NCT03630705

Safety and Immunogenicity of a 3-Dose Schedule of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers

Phase III, open-label, randomized, parallel-group, active-controlled, multi-center study to describe the immunogenicity and safety of a 3-dose immunization schedule of MenACYW conjugate vaccine or a 4-dose immunization schedule of a licensed quadrivalent meningococcal conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico and to describe the immunogenicity and safety of a 3-dose immunization schedule of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation.

Clinical Study Protocol, Amendment 3

Health Authority File Numbers:	The Russian Federation: 4119206-20-1/IIII The United Mexican States (Mexico): 183300410A0144/2018
WHO Universal Trial Number (UTN):	U1111-1183-6409
Study Code:	MET33
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, Pennsylvania (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 (IM)
Indication For This Study:	MenACYW conjugate vaccine administered to healthy infants and toddlers at 2 to 12-15 months of age
Manufacturer:	Same as Sponsor
Coordinating Investigator:	[redacted]

Principal Investigators: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

Global Safety Officer

Clinical Trial Manager:

Version and Date of the Protocol: Version 5.0 dated 23 June 2021

History of Protocol Versions

Previous Versions	Date	Comments
1.0	12 March 2018	First version used in the study
2.0	04 October 2019	Protocol Amendment 1
3.0	04 March 2020	Was to be Protocol Amendment 2 – Not published. Approved protocol version 3.0 underwent a minor edit in Section 6.0 numbering and was reapproved and published as version 4.0
4.0	10 March 2020	Protocol Amendment 2

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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:	Safety and Immunogenicity of a 3-Dose Schedule of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers
Development Phase:	Phase III
Coordinating Investigator:	[redacted]
Principal Investigators:	[redacted]
Trial Centers:	This will be a multi-center, multinational study conducted at approximately 14 sites: 3 sites in Mexico and 11 sites in the Russian Federation. Investigators and sites are listed in the "List of Investigators and Trial Centers, Involved in the Trial" document.
Planned Trial Period:	4Q 2018 to 1Q 2022
Trial Design and Methodology:	This is a Phase III, open-label, randomized, parallel-group, active-controlled, multi-center study to describe the immunogenicity and safety of a 3-dose immunization schedule of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines (Prevnar 13®, Pentaxim®, ENGERIX-B®, and MMR) or routine pediatric vaccines administered alone in healthy infants and toddlers aged 2 to 12 months in the Russian Federation, and a 3-dose immunization schedule of MenACYW conjugate vaccine or a 4-dose immunization schedule of Menveo® (Meningococcal [Groups A, C, Y and W-135] Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine) when administered concomitantly with routine pediatric vaccines (Prevnar 13®, Hexacima®, RotaTeq®, and M-M-R®II) in healthy infants and toddlers aged 2 to 12 months in Mexico. A total of 525 subjects will be enrolled. Approximately 300 healthy, meningococcal-vaccine naïve infants aged 2 months will be randomized in a 2:1 ratio in Mexico, and 225 healthy, meningococcal-vaccine naïve infants aged 2 months will be randomized in a 2:1 ratio in the Russian Federation into the following groups: ***Mexico*** Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age Group 2 Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age

The Russian Federation

Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age

Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age

All subjects in Groups 1 and 2 will receive either MenACYW conjugate vaccine or Menveo® concomitantly with the following routine pediatric vaccines in accordance with available official recommendations ***in Mexico***:

- Prevnar 13® (pneumococcal 13-valent conjugate vaccine [PCV13]) at 2, 4, 6, and 12 months of age*
- Hexacima® (DTaP-IPV-HB-Hib) at 2, 4, 6, and 12 months of age
- RotaTeq® (pentavalent rotavirus vaccine [RV5]) at 2, 4, and 6 months of age
- M-M-R®II (measles, mumps, rubella [MMR] vaccine) at 12 months of age

All subjects in Group 3 will receive MenACYW conjugate vaccine concomitantly with the following routine pediatric vaccines; all subjects in Group 4 will receive the following routine pediatric vaccines alone in accordance with the National Immunization Calendar (NIC) recommendations in ***the Russian Federation***:

- Prevnar 13® (pneumococcal 13-valent conjugate vaccine [PCV13]) at 2 and 4.5 months of age*
- Pentaxim® (DTaP-Hib-IPV) at 3, 4.5, and 6 months of age†
- ENGERIX-B® (hepatitis B vaccine) at 6 months of age‡
- MMR vaccine at 12 months of age§

* No immunogenicity endpoints will be measured for this vaccine in the Russian Federation. The PCV13 routine vaccine recommended at 15 months of age in the Russian Federation is considered as out of scope for this study and will not be provided by the Sponsor but procured by the sites as per their standard practices.

