugate vaccine. Subjects in **Group 7** will receive 1 dose each of MenACYW conjugate vaccine and PCV13 vaccine. Subjects in **Group 9** will receive 1 dose of PCV13 vaccine.

***This call is made 8 to 10 days after the vaccination at Visit 1. If D08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported, and will remind the subject's parent to continue using the diary card up to Visit 2, to bring the diary card to the study center at Visit 2, and confirm the date and time of Visit 2.

List of Abbreviations

µg	microgram(s)
µL	microliter(s)
Ab	antibody
AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BL	blood sampling
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDM	Clinical Data Management
CFU	colony-forming unit
CI	confidence interval
C&MQO	Clinical and Medical Quality Operations
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios (English: Federal Commission for Protection against Sanitary Risks) (Mexican Health Authority)
CPM	counts per minute
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRF	electronic case report form
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	Day
DNA	deoxyribonucleic acid
DOD	delta optical density
DT	diphtheria toxoid
ECL	electrochemiluminescent
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
eSAE	electronic Serious Adverse Event (Form)
EU	ELISA units
FAS	Full Analysis Set
FDA	Food and Drug Administration

FHA	filamentous hemagglutinin
FIM2,3	fimbriae types 2 and 3
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
gp	glycoprotein
gpELISA	glycoprotein enzyme-linked immunosorbent assay
GPV	Global PharmacoVigilance
HBsAg	hepatitis B surface antigen
HepB	hepatitis B
HRP	horseradish peroxidase
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular
IMD	invasive meningococcal disease
IOM	Institute of Medicine
IRB	Institutional Review Board
IU	international unit(s)
IWRS	interactive web response system
LCLS	last contact, last subject
LDH	lactate dehydrogenase
LLT	lowest level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MSD	MesoScale Discovery
MFDS	Korean Ministry of Food and Drug Safety
MIT	Micrometabolic Inhibition Test
mg	milligram(s)
mIU	milli-international units
mL	milliliter(s)

MRC-5	Medical Research Council cell strain 5
NIP	National Immunization Program
NSAID	non-steroidal anti-inflammatory drug
OD	optical density
PFU	plaque-forming units
PnPS	pneumococcal capsular polysaccharide
PPAS	Per-Protocol Analysis Set
ppm	parts per million
PRN	pertactin
PRP	polyribosyl-ribitol phosphate
PS	polysaccharide(s)
PSO	Product Safety Officer
PT	pertussis toxoid
RCDC	reverse cumulative distribution curve
rDNA	recombinant deoxyribonucleic acid
RIA	radioimmunoassay
RLU	relative light units
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	statistical analysis plan
SC	subcutaneous
SMT	safety management team
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TCC	tissue culture control
TCID	tissue culture infectious doses
TMF	trial master file
TT	tetanus toxoid
UAR	unexpected adverse reaction
ULOQ	upper limit of quantitation
WHO	World Health Organization
WT	wild-type

1 Introduction

1.1 Background

This trial will evaluate the immunogenicity and safety of a single dose of the quadrivalent Meningococcal Polysaccharide (Serogroups A, C, Y and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in toddlers 12 to 23 months of age. The purpose of MET57 is to demonstrate that the immunogenicity and safety profiles of the MenACYW conjugate vaccine are comparable to when MenACYW conjugate vaccine is given concomitantly with licensed pediatric vaccine(s).

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria meningitidis (N. meningitidis)*, a Gram-negative diplococcus found exclusively in humans. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). At least 12 distinct meningococcal serogroups have been classified based on the immunochemistry of the capsular polysaccharides (PS). Some strains are more likely than others to cause infection (1) (2) (3). Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, X, Y, and W (2) (3) (4). Serogroup B is responsible for endemic disease and some outbreaks, while serogroup C is responsible for large outbreaks (5). Serogroup A is the main cause of epidemics in the world, and is especially dominant in Africa and Asia. Serogroup W has been seen in Africa, as well as in the United Kingdom in residents who participated in the Hajj pilgrimage to the Kingdom of Saudi Arabia (4) (6) (7) and more recently in Chile (8), Turkey (9) (10), China (11) (12), Argentina (13), and Brazil (14) (15) and in other parts of the world. Serogroup X causes substantial meningococcal disease in parts of Africa but rarely causes disease in other parts of the world (2) (16). Serogroup Y has not been associated with outbreaks, but its frequency as a cause of sporadic cases has gradually increased in the US and more recently in Canada and Europe (17) (18) (19). This serogroup is commonly associated with meningococcal pneumonia, particularly in older adults > 65 years of age (20). Outbreaks of serogroup B meningococcal disease have also been reported on college campuses in the US during the last five-year period: a prolonged outbreak of serogroup B on a university campus in Ohio from 2008-2010 and 2 universities in New Jersey and California in 2013 (21) (22).

The epidemiology of *N. meningitidis* can be described as complex, unpredictable, geographically variable, and changing over time. Meningococcal disease occurs worldwide in both endemic and epidemic forms with seasonal variation. In Europe, the incidence rate of IMD has remained stable over the last 5 to 10 years, with the highest peak occurring in the population less than 4 years of age and a smaller peak in the 15 to 19 year old group. The highest incidence rate in Europe is caused by serogroup B, followed by C (23). The highest proportion of meningococcal cases was due to serogroup B in the population under 5 years of age. The highest proportion of serogroup C cases was observed in the population 25 to 44 years of age while the proportion of serogroup Y cases was highest in the population aged 65 years and above.

Surveillance data from England and Wales showed an increase in endemic meningococcal serogroup W disease across all age groups, accounting for 15% of all IMD cases in 2013-2014 compared with an average of 1% to 2% of all IMD cases in earlier years (24). A gradual increase in serogroup Y IMD has also been recently reported in Sweden during 2005-2012 (25) (26).

Nearly 50% of all IMD was caused by serogroup Y in 2012 (25). Similarly, an increase in the proportion of IMD caused by serogroup Y has been observed in other Scandinavian countries, accounting for 31% in Norway in 2009-2010 and 38% in Finland in 2010 (27).

The recent spread of the serogroups W, which started in Saudi Arabia in 2000, has caused large meningococcal disease epidemics in the African meningitis belt and endemic disease in South America, Europe and China (28). The serogroup W associated disease has also been reported from Singapore (29), China (30), Taiwan (31), Malaysia (32), India (33), and Japan (34). Similar cases of serogroup W linked IMD have also been reported from Brazil, Chile, and Argentina (35) (36).

A sudden increase in the number of serogroup Y associated IMD cases, some associated with country specific outbreaks, have been reported from various countries across Europe more notably Switzerland, Sweden, Norway, and Finland (37).

Even though traditionally the vaccination against meningococcal disease has been limited to vaccination against either serogroups A or C, the recent evolution of the global epidemiology does merit vaccination against serogroups Y and W thus building a case for a quadrivalent (A, C, Y, and W) conjugated meningococcal vaccine.

The goal for MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, Y, and W in all age groups: children as young as 6 weeks of age, adolescents, and adults including those 56 years of age and older.

1.2 Background of the Investigational Product

1.2.1 Non-clinical Safety

[redacted]

1.2.2 Clinical

The MenACYW conjugate vaccine formulation was finalized based on data provided by 2 studies: MET28, a Phase I study in infants, toddlers, and adults 18 to 55 years of age; and MET32, a Phase I/II study in toddlers.

The formulation has been evaluated in over 1639 subjects (infants, toddlers, adolescents, and adults > 55 years of age) in MET39, MET44, MET50, and MET54. MenACYW conjugate vaccine has also been evaluated in a Phase III study (MET56 in adolescents and adults). The relevant Phase II studies are discussed below.

The MenACYW conjugate vaccine was found to be well tolerated and no unanticipated or new significant safety concerns have been identified in the clinical trials completed to date.

1.2.2.1 Study MET32 (Phase I/II)

MET32 was a Phase I/II, exploratory, randomized, observer-blinded, active-controlled, parallel, multi-center study in toddlers conducted in Australia. This study evaluated 5 formulations of MenACYW conjugate vaccine. Subjects in Group 1 through Group 3 received 1 dose of MenACYW conjugate vaccine formulation 1 (low-, intermediate-, and high-dose polysaccharides, respectively); subjects in Group 4 and Group 6 received 1 dose of MenACYW conjugate vaccine formulation 2 (low- and high-dose polysaccharides, respectively). Group 7 received 1 dose of NeisVac-C®.

Immunogenicity

The 5 formulations evaluated were all immunogenic in toddlers. The percentage of subjects achieving a serum bactericidal assay using human complement (hSBA) threshold titer of ≥ 1:8 ranged from 75% to 100%, 84% to 96%, 66% to 91%, and 62% to 70% for serogroups A, C, Y, and W, respectively. There was a trend toward higher antibody responses in the high dose groups.

Safety

All formulations of MenACYW conjugate vaccine were well tolerated. There were no significant differences in the overall safety profiles of any of the treatment groups. The safety profile of a single administration of MenACYW conjugate vaccine at different doses was comparable to that of a single administration of the licensed comparator vaccine (NeisVac-C®).

No deaths occurred in the study. Of 7 SAEs that occurred, [redacted]. There were no AEs or SAEs that led to study discontinuation.

1.2.2.2 Study MET39 (Phase II)

MET39 was a Phase II, randomized, open-label, multi-center study conducted in the US for which 580 healthy subjects from 2 to 15 months of age were enrolled. This study evaluated the optimal vaccination schedule in the infant/toddler population. Subjects in Group 1 through Group 4 received 1, 2, or 3 primary doses plus an additional dose of the MenACYW conjugate vaccine in the second year of life, concomitantly with routine pediatric vaccines at several different vaccination schedules. Subjects in Group 5 received 1 dose of the MenACYW conjugate vaccine concomitantly with routine pediatric vaccines. The routine pediatric vaccines given concomitantly with MenACYW conjugate vaccine at various schedules included Prevnar® or Prevnar 13®, Pentacel®, ROTARIX® or RotaTeq®, hepatitis B vaccine, M-M-R®II, and VARIVAX®.

Immunogenicity

After the primary series consisting of 1, 2, or 3 doses of MenACYW conjugate vaccine, protective serum hSBA threshold titers of ≥ 1:8 were attained by > 88% of subjects for serogroup C and by 62% to 74% for serogroup A. For serogroups Y and W, ≥ 90% achieved the threshold titer after

3 doses, 75% to 84% after 2 doses, but only 25% after a single dose administered at 6 months of age.

After an additional dose of MenACYW conjugate vaccine in the second year of life (12 or 15 months), between 91% and 100% of the subjects achieved the protective threshold regardless of the number of doses they received in the first year of life.

Safety

MenACYW conjugate vaccine was well tolerated in infants and toddlers regardless of the immunization schedule and the number of doses administered. Safety results were comparable to those seen in control group subjects regardless of the immunization schedule and the number of doses administered. The safety profile of the licensed vaccines given concomitantly with MenACYW conjugate vaccine was similar to that of the licensed vaccines given concomitantly without MenACYW conjugate vaccine.

No deaths occurred within 30 days. There were 2 subjects in Group 4 who died during the study, 1 as a result of hypoxic ischemic encephalopathy which started 96 days after the 6-month vaccination and 1 as a result of non-accidental head trauma 36 days after the 12-month vaccination. These events were considered by the Investigator as unrelated to study vaccine. There were 2 other subjects who discontinued the study due to a serious adverse event (SAE) and the receipt of intravenous immunoglobulin treatment: 1 subject in Group 2 with Kawasaki disease, 106 days after the 6-month vaccination; and 1 subject in Group 3 with middle lobe pneumonia and Kawasaki disease, 50 and 52 days, respectively, after the 4-month vaccinations. One other subject in Group 4 was discontinued due to a non-serious adverse event (AE) (viral rash 1 day after the 6-month vaccinations). None of these AEs leading to discontinuation were considered by the Investigator as related to the vaccine. There were no related SAEs during this study.

1.2.2.3 Study MET44 (Phase II)

MET44 was a Phase II, randomized, open-label (the laboratory technicians were blinded to group assignment), multi-center study conducted in the US. This study evaluated the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine when administered to adults 56 years of age and older. A total of 301 subjects aged 56 years and older on the day of enrollment were randomized to receive a single dose of MenACYW conjugate vaccine or Menomune® - A/C/Y/W-135 vaccine; each group was stratified according to age into 2 subsets (subjects 56 to 64 years of age and subjects ≥ 65 years of age).

Immunogenicity

The proportions of subjects with hSBA titers ≥ 1:8 obtained after MenACYW conjugate vaccine administration (Group 1) for serogroups A and C were comparable to, or for serogroups Y and W higher than, those obtained after Menomune - A/C/Y/W-135 vaccine administration (Group 2): 93.8% in Group 1 and 85.1% in Group 2 for serogroup A; 74.9% in Group 1 and 62.8% in Group 2 for serogroup C; 80.5% in Group 1 and 59.6% in Group 2 for serogroup Y; 79.5% in Group 1 and 60.6% in Group 2 for serogroup W.

Safety

Vaccination with MenACYW conjugate vaccine or Menomune - A/C/Y/W-135 vaccine among adults 56 years of age and older was found to be well tolerated, with no safety concerns identified. There were no immediate unsolicited AEs/reactions reported in either group. There were no deaths, SAEs or AEs that led to study discontinuation reported during the study.

1.2.2.4 Study MET54 (Phase II)

MET54 was a Phase II, randomized, open-label, active-controlled, multi-center study conducted in Europe (Finland) in 2015. This study evaluated the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine when given alone in healthy, meningococcal vaccine-naïve toddlers compared to that of the licensed vaccine Nimenrix®. A total of 188 meningococcal vaccine-naïve subjects aged 12 to 23 months on the day of enrollment were randomized to 1 of 2 groups. Group 1 received a single dose of MenACYW conjugate vaccine and Group 2 received a single dose of Nimenrix®.

Immunogenicity

Antibody responses to the antigens (serogroups A, C, Y, and W) were evaluated by rSBA and hSBA. MenACYW conjugate vaccine immune responses evaluated by rSBA and hSBA were generally comparable to Nimenrix® immune responses with some variation by serogroup:

rSBA

Most subjects had rSBA titers ≥ 1:128 at D30. The percentages after MenACYW conjugate vaccine were similar (100.0% [91/91] for serogroups A, Y, and W) or numerically higher (100.0% [91/91] for serogroup C) compared to Nimenrix® (100.0% [86/86] for serogroups A, Y, and W and 94.2% [81/86] for serogroup C). At D30, most subjects in both groups demonstrated an rSBA vaccine seroresponse as defined in the SAP and as defined in the protocol. The percentage of subjects with any rSBA vaccine seroresponse by either definition for serogroup A was numerically lower after MenACYW conjugate vaccine (91.2% [83/91]) than Nimenrix® (98.8% [85/86]) and the percentages of subjects with any rSBA vaccine seroresponse by either definition were similar or comparable between the 2 groups for serogroups C, Y, and W (all > 96%).

hSBA

Most subjects in both groups had hSBA titers ≥ 1:8 at D30: the percentages after MenACYW conjugate vaccine for serogroups A, Y, and W (ranging from 97.8% [89/91] to 98.9% [90/91]) were comparable to those after Nimenrix® (ranging from 91.9% [79/86] to 100.0% [86/86]). The percentage of subjects with hSBA titers ≥ 1:8 for serogroup C was higher after MenACYW conjugate vaccine (100.0% [91/91]) than after Nimenrix® (89.5% [77/86]). At D30, most subjects in both groups demonstrated an hSBA vaccine seroresponse. The percentage of subjects with an hSBA vaccine seroresponse for serogroups A, Y, and W was comparable in both groups (ranging from 96.7% [87/90] to 98.9% [90/91] after MenACYW conjugate vaccine and from 91.9% [79/86] to 98.8% [85/86] after Nimenrix®). The percentage of subjects with an hSBA vaccine seroresponse for serogroup C was higher after MenACYW conjugate vaccine (100.0% [91/91]) than after Nimenrix® (86.0% [74/86]).

Safety

Overall, vaccination with MenACYW conjugate vaccine among toddlers aged 12 to 23 months was found to be safe with no safety concerns identified. The MenACYW conjugate vaccine was well tolerated with no immediate AEs or ARs, no discontinuations due to an SAE or other AE, and no related SAEs.

The safety profile of MenACYW conjugate vaccine was comparable to that of the licensed vaccine, Nimenrix®.

No new clinically important findings were identified with administration of the MenACYW conjugate vaccine.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

MenACYW conjugate vaccine is an investigational vaccine that is undergoing active clinical investigation. There may be no direct benefit from receiving it. However, based on the data from previous studies, evaluation of the immunogenicity profile of MenACYW conjugate vaccine in different age groups shows that the majority of subjects develop seroprotective levels of antibodies after vaccination. The safety evaluation indicates that the vaccine is well-tolerated, and no safety issues have been detected to date. In all, the data support the further evaluation of MenACYW conjugate vaccine in humans.

Subjects who receive the measles-mumps-rubella vaccine (MMR) and the varicella vaccine (V) will likely be protected against measles, mumps, rubella, and varicella. Subjects who receive the pneumococcal conjugate vaccine (PCV13) will likely be protected against infection with 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) of *Streptococcus pneumoniae* bacteria. Subjects who receive the hexavalent vaccine (DTaP-IPV-HB-Hib) will likely be protected against diphtheria, tetanus, pertussis, polio, hepatitis B, and invasive disease caused by *Haemophilus influenzae* type b bacteria.

As with any vaccine, MenACYW conjugate vaccine and the licensed pediatric vaccines included in this study may not protect 100% of individuals against the disease they are designed to prevent.

Following completion of the trial, subjects who received only licensed pediatric vaccine(s) (in Groups 3, 6, 9, and 12) will be offered vaccination with a licensed quadrivalent conjugated meningococcal vaccine available in each country to provide protection against meningococcal infection as a benefit for participation in this trial. This vaccine is offered outside of the scope of the protocol, free of charge.

In Mexico for the subjects in Group 5 (MenACYW conjugate vaccine), as a benefit for participation in this trial and to ensure a benefit equal to that of the other trial subjects, DTaP-IPV-HB-Hib vaccine will be offered after completion of the trial in case the vaccine is not yet launched in the country. This vaccine is offered outside of the scope of the protocol, free of charge.

In Thailand, for subjects in Group 11 (MenACYW conjugate vaccine), as a benefit for participation in this trial and to ensure a benefit equal to that of the other trial subjects, MMR and

Varicella vaccines will be offered after completion of the trial. These vaccines will be offered outside of the scope of the protocol, free of charge.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine and the licensed pediatric vaccines included in this study may cause injection site reactions such as pain, swelling, and erythema, or certain systemic events such as fever, irritability, drowsiness, loss of appetite, abnormal crying, and vomiting. Some of the other common reactions following the licensed pediatric vaccines also include (but are not limited to) injection site rash, pruritus, and induration, and systemic events of decreased sleep and diarrhea. There may be a rare possibility of an allergic reaction, which could be severe, and febrile convulsion in toddlers who experience high fever. Extensive limb swelling and hypotonic-hyporesponsive episodes have been rarely reported following administration of DTaP-IPV-HB-Hib vaccine. There may be other risks for MenACYW conjugate vaccine that are not yet known.

[redacted] Importantly, no similar cases have been reported following the administration of MenACYW conjugate vaccine in any other trials.

Guillain-Barré syndrome (GBS) has been reported mostly in persons aged 11 to 19 years who had symptom onset within 6 weeks of administration of a US licensed meningococcal conjugate vaccine (38). A retrospective cohort study carried out in the US using healthcare claims data found no evidence of increased GBS risk associated with the use of that vaccine. The study was able to exclude all but relatively small incremental risks (39).

A review by the Institute of Medicine (IOM) found inadequate evidence to accept or reject a causal relationship between tetanus toxoid-containing vaccines and GBS (40). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (41). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (42).

No occurrences of GBS, brachial neuritis, or Arthus reaction have been reported with the use of MenACYW conjugate vaccine in the completed clinical trials.

The potential risks associated with blood drawing include local pain, bruising and, rarely, fainting or infection.

The potential risks listed here are not exhaustive. Refer to the package inserts / summaries of product characteristics (SPCs) of the marketed vaccines (43) (44) (45) (46) and the Investigator's Brochure of the investigational vaccine for additional information regarding potential risks.

1.4 Rationale for the Trial

The MenACYW conjugate vaccine is designed for the immunization of individuals of all ages (infants 6 weeks of age and older through and including older adults > 65 years of age) against IMD. The purpose of the vaccine is to provide broad coverage against circulating meningococcal strains from serogroups A, C, Y, and W. The MenACYW conjugate vaccine is prepared using tetanus toxoid as the carrier protein. Conjugation of PS antigens to a protein carrier can induce T-cell-dependent immune responses, which are anticipated to give rise to higher antibody (Ab) titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of PS-specific total immunoglobulin G (IgG) and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials including those with the final formulation (MET39 and MET44) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above trials using the final formulation or in the earlier trials.

The purpose of MET57 is to demonstrate that the immunogenicity and safety profiles of a single MenACYW conjugate vaccine in toddlers 12 to 23 months old are comparable to when MenACYW conjugate vaccine is given concomitantly with licensed pediatric vaccine(s), and that the immunogenicity and safety of vaccines routinely administered to toddlers are not affected by concomitant administration with the MenACYW conjugate vaccine.

2 Trial Objectives

2.1 Primary Objective

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).

The endpoints for the primary objective are presented in Section 9.1.1.1.

2.2 Secondary Objective

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.

The endpoints for the secondary objective are presented in Section 9.2.1.1.

2.3 Observational Objectives

Immunogenicity

To describe the Ab responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugated vaccine measured by serum bactericidal assay using baby rabbit complement (rSBA) in all subjects in Group 1 and Group 2 and in a subset of subjects in Group 4, Group 5, Group 7, and Group 8 (100 subjects per group in Groups 1, 4, and 7; 50 subjects per group in Groups 2, 5, and 8) (South Korea, Mexico, and the Russian Federation only).

Safety

- To describe the safety profile of MenACYW conjugate vaccine when administered alone or concomitantly with licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13)
- To describe the safety profile of licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) when administered alone or concomitantly with MenACYW conjugate vaccine

The endpoints for the observational objectives are presented in Section 9.3.1.1 and Section 9.3.2.2, for immunogenicity and safety, respectively.

3 Investigators and Trial Organization

This trial will be conducted in approximately 29 centers in South Korea, Mexico, the Russian Federation, and Thailand. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by one Coordinating Investigator in each country, with the exception of sites in Thailand. Details of the trial centers and the Investigators at each center are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal safety management team (SMT) will perform a blinded safety analysis on safety data after vaccination(s).

The Sponsor's Responsible Medical Officer (RMO) (the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted] Clinical Team Leader (CTL).

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form(s) (ICF), subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and / or the Sponsor are responsible for obtaining this approval and / or favorable opinion before the start of the trial. If the protocol is subsequently amended, approval must be re-obtained for each

substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator to the Sponsor together with the composition of the IEC / IRB (the names and qualifications of the members attending and voting at the meetings).

The Investigator or Sponsor will submit written summaries of the status of the trial to the IEC / IRB annually, or more frequently if requested.

All SAEs occurring during the trial that are related to vaccination will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy and to local regulatory requirements.

In South Korea: All SAEs that occur during the study whether related to vaccination or not must be reported to the Health Authority and to the IRB, according to local regulatory requirements.

In Mexico: All SAEs that occur in subjects enrolled at Mexican sites, whether related to vaccination or not, must be reported to the IEC and Ministry of Health of Mexico.

In the Russian Federation: The Sponsor will inform the National Ethics Board and relevant Health Authorities of any reportable SAEs (suspected unexpected serious adverse reaction [SUSAR] cases only) according to local regulatory requirements.

In Thailand: All SAEs that occur during the study whether related to vaccination or not must be reported to the IRB. Any reportable SAEs (suspected unexpected serious adverse reaction) will be reported to Health Authority, according to local regulatory requirements.

5 Investigational Plan

5.1 Description of the Overall Trial Design and Plan

5.1.1 Trial Design

This is a Phase III, open-label (immunology laboratory technicians will be 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 compared to when administered concomitantly with other pediatric vaccine(s) in healthy toddlers in South Korea and Thailand (measles-mumps-rubella vaccine [MMR] + varicella vaccine [V]), Mexico (diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type-b conjugate vaccine [DTaP-IPV-HB-Hib]), 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 will be randomized in a 2:1:1 ratio (by country) to the following groups:

South Korea:

Group 1: MenACYW conjugate vaccine + MMR + V on Day (D) 0
Group 2: MenACYW conjugate vaccine on D0
Group 3: MMR + V on D0

Mexico:

Group 4: MenACYW conjugate vaccine + DTaP-IPV-HB-Hib vaccine 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 will be 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 have not received the 3rd dose of PCV13, aged 15 to 23 months on the day of enrollment will be 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

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 take place on the same day, or Visit 1 may take 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 will be 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 will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at Visit 2 (30 to 44 days after vaccination[s]). Solicited AE information will be collected for 7 days after vaccination(s); unsolicited AE information will be collected from Visit 1(D0) to Visit 2, and SAE information will be 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 should receive the remainder of the recommended toddler vaccines, which are 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 sites in 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 being tested for study vaccine immunogenicity assessment, the blood of subjects enrolled at sites in the Russian Federation will be tested for complete blood count (CBC) and blood chemistry. These subjects will also provide a urine sample for urinalysis. Samples will 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 will be examined by a neurologist at Visit 0 and at Visit 2.

The examinations by a neurologist and additional biological analyses have been implemented for subjects enrolled at sites in the Russian Federation per the request of the Russian Federation Health Authorities only and not to address any concern of the Sponsor regarding biological safety issues.

5.1.2 Justification of the Trial Design

The purpose of MET57 is to demonstrate that the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine in toddlers 12 to 23 months old are comparable to when MenACYW conjugate vaccine is given concomitantly with licensed pediatric vaccine(s).

The concomitant administration of standard of care pediatric vaccines together with 5 different administration schedules of the MenACYW conjugate vaccine has been assessed in infants/toddlers 2 to 15 months of age in the US in the MET39 study. The subjects received during, or prior to the study, a number of licensed recommended vaccines at 2, 4, and 6 months of age: Pentacel®, either Prevnar® or Prevnar 13®, RotaTeq® or ROTARIX®, and ENGERIX-B® or RECOMBIVAX HB®. All subjects received M-M-R® II and VARIVAX® at 12 months. A total of 457 subjects completed the study. Samples from the subjects were assessed for both meningococcal antibodies (using both rSBA and hSBA) and antibodies elicited in response to selected licensed infant and toddler vaccines administered concomitantly. The immunogenicity profiles of selected licensed pediatric vaccines (Pentacel®, Prevnar® or Prevnar 13®, M-M-R® II, and VARIVAX®) were assessed when administered either concomitantly with or without MenACYW conjugate vaccine. There was no evidence of interference with the pediatric routine vaccines administered concomitantly with MenACYW conjugate vaccine.