† The 4th dose of Pentaxim®, which is administered at 18 months of age, is considered out of the scope of the study and it will not be provided by the Sponsor but procured by the sites as per their standard practices. Subjects will be instructed to receive it for completion of the Pentavalent series as per the NIC of the Russian Federation recommendation.

‡ In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead. Further details will be provided in the Clinical Study Report (CSR).

§ In the event M-M-R®II combination vaccine cannot be supplied or is unavailable in the Russian Federation, locally licensed MMR or MM+R vaccines will be administered instead. Further details will be provided in the CSR.

Note about Screening / Enrollment Visits
Visit 0 = Screening visit for subjects in the Russian Federation only
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.

Blood sampling

Subjects will provide blood samples for immunogenicity assessments according to the following schedules.

Mexico

Groups 1 and 2:

- A blood sample at baseline (before the first study vaccination at Visit 1)
- A blood sample 30 days (+14 days) after the 2nd dose of MenACYW conjugate vaccine or 3rd dose of Menveo® (Visit 4)
- A blood sample 30 days (+14 days) after the 3rd dose of MenACYW conjugate vaccine or 4th dose of Menveo® (Visit 6)

Russian Federation

Group 3:

- A blood sample at baseline (before the first study vaccination, at Visit 0)
- A blood sample 30 days (+14 days) after the 2nd dose of MenACYW conjugate vaccine (Visit 5)
- A blood sample 30 days (+14 days) after the 3rd dose of MenACYW conjugate vaccine (Visit 7)

Group 4:

- A blood sample at baseline (before the first study vaccination, at Visit 0)
- A blood sample 30 days (+14 days) after the 1st dose of ENGERIX B® and 3rd dose of Pentaxim® vaccines (Visit 5)
- A blood sample 30 days (+14 days) after the 1st dose of MMR vaccine (Visit 7)

Additional blood sampling – for the Russian Federation only

Subjects enrolled at sites in the Russian Federation will also provide additional blood sample (depending on local laboratory needs) for complete blood count (CBC) and blood chemistry testing at Visit 0 (Screening visit) and at Visit 7 in accordance with local regulations.

Total blood volume collected will be approximately 6 mL per blood draw at Visit 0, Visit 5, and Visit 7.

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 and Visit 7. In this case, the blood sample volume collected at Visit 0 and Visit 7 will be 4 mL.

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 7 per Health Authority request and in accordance with local regulations.

Upon completion of all study procedures and termination from the trial, study participants should receive the remainder of the recommended toddler vaccines from their health care provider, according to the respective NIC for each country.

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: In this document, "days" refers to calendar days.

Collection of Safety Data

All subjects will be followed for safety from Visit 1 to the last study visit.

- 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 (eCRF). • The subject's parent / guardian will record information in a diary card about solicited injection-site reactions and solicited systemic reactions from D0 to D07 after each vaccination and unsolicited AEs will be recorded from D0 after each vaccination until the subject returns for the next study visit. • Serious adverse events (SAEs, including adverse events of special interest [AESIs]) will be recorded in a diary card throughout the study. The subject's parent / guardian will be asked to notify the site immediately about any potential SAEs at any time during the trial. • A member of the study staff will contact the subject's parent / guardian by telephone 8 days (+2 days) after each vaccination visit to identify the occurrence of any SAE (including AESIs) not yet reported and to remind them to complete the diary card after each vaccination visit and to bring it back to the next study visit. • The completed diary cards will be collected and reviewed with the subject's parent / guardian at subsequent visits. • A member of the study staff will contact the subject's parent / guardian by telephone 14 days (+2 days) before the first study visit of the subject's second year of life to identify the occurrence of any SAE not yet reported and to remind them to complete the diary card and to bring it back to the next study visit so it can be reviewed at the study site. *For the Russian Federation only:* In accordance with local practice of conduct of clinical trials in Russian Federation, in addition to the immunogenicity assessment of the study vaccine, the blood of subjects enrolled at sites in the Russian Federation will also be tested for 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 7 (30 days [+14 days] after the 3rd dose of MenACYW conjugate vaccine [Group 3] or the 1st dose of MMR vaccine [Group 4]). The additional biological analyses have been implemented for subjects enrolled at sites in the Russian Federation per local practices of conduct of clinical trials only and were not implemented to address any concern of the Sponsor regarding safety issues. Clinical laboratory evaluations of MenACYW conjugate vaccine were performed in the Phase I studies (MET28 and MET32) with no findings considered to be of clinical relevance. Throughout the clinical development, no concerns in terms of abnormal blood count or blood chemistry parameters reported as AEs have been observed. The same type of biological analysis was performed in the frame of another MenACYW phase III study in toddlers in Russia (MET57), no abnormalities in biological parameters were identified.
Interruption of the Study:	The study may be discontinued if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in the countries where the study is taking place. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subjects' parents/guardians and should assure appropriate subject therapy and/or follow-up. There will be an internal team at the level of the Sponsor (Safety Management Team