Four countries (i.e., Mexico, the Russian Federation, South Korea, and Thailand) have been selected for the conduct of the MET57 study. The concomitant pediatric vaccines selected to be administered together with MenACYW conjugate vaccine in each country were determined taking into consideration their respective pediatric vaccination schedule: DTaP-IPV-HB-Hib for Mexico, pneumococcal conjugate vaccine (PCV13) for the Russian Federation, and measles-mumps-rubella vaccine (MMR) + varicella vaccine (V) for South Korea and Thailand. These countries and the concomitant vaccines to be administered have been strategically selected based on vaccine

availability and market and licensure strategy, and/or to fulfill Health Authority licensing and World Health Organization (WHO) pre-qualification requirements.

Since the primary and secondary objectives of this study have serological endpoints, study groups receive either 1, 2, or 3 vaccines, and the vaccines of the study groups have different appearance and administration methods, the study has an open-label design; the protocol, however, provides for the laboratory technicians responsible for running the serological testing to remain blinded to the subjects' group allocations throughout the entire study up to the database lock to avoid any bias.

5.1.3 Trial Plan

Vaccination

South Korea (planned number of subjects is approximate)

- Subjects in Group 1 will receive 1 dose of MenACYW conjugate vaccine, 1 dose of MMR vaccine and 1 dose of V vaccine on D0 (n=100)
- Subjects in Group 2 will receive 1 dose of MenACYW conjugate vaccine on D0 (n=50)
- Subjects in Group 3 will receive 1 dose of MMR vaccine and 1 dose of V vaccine on D0 (n=50)

Mexico

- Subjects in Group 4 will receive 1 dose of MenACYW conjugate vaccine and 1 dose of DTaP-IPV-HB-Hib vaccine on D0 (n=200)
- Subjects in Group 5 will receive 1 dose of MenACYW conjugate vaccine on D0 (n=100)
- Subjects in Group 6 will receive 1 dose of DTaP-IPV-HB-Hib vaccine on D0 (n=100)

The Russian Federation

- Subjects in Group 7 will receive 1 dose of MenACYW conjugate vaccine and 1 dose of PCV13 vaccine on D0 (n=200)
- Subjects in Group 8 will receive 1 dose of MenACYW conjugate vaccine on D0 (n=100)
- Subjects in Group 9 will receive 1 dose of PCV13 vaccine on D0 (n=100)

Thailand (planned number of subjects is approximate)

- Subjects in Group 10 will receive 1 dose of MenACYW conjugate vaccine, 1 dose of MMR vaccine and 1 dose of V vaccine on D0 (n=100)
- Subjects in Group 11 will receive 1 dose of MenACYW conjugate vaccine on D0 (n=50)
- Subjects in Group 12 will receive 1 dose of MMR vaccine and 1 dose of V vaccine on D0 (n=50)

Note: A total of 400 subjects are planned to be enrolled in South Korea and Thailand (in Groups 1, 2, 3, 10, 11, and 12). Approximately 200 subjects will be enrolled in South Korea and the remaining subjects will be enrolled in Thailand.

Blood Sampling

All subjects will provide a pre-vaccination blood sample at Visit 0 (screening visit in the Russian Federation only) or 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 5.1 presents the antibodies that will be measured (in the respective assays) for each group.

Table 5.1: Schedules of blood sampling and antigen testing

Group	Blood Sampling / Antigen Testing*	
	Visit 0 / Visit 1† (pre-vaccination)	Day 30 (+14 days)
1	MenACYW conjugate vaccine‡ MMR+V vaccines§	MenACYW conjugate vaccine‡ MMR+V vaccines§
2	MenACYW conjugate vaccine‡	MenACYW conjugate vaccine‡
3	MMR+V vaccines§	MMR+V vaccines§
4	MenACYW conjugate vaccine‡ DTaP-IPV-HB-Hib vaccine**	MenACYW conjugate vaccine‡ DTaP-IPV-HB-Hib vaccine**,††
5	MenACYW conjugate vaccine‡	MenACYW conjugate vaccine‡
6	DTaP-IPV-HB-Hib vaccine**	DTaP-IPV-HB-Hib vaccine**,††
7	MenACYW conjugate vaccine‡ PCV13 vaccine‡‡	MenACYW conjugate vaccine‡ PCV13 vaccine‡‡
8	MenACYW conjugate vaccine‡	MenACYW conjugate vaccine‡
9	PCV13 vaccine‡‡	PCV13 vaccine‡‡
10	MenACYW conjugate vaccine‡ MMR+V vaccines§	MenACYW conjugate vaccine‡ MMR+V vaccines§
11	MenACYW conjugate vaccine‡	MenACYW conjugate vaccine‡
12	MMR+V vaccines§	MMR+V vaccines§

*Sera will be tested for antibodies elicited by the antigens contained in the respective vaccines.

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

‡Ab titers against meningococcal serogroups A, C, Y, and W measured by hSBA (in 100% of subjects) and by rSBA (in 50 subjects per group in Groups 2, 5, and 8; and in 100 subjects per group in Groups 1, 4, and 7).

§Anti-measles, anti-mumps, anti-rubella, and anti-varicella Ab concentrations

**Anti-tetanus and anti-pertussis (pertussis toxoid [PT] and filamentous hemagglutinin [FHA] Ab concentrations measured at Visit 1 and Day 30

††Anti-diphtheria, anti-polyribosyl-ribitol phosphate (PRP), anti-hepatitis B surface antigen Ab concentrations, and anti-poliovirus types 1, 2, and 3 Ab titers measured at Day 30

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

For sites in the Russian Federation only:

Subjects enrolled at sites in the Russian Federation will also provide approximately 2 mL of additional blood sample, (depending on local laboratory needs) for CBC and blood chemistry testing Visit 0 (screening visit) and at Visit 2 (30 days [+14 days] after D0) per Health Authority

request and in accordance with local regulations (total blood volume collected will be approximately 7 mL per blood draw).

Laboratory tests done as part to the CBC and blood chemistry are presented in Section 9.3.3.1, and Section 9.3.3.2, respectively.

Urine Sampling (for Sites in the Russian Federation Only)

Subjects enrolled at sites in the Russian Federation will also provide an approximately 8-mL urine sample (depending on local laboratory needs) for urinalysis before vaccination on Visit 0 and at Visit 2 (30 days [+14 days] after D0) per Health Authority request and in accordance with local regulations.

Laboratory tests done as part of the Urinalysis are presented in Section 9.3.3.3.

Collection of Safety Data (All Countries)

- All subjects will be 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 will be recorded as immediate unsolicited systemic AEs in the electronic case report form (CRF).
- The subject's parent / guardian will 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 will be reported throughout the duration of the trial.
- In addition, the subject's parent / guardian will be asked to notify the site immediately about potential SAEs at any time during the trial.
- Staff will 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 will 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) will be reported as medical history (for Visit 0 results) or as AEs (for Visit 2 results). All laboratory tests will be sampled and analyzed locally. Results of lab tests will be assessed by the Investigator. The laboratory values for CBC, blood chemistry, and urinalysis and results of neurological examinations will only be collected in the CRF if they are clinically significant. Laboratory tests are 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

5.1.4 Visit Procedures

Visit 0: Inclusion, Allocation of Subject's number, Blood Sample ***(For the Russian Federation only)***

1) Give the subject's parent(s) information about the trial, answer any questions, obtain written informed consent in duplicate (in 2 originals) and give him / her 1 signed original as per local regulations and practice.
2) Check inclusion and exclusion criteria for eligibility.
3) Collect demographic data.
4) Obtain medical history about the subject.
5) Perform a physical examination, including but not limited to examination of the head (including ear, nose, and throat), neck, thorax (including heart and lungs), abdomen, and extremities. If a routine examination, including examination by a neurologist, CBC, biochemistry, and urinalysis laboratory tests, had been performed within the last 7 days before Visit 0 by the Investigator, a sub-Investigator, or a licensed practitioner; it does not need to be repeated unless the Investigator considers it is necessary to repeat.
6) Perform a neurological examination by a neurologist[a]
7) Take the subject's temperature by the axillary route.
8) Connect to the Interactive Web Response System (IWRS) for allocation of subject identification number
9) Obtain the first 7-mL blood sample[b] (see Section 7 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (after reasonable attempts as per local regulations / practice), then Visit 0 can be rescheduled to a later date at which point inclusion/exclusion criteria must be re-validated. If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.
10) Obtain a urine sample (approximately 8 mL)[c]
11) Collect reportable concomitant medications information
12) Complete relevant source documentation and CRF pages for the visit
13) Confirm subject's eligibility based on the results of the baseline testing of CBC, blood chemistry, and urinalysis, and neurological examination.

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[a] The results (discharge summary) of the neurologist's examination, performed for the subject in terms of routine practice, can be used, if the examination was done within 7 days before Visit 0.

[b] The results of CBC and biochemistry laboratory tests, performed for the subject in terms of routine practice, can be used, if the tests were done within 7 days before Visit 0. In this case, the blood sample volume collected at Visit 0 will be 5 mL.

[c] The results of urine laboratory tests, performed for the subject in terms of routine practice, can be used if the tests were done within 7 days before Visit 0. In this case, no urine sample will be collected at Visit 0.

Note: If Visit 1 (the vaccination visit) is performed on the same day as Visit 0, only the procedures from step number 4 onwards in the Study Procedures listed under Visit 1 below are to be followed.

Visit 1 (D0): Randomization and Vaccination ***(For the Russian Federation only)***

Steps 1 through 3 only for subjects with Visit 0 and Visit 1 not on the same day:

1) Check inclusion and exclusion criteria for eligibility
2) Perform a physical examination
3) Take the subject's temperature by the axillary route.

Steps 4 through 10 for all subjects:

4) Connect to the Interactive Web Response System (IWRS) for subject randomization and obtain group of vaccination allocated.
5) Inject the appropriate study vaccine(s). For Group 7, MenACYW conjugate vaccine should be given first. Each vaccine should be given in an assigned location (either the right or left respective limb) and documented appropriately.

   MenACYW conjugate vaccine (**Groups 7 and 8**): Inject IM into the anterolateral area of the thigh or the deltoid muscle of the arm.

   PCV13 vaccine (Groups 7 and 9, the Russian Federation only): Inject IM into the anterolateral area of the thigh or the deltoid muscle of the arm.
6) Keep the subject under observation for 30 minutes, and record any AE in the source document.
7) Give the parent a diary card, a thermometer, and a ruler, and go over the instructions for their use.
8) Remind the parent to expect a telephone call 8 days (+2 days) after Visit 1 and to bring back the diary card when they return for Visit 2 at a specified date and time.
9) Remind the parent to notify the site in case of an SAE.
10) Complete the relevant CRF pages for this visit.

Visit 1 (D0): Inclusion, Randomization, Blood Sample, and Vaccination ***(for South Korea, Mexico, and Thailand)***

1) Give the subject's parent(s) / guardian information about the trial, answer any questions, obtain written informed consent in duplicate (in 2 originals, or a photocopy of the signed consent) and give him / her 1 signed original or the copy as per local regulations and practice.
2) Check inclusion and exclusion criteria for eligibility.
3) Collect demographic data.
4) Obtain verbal medical history about the subject.

5) Perform a physical examination, including but not limited to examination of the head (including ear, nose, and throat), neck, thorax (including heart and lungs), abdomen, and extremities. If a routine examination had been performed within the last month by the investigator, a sub-investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area.
6) Take the subject's temperature by either the rectal or axillary route.
7) Connect to the Interactive Web Response System (IWRS) for subject identification number and randomization.
8) Obtain the first 5-mL blood sample (see Section 7 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (after reasonable attempts as per local regulations / practice), then Visit 1 can be rescheduled to a later date at which point informed consent and inclusion/exclusion criteria must be re-validated. If the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.
9) Inject the appropriate study vaccine(s). Of the injected vaccines, MenACYW conjugate vaccine should be given first. Each vaccine should be given in an assigned location (either the right or left respective limb) and documented appropriately.
For South Korea and Thailand only, the order of the remaining vaccines is not critical, as long as each is given in an assigned location and documented appropriately. To avoid confusion, staff should follow normal office procedure for order of vaccine administration. If injections are given in the same limb, the injection sites should be at least 2.5 cm (1 inch) apart. If injection(s) and blood sampling are done in the same limb, the injection site(s) and blood sampling site should be at least 2.5 cm (1 inch) apart or can be done according to local clinical practice as per the Investigator's judgment.

   MenACYW conjugate vaccine (Groups 1, 2, 4, 5, 10, and 11): Inject IM into the anterolateral area of the thigh or the deltoid muscle of the arm.

   MMR vaccine and V vaccine (Groups 1, 3, 10, and 12; South Korea and Thailand only): Inject SC into the fatty tissue over the triceps on the upper arm or fatty tissue over the anterolateral thigh muscle

   DTaP-IPV-HB-Hib vaccine (Groups 4 and 6, Mexico only): Inject IM into the anterolateral area of the thigh or the deltoid muscle of the arm.
10) Keep the subject under observation for 30 minutes, and record any AE in the source document.
11) Give the parent / guardian a diary card, a thermometer, and a ruler, and go over the instructions for their use.
12) Remind the parent / guardian to expect a telephone call 8 days (+2 days) after Visit 1 and to bring back the diary card when they return for Visit 2 at a specified date and time.
13) Remind the parent / guardian to notify the site in case of an SAE.
14) Complete the relevant CRF pages for this visit.

Telephone Call 1 (8 days [+2 days] after Visit 1)

Note: If D08 falls on a weekend or a holiday, the telephone call may be made on the following business day.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Remind the parent / guardian to do the following:
   - Complete the D0 to D07 pages of the diary card.
   - Complete the remaining pages of the diary card, and bring them to Visit 2.
   - Notify the site in case of an SAE.
   - Confirm the date for the next visit

Visit 2 (30 days [+14 days] after Visit 1): Collection of Safety Information and Blood Sample

1) Review the pages of the diary card with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. The parent / guardian must return the diary card.
2) Review the temporary contraindications for Visit 2 blood draw (see Section 5.2.8).
3) ***For subjects enrolled at sites in the Russian Federation only:*** Obtain the second 7-mL blood sample (for CBC, blood chemistry, and immunogenicity assessment) and urine sample for urinalysis. Perform a neurological examination by a neurologist.
4) ***For subjects enrolled at sites in South Korea, Mexico, and Thailand only:*** Obtain the second 5-mL blood sample (see Section 7.1 for detailed instructions regarding the handling of blood samples).
5) Complete the termination record of the CRF
6) If the subject's parent / guardian does not return for Visit 2, and the diary card is not received at the site, site personnel will contact the subject's parent / guardian by telephone. During the telephone call, the subject's parent / guardian will be reminded to return the diary card to the study site. Telephone calls will be documented on the Telephone / Interview Record. If the study personnel are unable to contact the subject's parent / guardian with 3 attempts, the study personnel will follow instructions given in Section 5.2.10.

SAEs and AEs That Are Related to Vaccination or That Led to Discontinuation:

At any time during the study, a subject who experiences an SAE or an AE must be followed if *either* of the following is true:

The SAE or AE is considered by the Investigator to be related to vaccination, and is not resolved by the end of the subject's participation in the trial

The subject has been discontinued from the trial because of the SAE or AE

Any such subject must be followed until the condition resolves, becomes stable, or becomes chronic.

5.1.5 Planned Trial Calendar

The following dates are approximate. The actual dates may differ as, for example, the trial will not start until all the appropriate regulatory and ethical approvals have been obtained.

Planned subject participation – FVFS (first visit, first subject) to LVLS (Last visit, last subject):	07 November 2016 to 11 June 2018
Planned inclusion period - FVFS to FVLS (first visit, last subject):	07 November 2016 to 30 April 2018
Planned vaccination period:	07 November 2016 to 30 April 2018
Planned end of trial (last assay results available):	04 September 2018
Planned date of final clinical study report:	31 January 2019

The date that the last assay results are available is considered as the end of the study.

5.1.6 Early Safety Data Review

This trial will not include an early safety data review (i.e., no early safety review[s] of preliminary safety data occurring at pre-determined milestones defined in the protocol, with pause in enrollment). However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IECs / IRBs, or the governing regulatory authorities in the country where the trial is taking place.

If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs / IRBs, and the regulatory authorities of the reason for the termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the subject's parents / guardian and should assure appropriate therapy and follow-up.

5.2 Enrollment and Retention of Trial Population

5.2.1 Recruitment Procedures

Before the start of the trial, the Investigator and / or study staff may contact the parent / guardian of an appropriate pool of potential subjects and invite them to participate in the study. The site will ensure that any advertisements used to recruit subjects (e.g., letters, pamphlets, and posters) (if applicable, according to country regulation and practice) are submitted to Sanofi Pasteur for review prior to submission to the IEC/ IRB for approval.

In addition, a parent who brings a child to the trial site for a routine visit will be invited to enroll the subject in the trial, if eligible. Subjects may also be recruited from the general population.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject's parent(s) / guardian voluntarily confirms his or her willingness to allow the child to participate in a particular trial. Informed consent must be

obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF.

In accordance with GCP, prior to signing and dating the consent form, the subject's parent / guardian must be informed by appropriate study personnel about all aspects of the trial that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

For subjects enrolled in Mexico, South Korea, and Thailand: If the subject's parent / guardian is not able to read and sign the ICF, then it must be signed and dated by an impartial witness(es) who is independent of the Investigator, according to local regulations. A witness who signs and dates the consent form is certifying that the information in this form and any other written information had been accurately explained to and understood by the subject or his / her representative. This does not apply to subjects enrolled in the Russian Federation.

The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB and the appropriate regulatory agencies according to local regulations prior to the form being used.

If new information becomes available that may be relevant to the subject's parent / guardian's willingness to continue participation in the trial, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

ICFs will be provided in duplicate (as originals), or a photocopy of the signed consent will be made, as per local regulations and practice. The original will be kept by the Investigator, and the copy, or the other original (as applicable) will be kept by the subject's parent / guardian.

Documentation of the consent process should be recorded in the source documents.

In the Russian Federation

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.

The signature of only one of the parents will be required on the ICF.

5.2.3 Screening Criteria

For South Korea, Mexico, and Thailand, there are no screening criteria other than the inclusion and exclusion criteria.

For the Russian Federation, as per Guideline for the conduct of clinical trials of the Russian Federation Health Authorities and in accordance with local practices, in addition to being tested for study vaccine immunogenicity assessment, the blood of subjects enrolled at sites in the Russian Federation will be tested for complete blood count (CBC) and blood chemistry. These subjects will also provide a urine sample for urinalysis. According to recommendations of Russian Health Authorities, the subjects will be examined by a neurologist.

The examinations by a neurologist and additional biological analyses have been implemented for subjects enrolled at sites in the Russian Federation per the request of the Russian Federation Health Authorities only and not to address any concern of the Sponsor regarding safety issues.

5.2.4 Inclusion Criteria

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

1) **For South Korea**: Korean males and females aged 12 to 23 months on the day of the first study visit[a]
   For Mexico: Males and females aged 12 to 23 months on the day of the first study visit
   For the Russian Federation: Males and females aged 12 to 14 months or 16 to 23 months on the day of the first study visit (eligible for enrollment to Group 8) or 15 to 23 months on the day of the first study visit (eligible for enrollment to Group 7 or 9).[b]
   For Thailand: Thai males and females aged 12 to 23 months on the day of the first study visit.[a]

2) Subject had received all recommended standard of care vaccinations according to his/her age as per local regulations.[c]
   For the Russian Federation only, subjects aged 15 to 23 months on the day of the first study visit (eligible for enrollment to Group 7 or 9) must not have received the third 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 MMR or V vaccination corresponding to his or her age at inclusion.

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[a] "12 to 23 months" means from the 1st day of the 12th month after birth to the day before the 24th month after birth

[b] "12 to 14 months" means from the 1st day of the 12th month after birth to the day before the 15th month after birth; "15 to 23 months" means from the 1st day of the 15th month after birth to the day before the 24th month after birth; "16 to 23 months" means the 1st day of the 16th month after birth to the day before the 24th month after birth.

[c] 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 (e.g., 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 first doses of MMR and V vaccines have not been administered prior to inclusion.*

3) Informed consent form 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)[a]
4) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures

5.2.5 Exclusion Criteria

An individual fulfilling *any* of the following criteria is to be excluded from trial enrollment:

1) Participation in the 4 weeks preceding the first trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
2) Receipt of any vaccine in the 4 weeks (28 days) preceding the first trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after the study investigational vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.
3) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B vaccine)
4) **For subjects enrolled at sites in the Russian Federation**: previous vaccination with the third dose of PCV13 in subjects 15 to 23 months of age (eligible for Group 7 or 9)
5) **For subjects enrolled at sites in Mexico**: known history of seizures, or uncontrolled neurologic disorder (including epilepsy); or encephalopathy of unknown etiology occurring within 7 days following previous vaccination with pertussis containing vaccine; previous vaccination with DTaP-IPV-HB-Hib or DTaP-containing vaccine at 12 to 23 months of age.
6) **For subjects enrolled at sites in South Korea and Thailand**: known history of seizures, cerebral injury, or encephalopathy; previous vaccination with MMR or V at or before 12 to 23 months of age.
7) Receipt of immune globulins, blood or blood-derived products in the past 3 months
8) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)
9) History of meningococcal infection, confirmed either clinically, serologically, or microbiologically
10) At high risk for meningococcal infection during the trial, according to the Investigator's judgment (specifically, but not limited to, subjects with persistent complement deficiency,

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

with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease)

11) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine(s) used in the trial or to a vaccine containing any of the same substances[a]

12) Verbal report of thrombocytopenia, as reported by the parent/guardian, contraindicating intramuscular vaccination by the Investigator's judgment

13) Known bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination by the Investigator's judgment

14) Personal history of Guillain-Barré syndrome (GBS)

15) Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine

16) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion[b]

17) **For subjects enrolled at sites in South Korea, Mexico, and Thailand**: Moderate or severe acute illness/infection (according to Investigator's judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

18) **For subjects enrolled at sites in the Russian Federation**: Acute disease of any severity on the day of vaccination or febrile illness (axillary temperature ≥ 37.0°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

19) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

20) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

5.2.6 Medical History

Prior to enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant medical history (reported as diagnosis) including conditions for which the subject is or has been followed by a physician or conditions that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRF. The significant medical history section of the CRF contains a core list of body systems and disorders that could be used to

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[a] The components of the MenACYW conjugate vaccine are listed in Section 6.1.1.1 and in the Investigator's Brochure. The components of MMR, V, DTaP-IPV-HB-Hib, and PCV13 are listed in Section 6.1.2.1, Section 6.1.3.1, Section 6.1.4.1, and Section 6.1.5.1., respectively.

[b] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases.

prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

For each condition, the data collected will be limited to:

- Diagnosis (this is preferable to reporting signs and symptoms)
- Presence or absence of the condition at enrollment

The reporting of signs and symptoms is strongly discouraged.

Dates, medications, and body systems are not to be recorded, and the information collected will not be coded. Its purpose is to assist in the later interpretation of safety data collected during the trial.

For the Russian Federation Only

Any clinically significant abnormal results of the Visit 0 CBC, blood chemistry, urinalysis, or neurological examination, according to Investigator judgment will be reported as medical history. All laboratory tests will be sampled and analyzed locally. Results of the lab tests will be assessed by the Investigator. The Investigator should choose to not include the subject in the study if any of these laboratory tests have the potential to impact the health of the subject after vaccination. The laboratory values for CBC, blood chemistry, urinalysis, and the results of neurological examinations will only be collected in the CRF if they are clinically significant. Visit 0 laboratory tests are 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

5.2.7 Contraindications for Subsequent Vaccinations

Not applicable since only one dose of the vaccine(s) will be administered on D0 in this trial.

5.2.8 Temporary Contraindications for Visit 2 Blood Draw

Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw indicated in the Table of Study Procedures. If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

5.2.9 Conditions for Withdrawal

Parents / guardians will be informed that they have the right to withdraw their child from the trial at any time. A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns (withdrawal) without the subject's permission
- At the request of the subject's parent / guardian (dropout)

The following will result in automatic withdrawal or exclusion of a subject from the study:

- Significant non-compliance with the protocol, based on the Investigator's judgment

The reason for a withdrawal or dropout should be clearly documented in the source documents and on the CRF.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in which case, the reason for discontinuation will be noted as "SAE" or "other AE" as appropriate) or for another reason.

Withdrawn subjects will not be replaced.

5.2.10 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (i.e., documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the CRF and in the source documents.

5.2.11 Classification of Subjects Who Discontinue the Trial

For any subject who discontinues the trial prior to completion, the most significant reason for early termination will be checked in the CRF. Reasons are listed below from the most significant to the least significant (refer to the CRF completion guidelines for additional details and examples):

- **Serious adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an SAE, as defined in Section 9.3.2.1.
- **Other adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an AE other than an SAE, as defined in Section 9.3.2.1.
- **Non-compliance with protocol:** To be used when the Investigator withdraws a subject from the study because of failure to follow the protocol, including when it is retrospectively discovered that a subject did not fulfill the eligibility criteria. The Investigator will provide a comment as to the specific cause of non-compliance.
- **Lost to follow-up:** To be used when the Investigator withdraws a subject from the study because of failure to establish contact, as outlined in Section 5.2.10. The Investigator will provide documentation that contact was attempted (i.e., return of unsigned certified letter receipt).
- **Voluntary withdrawal not due to an adverse event:** To be used when a subject drops out of the study for any reason other than those listed above.

5.2.12 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the trial because of an SAE, other type of AE, non-compliance with the protocol, or loss of eligibility, including definite contraindications.

For subjects where the reason for early termination was lost to follow-up or if the subject withdrew informed consent and specified that they do not want to be contacted again and it is documented in the source document, the site will not attempt to obtain further safety information.

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on trial related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center - available 24 hours a day, 7 days a week - that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

This process does not replace the need to report an SAE. The investigator is still required to follow the protocol defined process for reporting SAEs to Global PharmacoVigilance (GPV) (Please refer to Section 10).

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.4.

5.4 Modification of the Trial and Protocol

Any amendments to this trial plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version.

An administrative amendment to a protocol is one that modifies some administrative or logistical aspect of the trial but does not affect its design or objectives or have an impact on the subjects' safety. A substantial amendment to a protocol is one that affects the conduct of the trial or the safety of the subjects. Protocol amendments will be submitted for approval and implementation according to local IEC / IRB / HA policy.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which IEC / IRB approval has already been given, are not initiated without IEC / IRB review and approval, except to eliminate apparent immediate hazards to subjects.