	[SMT]), which will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The SMT is empowered to recommend a pause in both recruitment and / or further vaccination while it investigates any potential signal or concern.
Primary Objectives:	1) To describe the vaccine seroprotection (antibody titer ≥1:8) to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine or Menveo® measured by serum bactericidal assay using human complement (hSBA), for Groups 1 and 2 when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico 2) To describe the vaccine seroprotection (antibody titer ≥1:8) to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by hSBA, for Group 3, when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation
Primary Endpoints:	1) Meningococcal serogroups A, C, Y, and W antibody titers ≥1:8 measured by hSBA, assessed at 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine or Menveo® in Mexico (Group 1 and Group 2) 2) Meningococcal serogroups A, C, Y, and W antibody titers ≥1:8 measured by hSBA assessed at 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine in the Russian Federation (Group 3)
Secondary Objectives:	1) To describe the hSBA vaccine seroresponse to the antigens (meningococcal serogroups A, C, Y, and W) for Groups 1 and 2, 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®), when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico 2) To describe the hSBA vaccine seroresponse to the antigens (meningococcal serogroups A, C, Y, and W) for Group 3, 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine), when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation 3) To describe the immunogenicity profile of routine pediatric vaccines when administered concomitantly with MenACYW conjugate vaccine (Groups 1 and 3) or Menveo® (Group 2); or when administered alone (Group 4) 4) To describe the hSBA antibody responses against meningococcal serogroups A, C, Y, and W when MenACYW conjugate vaccine and Menveo® are administered concomitantly with routine pediatric vaccines in Mexico and the Russian Federation (Groups 1, 2 and 3). 5) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine and Menveo®, measured by serum bactericidal assay using baby rabbit complement (rSBA) before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®), when administered concomitantly with routine pediatric vaccines in a subset of subjects (100 subjects in Group 1, and 50 subjects in Group 2) in Mexico 6) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine), when administered concomitantly with routine pediatric vaccines in a subset of subjects (100 subjects in Group 3) in the Russian Federation

	7) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine and Menveo® measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life, when administered concomitantly with routine pediatric vaccines in a subset of subjects (100 subjects in Group 1, and 50 subjects in Group 2) in Mexico 8) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life, when administered concomitantly with routine pediatric vaccines in a subset of subjects (100 subjects in Group 3) in the Russian Federation
Secondary Endpoints:	1) Meningococcal serogroups A, C, Y, and W antibody titers measured by hSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine or Menveo® (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®) in Mexico (Group 1 and Group 2) (vaccine seroresponse*) *hSBA vaccine seroresponse for serogroups A, C, W, and Y 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 ≥ 4-fold greater than the pre-vaccination titer. 2) Meningococcal serogroups A, C, Y, and W antibody titers measured by hSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine (Dose 2 of MenACYW conjugate vaccine) in the Russian Federation (Group 3) (vaccine seroresponse) 3) The following serological endpoints will be described for Mexico (Groups 1 and 2): • Day 0 (before the first vaccinations with Hexacima® and RotaTeq®): o Anti-pertussis antibody concentrations (PT and FHA) o Anti-rotavirus serum immunoglobulin (Ig) A antibody concentrations • 30 days after the 6-months vaccinations with Prevnar 13® and RotaTeq®: o Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F o Anti-pneumococcal antibody concentrations (PCV13) ≥ 0.35 µg/mL and 1.0 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F o Anti-rotavirus serum IgA antibody concentrations o Anti-rotavirus serum IgA antibody concentrations with ≥ 3-fold and ≥4-fold rise over baseline • 30 days after the 12-months vaccinations with M-M-R®II, Prevnar 13®, and Hexacima®: o Antibody concentrations/titers for all antigens o Anti-pneumococcal antibody concentrations (PCV13) ≥ 0.35 µg / mL and 1.0 µg / mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F o Anti-measles antibody concentrations (serostatus cutoff 225 mIU / mL) o Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units / mL) o Anti-rubella antibody (serostatus cutoff: 10 IU / mL) o Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL o Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL o Anti-pertussis (PT and FHA) vaccine response†

- Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
- Anti-PRP antibody concentrations ≥ 0.15 µg / mL and 1.0 µg / mL
- Anti-HBs concentrations ≥ 10 mIU / mL and 100 mIU / mL

†Pertussis vaccine response definition:

- If the pre-vaccination concentration is >= 4 x LLOQ, then the post-vaccination concentration is >= pre- vaccination concentration
- If the pre-vaccination concentration is < 4 x LLOQ, then the post-booster vaccination concentration is >= 4 x LLOQ

The following serological endpoints will be described for the Russian Federation (Groups 3 and 4):

- Day 0 (before the first vaccination with Pentaxim®):
  - Anti-pertussis antibody concentrations (PT and FHA)
- 30 days after the 6-months vaccinations with Pentaxim® and ENGERIX-B®:
  - Antibody concentrations/titers for all antigens
  - Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-pertussis (PT and FHA) vaccine response
  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations and ≥ 0.15 µg / mL and 1.0 µg / mL
  - Anti-HBs concentrations ≥ 10 mIU / mL and 100 mIU / mL
- 30 days after the 12-months vaccination with MMR:
  - Antibody concentrations for measles, mumps and rubella
  - Anti-measles antibody concentrations (serostatus cutoff 225 mIU / mL)
  - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units / mL)
  - Anti-rubella antibody (serostatus cutoff: 10 IU / mL)

4) The following serological endpoints will be assessed for Groups 1, 2, and 3:

- D0 (before first vaccination) for Group 1, Group 2, and Group 3:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
- 30 days after the 6-month vaccination (after the 2nd dose) with MenACYW conjugate vaccine for Group 1 and Group 3:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and reverse cumulative distribution curves (RCDCs)
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
- 30 days after the 6-month vaccination (after the 3rd dose) with Menveo vaccine for Group 2:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and RCDCs
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
- 30 days after the 12-month vaccination (after the 3rd dose) with MenACYW conjugate vaccine for Group 1 and Group 3:

	○ hSBA meningococcal serogroups A, C, Y, and W antibody titers ○ Titer distribution and RCDCs ○ hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8 ○ hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination ○ hSBA meningococcal serogroups A, C, Y, and W vaccine seroresponse • 30 days after the 12-month vaccination (after the 4th dose) with Menveo vaccine for Group 2: ○ hSBA meningococcal serogroups A, C, Y, and W antibody titers ○ Titer distribution and RCDCs ○ hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8 ○ hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination ○ hSBA meningococcal serogroups A, C, Y, and W vaccine seroresponse 5) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine or Menveo® (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®) in Mexico (Group 1 and Group 2) 6) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine (Dose 2 of MenACYW conjugate vaccine) in the Russian Federation (Group 3) 7) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first study vaccination (Visit 1) and 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine or Menveo® in Mexico (Group 1 and Group 2) 8) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA before the first study vaccination (Visit 1) and 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine in the Russian Federation (Group 3)
Observational Objectives:	***Safety*** 1) To describe the safety profile of MenACYW conjugate vaccine and Menveo® when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico (Group 1 vs Group 2) 2) To describe the safety profile of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation (Group 3) 3) To describe the safety profile of routine pediatric vaccines in healthy infants and toddlers in Mexico (Groups 1 and 2) and the Russian Federation (Groups 3 and 4)
Observational Endpoints	***Safety*** The following endpoints will be used for all subjects for the evaluation of safety: • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination • Occurrence, time of 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 from D0 to D07 after each vaccination • Occurrence, time of 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 from D0 to D07 after each vaccination • Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination • Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the trial from D0 to the last study visit
Planned Sample Size:	A total of 525 subjects are planned to be enrolled (300 subjects from Mexico and 225 subjects from the Russian Federation), into the following groups: ***Mexico*** Group 1 (MenACYW conjugate vaccine + routine pediatric vaccines): n=200 Group 2 (Menveo® + routine pediatric vaccines): n=100 ***The Russian Federation*** Group 3 (MenACYW conjugate vaccine + routine pediatric vaccines): n=150 Group 4 (Routine pediatric vaccines): n=75
Schedule of Study Procedures:	***Vaccination*** Subjects will receive MenACYW conjugate vaccine or Menveo® and routine pediatric vaccinations (Groups 1 and 2), or MenACYW conjugate vaccine and routine pediatric vaccinations (Group 3), or routine pediatric vaccinations administered alone (Group 4), according to the following schedules: ***Mexico*** Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age ***The Russian Federation*** Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age ***S1 : Schedule of vaccination—Mexico Groups 1 and 2***