5.5 Interruption of the Trial

The trial may be discontinued if new data about the investigational product resulting from this or any other trials become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, and / or the IECs / IRBs. If the trial is prematurely terminated or suspended, the

Sponsor shall promptly inform the Investigators, the regulatory authorities, and the IECs / IRBs of the reason for termination or suspension, as specified by the applicable regulatory requirements.

The Investigator shall promptly inform the trial subjects' parent(s) or guardian(s) (if applicable) and assure appropriate therapy and / or follow-up for them.

6 Vaccines Administered

6.1 Identity of the Investigational Products

6.1.1 Identity of Trial Product 1

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

Form: Liquid solution

Dose: 0.5 milliliter (mL)

Route: IM

Batch number: To be determined

6.1.1.1 Composition

Each 0.5 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 µg
Serogroup C..... 10 µg
Serogroup Y..... 10 µg
Serogroup W..... 10 µg

Tetanus toxoid protein carrier ..... approximately 65 µg

6.1.1.2 Preparation and Administration

MenACYW conjugate vaccine is supplied in single-dose (0.5 mL) vials.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. Another dose is to be used, and the event is to be reported to the Sponsor.

The rubber stopper should not be removed from any of the vaccine vials.

One dose (0.5 mL) of MenACYW will be administered IM into the anterolateral area of the thigh or the deltoid muscle of the arm, as per local country preferences, the Investigator's criteria, and depending upon the number of vaccinations received. The site of injection should be documented.

The site of injection should be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle will be disposed of in accordance with currently established guidelines.

Subjects must be kept under observation for 30 minutes after vaccination under the supervision of a responsible healthcare professional at each study site to ensure their safety, and any reactions during this period will be documented in the CRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

6.1.1.3 Dose Selection and Timing

All subjects in Groups 1, 2, 4, 5, 7, and 8 will receive 1 dose of MenACYW conjugate vaccine on D0.

6.1.2 Identity of Trial Product 2 - Measles, Mumps, Rubella Vaccine

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

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

Dose: 0.5 mL

Route: Subcutaneous (SC)

Batch number: To be determined

6.1.2.1 Composition

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

Measles virus: not less than 1000 tissue culture infectious doses ($TCID_{50}$)
Mumps virus: not less than 12,500 $TCID_{50}$
Rubella virus: not less than 1000 $TCID_{50}$

Each 0.5 mL dose is 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 (≤ 0.3 mg), fetal bovine serum (< 1 part per million [ppm]), other buffer and media ingredients, and approximately 25 µg of neomycin. The product contains no preservative.

6.1.2.2 Preparation and Administration

M-M-R®II is supplied as a vial of lyophilized vaccine and a vial of diluent for reconstitution to prepare a single dose (0.5 mL).

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. Another dose is to be used, and the event is to be reported to the Sponsor.

One dose (0.5 mL) of M-M-R®II will be administered SC into the fatty tissue over the triceps on the upper arm or fatty tissue over the anterolateral thigh muscle, as per local country preferences, the Investigator's criteria, and depending upon the number of vaccinations received. The site of injection should be documented. The site of injection should be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle will be disposed of in accordance with currently established guidelines.

Subjects must be kept under observation for 30 minutes after vaccination under the supervision of a responsible healthcare professional at each study site to ensure their safety, and any reactions during this period will be documented in the CRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

The procedures for preparing and administering the M-M-R®II are detailed in the package insert (43).

6.1.2.3 Dose Selection and Timing

All subjects in Groups 1 and 3 will receive 1 dose of M-M-R®II on D0.

6.1.3 Identity of Trial Product 3 - Varicella Vaccine

VARIVAX® (V): Varicella Virus Vaccine Live (Merck, Sharp & Dohme, Haarlem, The Netherlands (47)) (licensed in South Korea and Thailand)

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

Dose: 0.5 mL

Route: SC

Batch number: To be determined

VARIVAX [Patient Information Leaflet] Haarlem, (The Netherlands): Sanofi Pasteur MSD. https://www.medicines.org.uk/emc/medicine/17494

6.1.3.1 Composition

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

Each 0.5 mL dose also contains 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 contains 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, ethylenediaminetetraacetic acid (EDTA), neomycin, and fetal bovine serum. The product contains no preservative.

6.1.3.2 Preparation and Administration

VARIVAX® is supplied as a vial of lyophilized vaccine and a vial of diluent for reconstitution to prepare a single dose (0.5 mL).

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. Another dose is to be used, and the event is to be reported to the Sponsor.

One dose (0.5 mL) of VARIVAX® will be administered SC into the fatty tissue over the triceps on the upper arm or fatty tissue over the anterolateral thigh muscle, as per local country preferences, the Investigator's criteria, and depending upon the number of vaccinations received. The site of injection should be documented. The site of injection should be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle will be disposed of in accordance with currently established guidelines.

Subjects must be kept under observation for 30 minutes after vaccination under the supervision of a responsible healthcare professional at each study site to ensure their safety, and any reactions during this period will be documented in the CRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

The procedures for preparing and administering the VARIVAX® are detailed in the SPC (44).

6.1.3.3 Dose Selection and Timing

All subjects in Groups 1 and 3 will receive 1 dose of VARIVAX® of D0.

6.1.4 Identity of Trial Product 4 - Hexavalent Vaccine

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

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.1.4.1 Composition

Each 0.5 mL dose[a] is formulated to contain the following components:

Diphtheria Toxoid ..... ≥ 20 international units (IU)[b]
Tetanus Toxoid ..... ≥ 40 IU[b]
Bordetella pertussis antigens
Pertussis Toxoid ..... 25 µg
Filamentous Haemagglutinin ..... 25 µg
Poliovirus (Inactivated)[c]
Type 1 (Mahoney) ..... 40 D antigen units[d]
Type 2 (MEF-1) ..... 8 D antigen units[b]
Type 3 (Saukett) ..... 32 D antigen units[b]
Hepatitis B surface antigen[e] ..... 10 µg
Haemophilus influenzae type b polysaccharide ..... 12 µg
(Polyribosylribitol Phosphate)
conjugated to Tetanus Protein ..... 22-36 µg

The vaccine also contains the excipients: disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, and water for injections.

The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin, and polymyxin B, which are used during the manufacturing process.

6.1.4.2 Preparation and Administration

Hexaxim® is supplied as a suspension for IM injection in 0.5 mL single-dose prefilled syringes.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. Another dose is to be used, and the event is to be reported to the Sponsor.

One dose (0.5 mL) of Hexaxim® will be administered IM into the anterolateral area of the thigh or the deltoid muscle of the arm, as per local country preferences, the Investigator's criteria, and depending upon the number of vaccinations received. The site of injection should be documented. The site of injection should be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle will be disposed of in accordance with currently established guidelines.

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[a] Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al^{3+})

[b] As lower confidence limit (p=0.95)

[c] Produced on Vero cells

[d] Or equivalent antigenic quantity determined by a suitable immunochemical method

[e] Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

Subjects must be kept under observation for 30 minutes after vaccination under the supervision of a responsible healthcare professional at each study site to ensure their safety, and any reactions during this period will be documented in the CRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

The procedures for preparing and administering the Hexaxim® are detailed in the SPC (46).

6.1.4.3 Dose Selection and Timing

All subjects in Groups 4 and 6 will receive 1 dose of Hexaxim® on D0.

6.1.5 Identity of Trial Product 5 - Pneumococcal Vaccine

Prevenar 13® (PCV13): Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Pfizer Ireland Pharmaceuticals, Ireland) (licensed in the Russian Federation)

Form: Suspension for IM injection

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.1.5.1 Composition

Each 0.5 mL vaccine dose is 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 CRM_{197} carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer, and 125 µg aluminum as aluminum phosphate adjuvant.

6.1.5.2 Preparation and Administration

Prevenar 13® is supplied as a suspension for IM injection in 0.5 mL single-dose prefilled syringes.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. Another dose is to be used, and the event is to be reported to the Sponsor.

One dose (0.5 mL) of Prevenar 13® will be administered IM into the anterolateral area of the thigh or the deltoid muscle of the arm, as per local country preferences, the Investigator's criteria, and depending upon the number of vaccinations received. The site of injection should be documented. The site of injection should be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle will be disposed of in accordance with currently established guidelines.

Subjects must be kept under observation for 30 minutes after vaccination under the supervision of a responsible healthcare professional at each study site to ensure their safety, and any reactions during this period will be documented in the CRF. Appropriate medical equipment and emergency

medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

The procedures for preparing and administering the Prevenar 13® are detailed in the SPC (45).

6.1.5.3 Dose Selection and Timing

All subjects in Groups 7 and 9 will receive 1 dose of Prevenar 13® on D0.

6.1.6 Identity of Control Products

Not applicable.

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

MenACYW conjugate vaccine will be supplied by the Sponsor in single-dose vials in cartons, both with investigational labeling and packaging according to national regulations. The content of the labeling will also be in accordance with the local regulatory specifications and requirements. Each vial will have 1 fixed multilingual booklet label (in Korean, Russian, Spanish, and Thai) with room to view the product and each carton will have 1 fixed multilingual booklet label and 2 detachable labels enabling identification and providing information on the study. The detachable carton labels are for the sites to attach to source documents and the subject's vaccination card. See the Operating Guidelines for additional label detail.

Commercial lots of the licensed pediatric vaccines (M-M-RII®, VARIVAX®, Prevenar 13®, and Hexaxim®) will be supplied by Sanofi Pasteur, Inc.

For some countries, where acceptable and in accordance with local regulations, primary labels are in English with information in local language on the carton; for other countries primary and secondary labels are in local language in accordance with local regulations.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Clinical Logistics Coordinator or designee will contact the Investigator or a designee in order to determine the dates and times of delivery of products.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the

cold chain was maintained during shipment (i.e., verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a staff member to assume this responsibility.

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The vaccines must not be frozen. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the trial site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

6.3.2.3 Product Accountability

The person in charge of product management at the site will maintain records of product delivery to the trial site, product inventory at the site, the dose(s) given to each subject, and the disposal of or return to the Sponsor of unused doses.

The necessary information on the product labels is to be entered into the source document and the CRF. If applicable, information may also be entered into the subject's vaccination card.

The Sponsor's monitoring staff will verify the trial site's product accountability records against the record of administered doses in the CRFs and the communication from the IWRS (if applicable).

In case of any expected or potential shortage of product during the trial, the Investigator or an authorized designee should alert the Sanofi Pasteur representative as soon as possible, so that a shipment of extra doses can be arranged.

6.3.3 Replacement Doses

If a replacement dose is required (e.g., because the syringe broke or particulate matter was observed in the syringe), the site personnel must either contact the IWRS to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

Unused or wasted products will be either disposed of or returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the trial period.

6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigator(s) will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

This trial is open label; therefore, there is no need for code-breaking procedures.

Until database lock and to prevent biases, the laboratory personnel performing the serology testing will be blinded to the group assignment. The laboratory will have a written procedure detailing how the blinding will be maintained.

6.5 Randomization and Allocation Procedures

For sites in South Korea, Mexico, and Thailand: Each 12- to 23-month old subject whose parent(s) / guardian signs the ICF, and who meets the inclusion/exclusion criteria will be randomly assigned in a 2:1:1 ratio to the study groups by country.

For sites in the Russian Federation: Each toddler aged 12 to 14 months or 16 to 23 months on the day of enrollment will be 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. Those aged 15 to 23 months on the day of enrollment will be randomized in a 2:1 ratio to Groups 7 and 9.

Site staff will connect to the IWRS, enter identification and security information, and confirm a minimal amount of data in response to IWRS prompts. The IWRS will then provide the group assignment and have the site staff confirm it. The full detailed procedures for group allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the trial, then the information will only be recorded on the subject recruitment log.

Subject numbers that are assigned by the IWRS will consist of an 8-digit string (a 3-digit trial center identifier and a 5-digit subject identifier connected by "-"). For example, Subject 001-00001 is the first subject enrolled in center number 1. Subject numbers should not be reassigned for any reason.

6.6 Treatment Compliance

The following measures will ensure that the vaccine doses administered comply with those planned, and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified trial personnel
- The person in charge of product management at the site will maintain accountability records of product delivery to the trial site, product inventory at the site, dose(s) given to each subject, and the disposal of unused or wasted doses

6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications including other therapies e.g., blood products, should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during trial participation.

Documentation in the CRF of concomitant medication will be limited to specific categories of medication of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRF from the day of vaccination to the end of the solicited and unsolicited follow-up period (e.g., 30 day safety follow-up) as they may impact the response to the vaccination and impact the consistency of the information collected on concomitant medications at any vaccination.

The "reportable" medications are distributed according to 3 categories. These are:

- Category 1 antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other immune modulators.

Note: inhaled and topical steroids should not be captured.

- Category 2: Reportable medications used to define the Per-Protocol Analysis Set (PPAS). For example:
    - Influenza and other non-study vaccines: Influenza vaccine in the 2 weeks preceding the trial vaccination up to the subject's termination from the trial and any other vaccines (other than the study vaccine) in the 4 weeks preceding the trial vaccination up to the subject's termination from the trial
    - Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
    - Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy: used in the 6 months preceding the trial vaccination and the 4 weeks following the trial vaccination
- Category 3: Oral or injectable antibiotics, which may interfere with bioassays used for antibody testing when taken before a blood draw
    - The period of collection should be within 3 days before the first blood draw and up to the last scheduled blood draw.

Note: Inhaled and topical antibiotics (drops, creams or ointments) should not be captured.

The information reported in the CRF for each reported medication will be limited to:

- Trade name / International non-proprietary name
- Given as treatment or as prophylaxis
- Medication category
- Start and stop dates

Dosage and administration route will not be recorded. Homeopathic medication will not be recorded. Topical treatment will not be recorded.

The fact that a medication was given in response to an AE will be captured in the "Action Taken" column of the AE only. No details will be recorded in the concomitant medication module of the CRF unless the medication received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses, CBC, and blood chemistry, as well as urine samples, will be collected at Visits 0 (the Russian Federation only), 1, and 2. See the Tables of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

7.1.1 Blood Samples

For Immunogenicity:

At Visit 0 (the Russian Federation only), Visit 1 (Mexico, South Korea, and Thailand), and Visit 2, 5 mL of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity; will verify the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; and will attach the label to the tube.

If feasible, blood is to be taken from the limb opposite to the one that will be used for vaccination. If injection(s) and blood sampling are done in the same limb, the injection site(s) and blood sampling site should be at least 2.5 cm (1 inch) apart or can be done according to local clinical practice as per the Investigator's judgment.

For CBC and Blood Chemistry (Sites in the Russian Federation Only)

Blood samples for CBC and blood chemistry will be collected in a separate tube from the sample for immunogenicity. If only a limited volume of blood is available, the safety blood sample takes precedence over the blood sample for immunogenicity assessments. For blood samples of subjects enrolled at sites in the Russian Federation, tubes, labels, and other materials required for testing will be provided locally. Sample labeling and processing will be done according to the hospital's standard practice. See Operating Guidelines for further details.

7.1.2 Urine Samples for Urine Chemistry (Sites in the Russian Federation Only)

Approximately 8 mL of first-stream urine will be collected at the following times: Visit 0, and Visit 2. For urine samples of subjects enrolled at sites in the Russian Federation, tubes, labels, and other materials required for testing will be provided locally. Labeling procedures will be done the same way as for blood samples.

7.2 Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of antibody response are contained in the Operating Guidelines provided to the site. An overview of the procedures is provided here.

7.2.1 Serum Samples

For Immunogenicity

After the blood draw, the sampling tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours in order to allow the blood to clot. Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of +2°C to +8°C and must be centrifuged within a maximum of 24 hours.

The samples are then centrifuged, and the separated serum is transferred to the appropriate number of aliquoting tubes by pipetting; samples are handled 1 subject at a time to avoid the mix-up of the subjects' blood tubes. At least 1.5 mL of serum should be placed in the primary cryotube, and the remaining serum should be placed in the retention cryotubes. If less than 1.5 mL of serum is available, all of the sera should be placed in the primary cryotube, and no retention cryotubes should be used. These tubes are pre-labeled with adhesive labels that identify the study code, the subject's number, and the sampling stage or visit number.

The subject's number and the date of sampling, the number of aliquots obtained, the date and time of preparation, and the subject's consent for future use of his / her samples are to be specified on a sample identification list and recorded in the source document. Space is provided on this list for comments on the quality of samples.

For CBC and Blood Chemistry (Sites in the Russian Federation Only):

Blood samples for CBC and blood chemistry will be prepared at ambient temperature and sent to the site's local laboratory for testing. The testing will be done according to the site's routine practice and standard procedures.

7.2.2 Urine Samples for Urine Chemistry (Sites in the Russian Federation Only)

Samples will be prepared at ambient temperature and analyzed locally. The testing will be done according to the site's routine practice and standard procedures.

7.3 Sample Storage and Shipment

7.3.1 Serum Samples

For Immunogenicity

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C or below. The temperature will be monitored and documented on the appropriate form

during the entire trial. If it rises above -10°C for any period of time, the Clinical Logistics Coordinator must be notified. See the Operating Guidelines for further details.

In case a subject is found not eligible to participate by the study staff after the blood samples have been obtained but before the subject has been vaccinated, the subject's blood sample will be discarded as per local standard practices and not stored.

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the International Air Transport Association (IATA) 602 regulations.

Samples will be shipped to Global Clinical Immunology (GCI) at Sanofi Pasteur. The address is provided in the Operating Guidelines. Samples will be shipped outside the country only after approval from the relevant authorities.

For CBC and Blood Chemistry (Sites in the Russian Federation Only)

Blood samples for CBC and blood chemistry will be stored at ambient temperature and sent to the site's local laboratory for testing. The testing will be done according to the site's routine practice and standard procedures.

7.3.2 Urine Samples for Urine Chemistry (Sites in the Russian Federation Only)

Samples will be prepared at ambient temperature and analyzed locally. The testing will be done according to the site's routine practice and standard procedures.

7.4 Future Use of Stored Serum Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for at least 5 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested.

For Mexico, South Korea, and Thailand only: Depending on local regulations, subjects' parents / guardians will be asked to indicate in the ICF or country specific consent form whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. (Anonymity of samples will be ensured.) The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve laboratory methods. Genetic tests will never be performed on these samples without individual informed consent.

This does not apply to the Russian Federation. The unused stored serum samples from subjects in the Russian Federation will not be used for any testing other than that directly related to this study.

8 Clinical Supplies

Sanofi Pasteur will supply the trial sites with protocols, ICFs, CRFs, SAE reporting forms, diary cards, and other trial documents, as well as with the following trial materials: all study vaccines and injection materials, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

The means for performing Electronic Data Capture (EDC) will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the trial.

The Investigator will supply all vaccination supplies, phlebotomy, and centrifugation equipment, including biohazard and / or safety supplies. The biohazard and safety supplies include needles and syringes, examination gloves, laboratory coats, sharps disposal containers, and absorbent countertop paper. The site will ensure that all biohazard wastes are autoclaved and disposed of in accordance with local practices. The Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products and for the blood samples, and appropriate space in a temperature-monitored freezer for serum aliquots.

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines. They must allow approximately 1 week for an order to be filled and to have the supplies sent to their site.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Immunogenicity

9.1.1.1 Immunogenicity Endpoints

The primary endpoints for the evaluation of immunogenicity are:

Antibody (Ab) titers against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (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, and Thailand) (before vaccination[s]) and 30 days (+14 days) after vaccination(s) (all subjects).

9.1.1.2 Immunogenicity Assessment Methods

[redacted]

9.1.2 Safety

There are no primary objectives for safety.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the trial.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Immunogenicity

9.2.1.1 Immunogenicity Endpoints

The secondary endpoints for the evaluation of immunogenicity are:

- 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 (pertussis toxoid [PT] and filamentous hemagglutinin [FHA]) antigens 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 for Groups 7 and 9

9.2.1.2 Immunogenicity Assessment Methods

The assay methods to be used are summarized below. Laboratory technicians conducting the immunogenicity assays will be blinded to the group to which each subject was assigned.

Anti-Diphtheria, Tetanus and Pertussis Antibodies

The assay for measuring anti-diphtheria, tetanus, and pertussis antibodies will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

The DTP (Diphtheria , Tetanus, and Pertussis) ECL (electrochemiluminescent) is a multiplexed serological assay which allows for the simultaneous quantification of human antibodies to 6 specific antigens including diphtheria toxoid (DT), tetanus toxoid (TT), and four pertussis antigens: pertussis toxin, filamentous hemagglutinin (FHA), fimbriae types 2 and 3 (FIM2,3) and pertactin (PRN).

In this assay, each well of a 96-well microtiter plate is pre-coated in precise positions with the 6 different antigens in a multi-spot fashion. Following incubation with serum samples, antigen-specific antibodies bind to the respective antigens. The captured antibodies are then detected using a sulfotag conjugated anti-human IgG conjugate. Electrical stimulation of the conjugate in the presence of a chemiluminescent substrate results in the generation of a light signal from each specific spot that is captured by a camera in relative light units (RLU). The signal generated is directly proportional to the amount of antibodies present in the sample, which is quantified using software and based on an established reference standard sample curve.

The anti-diphtheria method will be performed only on BL2 samples collected from Groups 4 and 6 only.

The anti-tetanus method will be performed on BL1 and BL2 samples collected from Groups 4 and 6 only.

The anti-pertussis method will be performed on BL1 and BL2 samples collected from Groups 4 and 6 only.

Anti-Polio Antibodies

The assay for measuring anti-polio antibodies will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

Anti-poliovirus types 1, 2, and 3 will be measured by neutralization assay. Serial dilutions of sera are mixed with challenge poliovirus and incubated with cultured Vero cells that are sensitive to poliovirus. Specific neutralizing Ab contained in the sera bind to and neutralize the challenge poliovirus. The neutralized poliovirus does not affect cellular viability and these cells continue to metabolize and release CO_2, reducing the pH of the culture medium. Cell survival correlates with the change in the pH indicator (phenol red to yellow at pH $\leq$ 7.0) contained in the medium. In the absence of neutralizing Ab, the challenge poliovirus reduces cellular metabolism and CO_2 production. Therefore, the pH does not decrease and a color change is not detected. The poliovirus MIT measures the functional serum Ab response to poliovirus by utilizing Vero cells (African green monkey kidney cells) and wild type poliovirus strains 1, 2, and 3 (Mahoney, MEF-1, and Saukett, respectively) as the challenge virus. The Karber method is used to determine the serum

dilution that neutralized 50% of the challenge virus. Results are expressed as titers (1/dilution). The LLOQ of the anti-poliovirus types 1, 2, and 3 assays is 4 (1/dil).

This method will be performed only on BL2 samples collected from Groups 4 and 6.

Anti-Hepatitis B Antibodies

The assay for measuring anti-hepatitis B antibodies will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

Anti-hepatitis B Ab will be measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System using chemiluminescence detection technology. The VITROS ECi Immunodiagnostic system uses an Ab mediated antigen sandwich formation to detect the presence of anti-hepatitis B surface antigen (HBsAg) total immunoglobulin in human serum. This involves the reaction of anti-HBsAg in the sample with plasma-derived HBsAg (ad and ay subtypes) coated onto the wells. A horseradish peroxidase (HRP)-labeled HBsAg conjugate (ad and ay subtypes) then complexes with the bound anti-hepatitis Bs (HepBs), forming an antigen sandwich. Substrate is then added which catalyzes HRP, producing light. The light signals are read by the VITROS ECi/ECiQ. Immunodiagnostic System and the amount of HRP conjugate bound is directly proportional to the concentration of anti-HepBs antibodies present in the sample. Results are reported in milli-international units (mIU)/mL by comparison to a calibrator provided by the manufacturer that has been calibrated according to the WHO First International Reference Preparation for Antibody to HBsAg (1977). The LLOQ is 5 mIU/mL.

This method will be performed only on BL2 samples collected from Groups 4 and 6.

Anti-*Haemophilus influenza* type b *(Anti-PRP) Antibodies*

The assay for measuring anti-PRP antibodies will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

Anti-PRP concentrations will be measured using a Farr-type radioimmunoassay (RIA). Serum levels of anti-*Haemophilus influenzae* type b (Hib) Capsular Polysaccharide (PRP) Ab are determined by RIA, in which serum samples are incubated with radiolabeled PRP (^{3}H-PRP) in the presence of ^{36}Cl (volume marker). Specific Ab bind to tritiated capsular PS to form antigen-Ab complexes. These complexes are precipitated with ammonium sulfate and collected by centrifugation. The radioactivity is measured in the precipitated pellet, in counts per minute (CPM) and is proportional to the amount of anti-Hib capsular PS Ab present in the serum sample. The concentration of anti-PRP antibody in the serum sample is determined from the concentration response curve generated by the titration results of dilutions of the reference standard analyzed in the assay. Results are reported in µg/mL by comparison to the Center for Biologics Evaluation and Research (CBER), Lot No. 1983 reference standard. The LLOQ of the anti-PRP RIA is 0.06 µg/mL.

This method will be performed only on BL2 samples collected from Groups 4 and 6.

Anti-Pneumococcal Antibodies

The assay for measuring anti-pneumococcal antibodies will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

The pneumococcal capsular PS (PnPS) IgG Electrochemiluminescent (ECL) assay is used to quantitate the amount of anti-*Streptococcus pneumoniae* PS (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F) antibodies in human serum. In this method, purified antigen of 8 PnPS are coated into defined spots within the wells of a 96-well microtiter plate by MesoScale Discovery (MSD) using 3 types of plates to cover all 21 PnPS. Diluted serum samples (test samples, reference standard, and quality controls), pre-treated with pneumococcal cell wall absorbents (to reduce the interference of non-specific antibodies in the assay), are incubated in the wells. Specific antibodies in the serum samples bind to the immobilized antigen. Unbound antibodies are washed from the wells, and SULFO-TAG-conjugated anti-human immunoglobulin is added. The antibody conjugate binds to the antigen-antibody complex. Excess conjugate is washed away, and read buffer is added. The plate is read using electrochemiluminescence on an MSD imager. The intensity of the generated light is proportional to the amount of specific antibody bound to the antigen-coated spots. An international reference standard assayed on each plate is used to calculate the amount of anti-pneumococcal IgG antibodies (µg/mL) in human serum.

This method will be performed on BL1 and BL2 samples collected from Groups 7 and 9 only.

Anti-Measles Antibodies

The assay for measuring anti-measles antibodies will be performed by Merck, Richmond VA, USA.

The measles EIA (enzyme immunoassay) detects total IgG antibody to measles virus. Plates are coated using inactivated measles antigen that is bound to solid phase microtiter plates. The antigen is derived from measles Edmonston strain-infected Vero cells. Serum or plasma is added to the coated plates and samples positive for measles antibodies will bind to the measles antigen-coated plates, forming antibody-antigen complexes. The bound antibody-antigen complexes can then be detected using an alkaline phosphatase labeled anti-human IgG. Color development occurs as a result of the addition of an enzyme-specific substrate phenolphthalein monophosphate. The color intensity is then measured spectrophotometrically with the highest intensity of color correlating to a high level of measles antibody and lowest color intensity correlating to low levels of measles antibody. Measles specific titers (antibody concentration in mIU/mL) in the samples are determined by interpolation from a standard curve that is run on each assay plate. The serostatus cutoff for the measles assay is 120 mIU/mL.

Anti-Mumps Antibodies

The assay for measuring anti-mumps antibodies will be performed by Merck, Richmond, VA, USA.

The mumps enzyme-linked immunosorbent assay (ELISA) detects IgG antibodies to mumps virus. The assay uses an earlier passage of the Jeryl Lynn® mumps virus (Jeryl Lynn® 135 [JL135], < 12 passages) and is considered to be a wild-type (WT)-like strain. The reactivity of the sera to the mumps antigens prepared from JL135-infected Vero cells is subtracted from that of uninfected Vero cells (denoted as tissue culture control [TCC] wells). JL135 mumps virus antigen or TCC is bound to solid phase microtiter plates and serum containing mumps antibody is added. The mumps antibody bound to the WT mumps antigen-coated plates forms an antibody-antigen complex. The bound antibody-antigen complex is then detected using an enzyme-labeled anti-

human IgG. Color development occurs with the addition of a substrate and color intensity is measured spectrophotometrically. Results are obtained as a difference of the average duplicate of each optical density (OD) of JL135 mumps antigen wells and the average duplicate OD of TCC wells for each serum sample (noted as delta optical density [DOD]). Quantitation of the human IgG antibody to mumps virus, or antibody concentration, is determined by comparison of the resulting test DOD to a standard curve. The serostatus cutoff for the mumps assay is 10 Mumps Ab units/mL.

Anti-Rubella Antibodies

The assay for measuring anti-rubella antibodies will be performed by Merck, Richmond, VA, USA.

The rubella IgG EIA detects total IgG antibody to rubella virus. Plates are coated using inactivated rubella antigen that is bound to solid phase microtiter plates. The antigen is derived from Rubella HPV-77 infected Vero cells. Serum is added to the coated plate and samples positive for rubella antibodies will bind to the rubella antigen-coated plates, forming antibody-antigen complexes. The bound antibody-antigen complexes can then be detected using an alkaline phosphatase labeled anti-human IgG. Color development occurs as a result of the addition of an enzyme-specific substrate, phenolphthalein monophosphate. The color intensity is then measured spectrophotometrically with the highest intensity of color correlating to a high level of rubella antibody and lowest color intensity correlating to low levels of rubella antibody. Rubella specific titers (antibody concentration in IU/mL) in the samples are determined by interpolation from a standard curve that is run on each assay plate. The serostatus cutoff for the rubella assay is 10 IU/mL.

Anti-Varicella Antibodies

The assay for measuring anti-varicella antibodies will be performed by Merck, Richmond, VA, USA.

The glycoprotein enzyme-linked immunosorbent assay (gpELISA) detects antibodies to varicella zoster virus (VZV). The assay detects antibodies to VZV glycoprotein (gp), which have been purified from MRC-5 cells infected with the KMcC strain of VZV by lectin affinity chromatography. The reactivity of the sera to the gp antigens from uninfected MRC-5 cells (denoted as TCC wells]) is subtracted from the reactivity of the sera to the gp antigens purified from VZV-infected MRC-5 cells. The concentration of serum antibody to the VZV gp antigen as determined by gpELISA is shown to correlate with neutralizing antibody concentrations. The assay uses the “second antibody” format with varicella glycoprotein (gp) antigen and MRC-5 TCC glycoprotein coated on the solid phase microtiter plate. Diluted sera are dispensed into 2 VZV gp antigen coated wells and 2 MRC5 gp coated wells for each standard curve point, control, and sample. Antibody to the varicella virus in a test sample binds to the antigen coated plate. Antibody to varicella glycoprotein in a test sample, bound to the antigen on the solid phase microtiter plate, is subsequently detected using goat anti-human IgG alkaline phosphatase conjugate. After substrate addition for color development, quantitation is obtained by comparison of sample DOD to a standard curve. The DOD is determined by subtracting the average OD of the TCC coated wells from its corresponding VZV gp average OD. Results for the assay are reported as concentration of antibody in gpELISA units/mL. The serostatus cutoff for the varicella assay is 1.25 gpELISA Ab units/mL.

These anti-measles, mumps, rubella, and varicella methods will be performed on BL1 and BL2 samples collected from Groups 1, 3, 10, and 12 only.

9.2.2 Safety

There are no secondary objectives for safety.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the trial.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

9.3.1.1 Immunogenicity Endpoints

Ab titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine in 100 subjects from each of Groups 1, 4, and 7, and in 50 subjects from each of Groups 2, 5, and 8.

9.3.1.2 Immunogenicity Assessment Methods

[a] T60: Time of incubation duration of 60 minutes

9.3.2 Safety

9.3.2.1 Safety Definitions

The following definitions are taken from the International Conference on Harmonisation (ICH) E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Adverse Event (AE):

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore an AE may be:

- A new illness
- The worsening of a concomitant illness
- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

Surgical procedures are not AEs; they are the action taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the trial period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing condition worsens in frequency or intensity, or if in the assessment of the treating physician there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious* which is based on patient / event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability / incapacity[c]
- Is a congenital anomaly / birth defect
- Is an important medical event[d]

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions (AR).

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[a] The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or out-patient treatment with no hospitalization.

[c] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[d] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, GBS, new onset diabetes, or autoimmune disease.

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility)

Unexpected Adverse Reaction (UAR):

An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

A solicited reaction is an event that is prelisted in the CRF**.** The assessment of these AEs post-vaccination is mandatory. A solicited reaction is defined by a combination of:

- Symptom and
- Onset post-vaccination

Examples of solicited reactions include injection site pain between D0 and D07 post-vaccination, or headache between D0 and D07.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRF and considered as related to vaccination.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRF in terms of diagnosis and / or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D7 is a solicited reaction (i.e., prelisted in the CRF), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE.

An unsolicited non-serious AE is an unsolicited AE excluding SAEs.

Injection Site Reaction:

An injection site reaction[a] is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions.

Systemic AE:

Systemic AEs are all AEs that are not injection site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination site, e.g., erythema that is localized but that is not at the injection site.

[a] All injection site AEs are considered to be related to vaccination and are therefore all *injection site reactions*.

9.3.2.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination(s) of any unsolicited systemic AEs reported in the 30 minutes after vaccination(s).
- 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) injection site reactions occurring up to 7 days after vaccination(s).
- 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(s).
- 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 Visit 2 after vaccination(s).
- Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs throughout the trial.

9.3.2.3 Safety Assessment Methods

At Visit 2, the Investigator or a delegate will ask the parent / guardian about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRF according to the instructions provided by the Sponsor.

9.3.2.3.1 Immediate Post-vaccination Surveillance Period

Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination surveillance should be documented in the source document. Any AE that occurs during this period will be noted on the source document and recorded in the CRF, as follows:

- Any unsolicited systemic AE occurring during the first 30 minutes post-vaccination will be recorded on the CRF as immediate unsolicited systemic AE.
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded and analyzed as starting on the day of vaccination.
- Any SAE occurred during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in Section 10.

9.3.2.3.2 Reactogenicity (Solicited Reactions From Day 0 to Day 7 After Vaccination)

After vaccination, parents / guardians will be provided with a safety diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (i.e., D0 to D07) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event, if any (e.g., medication)

The action taken by the parent or guardian to treat any **solicited reactions** will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

4: Hospitalization (inpatient)

Parents / guardians will be contacted by telephone 8 days after vaccination to remind them to record all safety information in the diary card.

If the timing of the telephone call should fall on a weekend or a holiday, the call should be made on the next business day. If contact is not made on the designated day, study staff will continue calling until contact is made. Every telephone attempt and its outcome will be documented in the source document.

Table 9.1 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRF, together with the intensity scales.

Table 9.1: Solicited injection site reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Injection site tenderness	Injection site erythema	Injection site swelling
Diary card term	Tenderness	Redness	Swelling
Definition		Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3: Cries when injected limb is moved, or the movement of the injected limb is reduced	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

* For the subjective reaction of tenderness, parents / guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥ 38.0°C	Vomiting does not include spitting up	Inconsolable crying without a reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.5°C	Grade 1: 1 episode per 24 hours	Grade 1: < 1 hour	Grade 1: Sleepier than usual or less interested in surroundings	Grade 1: Eating less than normal	Grade 1: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C	Grade 2: 2–5 episodes per 24 hours	Grade 2: 1–3 hours	Grade 2: Not interested in surroundings or did not wake up for a feed / meal	Grade 2: Missed 1 or 2 feeds / meals completely	Grade 2: Requiring increased attention
	Grade 3: > 39.5°C	Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 3: > 3 hours	Grade 3: Sleeping most of the time or difficult to wake up	Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	Grade 3: Inconsolable

* For all reactions but fever, parents / guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Important notes for the accurate assessment of temperature:

Parents / guardians are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRF. The preferred route for this trial is rectal or axillary. Pre-vaccination temperature is also systematically collected by the Investigator in the source document. Tympanic thermometers must not be used.

9.3.2.3.3 Unsolicited Non-serious Adverse Events From Day 0 to Day 30 After Vaccination

In addition to recording solicited reactions, parents / guardians will be instructed to record any other medical events that may occur during the 30-day period after vaccination. Space will be provided in the diary card for this purpose.

For each unsolicited non-serious AE, the following information is to be recorded:

- Start and stop dates[a]
- Intensity of the event:
  - For measurable unsolicited non-serious AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9.1 and Table 9.2)
  - Other unsolicited non-serious AEs will be classified according to the following intensity scale:
    - Grade 1: No interference with activity
    - Grade 2: Some interference with activity
    - Grade 3: Significant; prevents daily activity
- Action taken for each AE, if any (e.g., medication)

The action taken by the subject / guardian to treat any **unsolicited AEs** will be classified in the CRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

[a] The stop date of all related AEs will be actively solicited. For other events, the investigator will provide the stop date when it becomes available. AEs for which no stop date was obtained during the course of the trial will be considered as ongoing at the end of the trial.

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

- Whether the AE led to discontinuation
- Whether the AE was related to vaccination (for unsolicited systemic AEs)

9.3.2.3.4 Serious Adverse Events

Information on SAEs will be collected and assessed throughout the trial, from inclusion until 30 days after vaccination.

Any SAE occurring at any time during the trial will be reported by the Investigator through the EDC system and according to the completion guidelines provided by the Sponsor. All information concerning the SAE is to be reported, either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). The Investigator will assess the causal relationship between the SAE and the investigational product as either "Not related" or "Related", as described in Section 10.4.

In case a subject experiences convulsion / seizure episode associated or not with fever, the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion" (48) and this event will be considered an SAE.

See Section 10 for further details on SAE reporting.

9.3.2.3.5 Adverse Events of Special Interest

Not applicable.

9.3.2.3.6 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and vaccination as either not related or related, based on the following definitions[a]:

0: Not related – The AE is clearly / most probably caused by other etiologies such as subject's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable)

1: Related – There is a "reasonable possibility" that the AE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship

[a] ICH Guidelines, Clinical Safety Data Management E2A

Note: By convention, all injection site AEs (solicited and unsolicited) and all solicited systemic reactions are considered to be related to vaccination and referred to as reactions, and therefore do not require the Investigator's opinion on relatedness.

AEs likely to be related to the product, whether serious or not, that persist at the end of the trial will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event.

9.3.3 Biological Safety Assessment Methods (Sites in the Russian Federation Only)

Biological safety tests (biochemistry and hematology) will be performed at the study center's laboratory. Biological endpoints will be assessed on samples taken at Visit 0 and Visit 2.

Normal ranges for each value will be provided by the study center. In case of out-of-range values, they may be re-checked upon the Investigator's judgment.

All laboratory tests will be sampled and analyzed locally. Results of lab tests will be assessed by the Investigator. Abnormal laboratory tests are to be recorded as medical history (Visit 0) or as AEs (Visit 2) only if they are considered clinically significant, i.e.:

- symptomatic
- requiring corrective treatment or additional consultation by relevant specialist
- leading to study vaccine discontinuation or postponing vaccination
- meet SAE criteria

9.3.3.1 Complete Blood Count

- Hemoglobin
- Red blood cell indices
- Total white blood cells
- Neutrophil granulocytes
- Lymphocytes
- Monocytes
- Eosinophil granulocytes
- Basophil granulocytes
- Platelet

9.3.3.2 Blood Chemistry

- Serum glucose
- Urea
- Bilirubin total
- Direct bilirubin

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Lactate dehydrogenase (LDH)
- Alkaline phosphatase
- Prothrombin

9.3.3.3 Urinalysis

- Urine specific gravity
- Protein
- Glucose
- Erythrocytes
- Leukocytes

9.3.4 Efficacy

No clinical efficacy data will be obtained in the trial.

10 Reporting of Serious Adverse Events

In order to comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship, and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational product(s). It is the responsibility of the Investigator to request all necessary documentation (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed into the electronic Serious Adverse Event (eSAE) Form.

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the trial or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The SAE form must be signed by a licensed physician (M.D. or D.O.) for whom the task is listed on the Study Task Delegation and Signature List after each update to the Form.

The Investigator must complete the "eSAE Form" in the EDC application. After validation, an e-mail alert will automatically be sent to the GPV mailbox, the CRA and the CTL. This message will include the country, the study code, the subject number, whether the report is initial or a follow-up, the diagnosis and / or symptoms, the seriousness criteria, the relationship, if related and the outcome, if fatal.

If the EDC system is unavailable, the site must notify the Sponsor using the paper version of the SAE Reporting Form, as follows:

The Investigator must complete the SAE Reporting Form, check off the "Initial Reporting Form" box, and send it to the Sponsor by one of the following means (preferably by fax or e-mail):

- By fax, to the following number: [redacted]
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted] (see the Operating Guidelines for directions on how to send a password protected email).
- By express mail, to the following address: Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global PharmacoVigilance
  Mail Drop: 45D38
  Discovery Drive
  Swiftwater, PA 18370

When the system becomes available, the Investigator must transcribe the information from the paper version of the eSAE Form into the EDC system.

If there is need for urgent consultation, the Investigator is to contact the RMO. If the RMO cannot be reached, the Investigator may contact the Call Center as described in Section 5.3.

10.2 Follow-up Reporting by the Investigator

The eSAE Form completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (e.g., outcome, precise description of medical history, results of the investigation). After validation, an e-mail alert will be sent automatically to the GPV Department and to the CRA. All relevant information must be included directly in the eSAE form. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by the GPV Department.

The anonymity of the subject must always be respected when forwarding this information.

10.3 Reporting of SAEs Occurring After a Subject Has Completed the Study

Any SAE that occurs after a subject has completed the study but that is likely to be related to the product or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.4 Assessment of Causality

The causal relationship between the SAE and the product will first be evaluated by the Investigator, using the following definitions:

0 - Not related: The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between

vaccination and the onset of the SAE is incompatible with a causal relationship; or the SAE started before the vaccination(s) (screening phase, if applicable).

1 - Related: There is a "reasonable possibility" that the SAE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship.

(ICH Guidelines, Clinical Safety Data Management E2A)

Following this, the Sponsor's Product Safety Officer (PSO) will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The decision to modify or discontinue the trial may be made after mutual agreement between the Sponsor and the Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

The Sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory requirements. Reporting to the health authorities will be according to the Sponsor's standard operating procedures.

The Sponsor's RMO, [redacted] will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the trial protocol.

11 Data Collection and Management

11.1 Data Collection and CRF Completion

Individual safety diary cards, specifically designed for this trial by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.3.2.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Parents or guardians will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct parents / guardians on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the parents / guardians to collect the information recorded in the diary card, and will attempt to clarify anything that is incomplete or unclear. All clinical trial information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRF. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The CRF has been designed specifically for this trial under the responsibility of the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the CRFs, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to all site staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion guidelines will be provided to assist with data entry during the course of the trial.

Upon completion of training, each user requiring access to the EDC system will be issued a unique username and password. In the event of a change in trial personnel, each newly assigned individual will receive a unique username and password; the username and password of a previous user may not be reissued. If any trial personnel leave the study, the Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be initiated in the EDC system at the time of the first data entry in order to track all modifications and to ensure database integrity.

The Investigator is responsible for the timeliness, completeness, and accuracy of the information in the CRFs; must provide explanations for all missing information; and must sign the CRF using an e-signature.

11.2 Data Management

Management of Clinical Data

Data generated during the trial will be managed following two different processes:

- Clinical data, defined as all data reported in the CRF, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.
- Data pertaining to SAEs, which are reported by the Investigator on the eSAE Forms or SAE Reporting Forms, will be handled by the Sponsor's GPV Department.

During the trial, clinical data reported in the CRFs will be integrated into the clinical database under the responsibility of the Sanofi Pasteur CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and / or consistency checks will be systematically applied in order to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the trial. Any questions pertaining to the reported clinical data will be submitted to the investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

The validation of the immunogenicity data will be performed at the laboratory level following the laboratory's procedures. Information from the laboratory will be checked for consistency before integration into the clinical database.

After integration of all corrections in the complete set of data, and after the SAE information available from CDM and the GPV Department has been reconciled, the database will be released for statistical analysis.

SAE Data Management

During the trial, data pertaining to SAEs reported on eSAE Forms will be integrated into the Sponsor's centralized GPV database.

Upon receipt of an eSAE Form, the data will be entered into the GPV database after a duplicate check. Each SAE case will be assigned a case identification number. Each case will be entered in the GPV database and assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. Assessment of related cases will be done in collaboration with the PSO and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

The information pertaining to SAEs in the GPV database will be reconciled with that in the clinical database.

11.3 Data Review

A review of the data is anticipated through the data review process led by Data Management before database lock. The safety of the investigational product will be continuously monitored by the Sponsor. Periodic safety data review will be performed by the Sponsor's Safety Management Team (SMT).

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

Clinical data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor. A statistical analysis plan (SAP) will be written and peer reviewed before any analyses. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

In general, categorical variables will be summarized and presented by frequency counts, percentages, and confidence intervals (CIs). The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages (49). For GMTs or geometric mean concentrations (GMCs), 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

12.1.1 Hypotheses and Statistical Methods for Primary Objective

12.1.1.1 Hypotheses

No hypotheses will be tested. Descriptive statistics will be presented.

12.1.1.2 Statistical Methods

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

- GMT and 95% CI
- Titer distribution and reverse cumulative distribution curves (RCDCs)
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse[a]

12.1.2 Hypotheses and Statistical Methods for Secondary Objective

12.1.2.1 Hypotheses

No hypotheses will be tested. Descriptive statistics will be presented.

12.1.2.2 Statistical Methods

The analyses on the concomitant vaccines will include GMTs and titer distribution or GMCs, and RCDCs, as well as % 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 (serostatus cutoff: 120 mIU/mL)
    - anti-mumps Ab concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
    - anti-rubella Ab concentrations (serostatus cutoff: 10 IU/mL)
- Anti-varicella Ab concentrations before and 30 days (+14 days) after vaccination with V vaccine (serostatus cutoff: 1.25 gpELISA Ab units/mL)

[a] 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 ≥ 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.

- 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 ≥ 0.1 and 1.0 IU/mL
    - anti-pertussis (PT, and FHA) Ab concentrations and pertussis vaccine response[a]
- 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 ≥ 0.1 and 1.0 IU/mL
    - anti-PRP Ab concentrations and ≥ 0.15 and 1.0 µg/mL
    - anti-poliovirus types 1, 2, and 3 Ab titers ≥ 1:8
    - anti-hepatitis B surface antigen Ab concentrations ≥ 10 and 100 mIU/mL
- Anti-pneumococcal Ab concentrations ≥ 0.35 µg/mL and 1.0 µg/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

12.1.3 Statistical Methods for Observational Objectives

Immunogenicity

The immunogenicity descriptive analyses will at least include the following:

Ab titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine:

- GMT and 95% CI
- Titer distribution and RCDCs
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
- Percentage of subjects with titer ≥4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with rSBA vaccine seroresponse[b]

Safety

Safety results will be described for subjects in all study groups. The main parameters for the safety endpoints will be described by 95% CIs (based on the Clopper-Pearson method).

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[a] Pertussis vaccine response:

- If the pre-booster vaccination concentration is < 4 x LLOQ, then the post-booster vaccination concentration is ≥ 4 x the pre-booster concentration;
- If the pre-booster vaccination concentration is ≥ 4 x LLOQ, then the post-booster vaccination concentration is ≥ 2 x the pre-booster concentration.

[b] rSBA vaccine seroresponse is defined as a post-vaccination titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8, or a post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8.

12.2 Analysis Sets

Three analysis sets will be used: the Full Analysis Set (FAS), the PPAS, and the Safety Analysis Set (SafAS).

12.2.1 Full Analysis Set

The FAS is defined as the subset of subjects who received at least one dose of the study vaccine(s) and had a valid post-vaccination blood sample result. All subjects will be analyzed according to the treatment group to which they were randomized.

12.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received at least one dose of the study vaccine(s) and have any safety data available. All subjects will have their safety analyzed according to the vaccine(s) they actually received. If the vaccine(s) received by a subject does not correspond to any study group, the subject will be excluded from the SafAS. The corresponding safety data will be presented in separate listings.

12.2.3 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not provide the post-dose serology sample at Visit 2 in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy / medication / vaccine
- Subject’s serology sample at Visit 2 did not produce a valid test result
- Subject had other protocol violation that affected the subject’s immune response, as determined by the clinical team prior to locking the database

12.2.4 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

All safety analyses will be performed on the SafAS. Subjects will be analyzed according to the vaccine(s) they actually received.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done. Missing safety data will not be replaced. All subjects with safety data and all safety data recorded in the CRFs will be included in the safety analyses. No search for outliers will be performed during the statistical analysis.

12.3.2 Immunogenicity

Missing immunogenicity data will not be imputed. All subjects in the appropriate population with valid immunogenicity data will be included in the immunogenicity analyses. No test or search for outliers will be performed.

In order to appropriately manage extreme values (undetectable responses < LLOQ and ≥ upper limit of quantitation [ULOQ]), the following computational rule is applied to the values provided in the clinical database for each blood sample drawn for analysis purposes:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the computed value ULOQ

The derived endpoint of fold-rise is computed as follows:

- Calculate the fold-rise of values as the ratio of post-baseline computed value divided by baseline computed value

If baseline or post baseline value is missing, then the seroconversion is missing.

12.4 Interim / Preliminary Analysis

No interim or preliminary analyses are planned.

12.5 Determination of Sample Size and Power Calculation

[redacted]

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Trial / Good Clinical Practice

The conduct of this trial will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and / or national regulations and directives.

13.2 Source Data and Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets. The purpose of trial source documents is to document the existence of subjects and to substantiate the integrity of the trial data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

For missing or discrepant data on a diary card, the study coordinator will obtain verbal clarification from the subject, enter the response into the "investigator's comment" page of the diary card, and transfer the information to the CRF.

The subject pre-screening log should list all individuals contacted by the Investigators to participate in the trial, regardless of the outcome.

The Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any later changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

13.3 Confidentiality of Data and Access to Subject Records

Prior to initiation of the trial, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur.

Sanofi Pasteur personnel (or designates), the IECs / IRBs, and regulatory agencies, including the US Food and Drug Administration (FDA), the Korean Ministry of Food and Drug Safety (MFDS), the Mexican Health Authority (Federal Commission for Protection against Sanitary Risks [COFEPRIS]), the Ministry of Health of the Russian Federation, and the Thai Food and Drug Administration require direct access to all study records, and will treat these documents in a confidential manner.

[a] Unless the electronic medical records are managed by validated computerized systems that are compliant with US 21 CFR Part 11, in which case they are acceptable on their own.

In the event a subject's medical records are not at the investigational site, it is the responsibility of the investigator to obtain those records if needed.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the trial (i.e., before the inclusion of the first subject in the first center) the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the trial protocol and the detailed trial procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRF completion, and the handling of samples and products. The Sponsor's staff or a representative will ensure and document that all material to be used during the trial has been received at the site; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the trial, GCP and regulatory requirements, and the Sponsor's procedures. Specific training sessions for the study investigator team and the CRAs on these topics may be performed as necessary, and should be documented.

The following instruction manuals will be provided: the CRF Completion Guidelines for entering data into the CRF, and the Operating Guidelines for detailed trial procedures such as the product management and sample-handling procedures.

After the start of the trial, the Sponsor's staff or a representative will be in regular contact with the investigational team through telephone calls and regular follow-up visits. The Investigator or delegate must be available for these visits, and must allow the Sponsor/delegate staff direct access to subject medical files and CRFs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the trial progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRFs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRF, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the trial, a close-out visit will be performed to ensure that:

- The center has all the documents necessary for archiving
- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's Clinical and Medical Quality Operations department (C&MQO) or by independent auditors to verify that the trial has been conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. The Investigator must allow direct access to trial documents during these inspections and audits.

13.4.3 Archiving

The Investigator must keep all trial documents after the completion or discontinuation of the trial, whatever the nature of the investigational center (private practice, hospital, or institution), for as long as required by applicable laws and regulations. In the absence of any applicable laws or regulations, trial documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). In no event, should study personnel destroy or permit the destruction of any trial documents upon less than 90 days advance written notification to the Sponsor. In addition, trial documents should continue to be stored, at Sponsor's sole expense, in the event that the Sponsor requests in writing that such storage continues for a period of time that exceeds that required by any applicable law or regulation or the CTA. The Investigator will inform Sanofi Pasteur of any address change or if they will no longer be able to house the trial documents.

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the trial, including certificates attesting that satisfactory audit and inspection procedures have been carried out, will be kept by the Sponsor in the Trial Master File (TMF). Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

A CTA will be signed by all the parties involved in the trial's performance, if relevant. The Sponsor has an insurance policy to cover any liabilities that may arise from use of the product and / or the study protocol.

13.6 Stipends for Participation

The subject's parent / guardian may be provided with a stipend or transportation aid according to local practice and regulations to compensate for the time and/or travel required for study visits and procedures.

13.7 Publication Policy

Data derived from this trial are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the trial must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the trial, any participating center may publish or otherwise use its own data provided that any publication of data from the trial gives recognition

to the trial group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

Sanofi Pasteur must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this trial at least 90 days prior to submission for publication / presentation. Any information identified by Sanofi Pasteur as confidential must be deleted prior to submission, it being understood that the results of this trial are not to be considered confidential.

Sanofi Pasteur's review can be expedited to meet publication guidelines.

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