Visit	1	2	3	4	5	6
Age	2 months	4 months	6 months	7 months	12 months*	13 months
M-M-R®II	--	--	--	--	X	--
Prevnar 13®	X	X	X	--	X	--
Hexacima®*	X	X	X	--	X	--
RotaTeq®	X	X	X	--	--	--

*Per the current National Immunization Program (NIP) and Health Authority recommendations in Mexico, the varicella vaccine is administered at or after 12 months of age; it is not administered within the scope of the study. However, VARIVAX® vaccine will be provided by the Sponsor as a benefit vaccine as per standard practices and the current recommendations of the NIP in Mexico. The study personnel / Investigator will be responsible for administering this vaccine at V6 after the last blood sample (BL0003) of the study. No endpoints will be measured for this vaccine, even if it is administered at V6 of the study.

S2: Schedule of vaccination—the Russian Federation Groups 3 and 4

Visit	1	2	3	4	5	6	7
Age (months)	**2**	**3**	**4.5**	**6**	**7**	**12**	**13**
MMR*	--	--	--	--	--	X	
Prevnar 13®†	X	--	X	--	--	--	
Pentaxim®‡	--	X	X	X	--	--	
ENGERIX--B®§	--	--	--	X	--	--	

*In the event M-M-R®II combination vaccine cannot be supplied or is unavailable in the Russian Federation, locally licensed MMR or MM+R vaccines will be administered instead. Further details will be provided in the CSR.

† No immunogenicity endpoints will be measured for this vaccine in the Russian Federation. The PCV13 routine vaccine recommended at 15 months of age in the Russian Federation is considered as out of scope for this study and will not be provided by the Sponsor but procured by the sites as per their standard practices.

‡The 4th dose of Pentaxim®, which is administered at 18 months of age, is considered out of scope for this study and will not be provided by the Sponsor but procured by the sites as per their standard practices. Subjects will be instructed to receive it for completion of the Pentavalent series as per the NIC of the Russian Federation recommendation.

§In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead. Further details will be provided in the CSR.

For the Russian Federation only:

Any clinically significant abnormal results of CBC, blood chemistry, or urinalysis will be reported as medical history (for Visit 0 results) or as AEs (for all subsequent visits). 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, 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 of vaccination
- Meet SAE criteria

Duration of Participation in the Trial:	The duration of each subject's participation will be approximately 11 months.
Investigational Product:	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA).
Form:	Liquid Solution

Composition:	Each 0.5 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 55 µg* *Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation.
Route:	Intramuscular (IM)
Batch Number:	TBD
Control Product (Mexico only):	**Menveo®**: Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine (GSK Vaccines, Srl, Bellaria-Rosia 53018, Sovicille (SI), Italy)
Form	Lyophilized powder and liquid components are combined to produce a solution
Composition	Each 0.5 mL dose of vaccine contain the following active ingredients: MenA oligosaccharide.....10 µg MenC oligosaccharide.....5 µg MenY oligosaccharide.....5 µg MenW-135 oligosaccharide .....5 µg CRM_{197} protein.....32.7 to 64.1 µg Other ingredients per 0.5 mL dose: residual formaldehyde < 0.30 µg.
Route	IM
Batch Number:	TBD
Other Product 1:	**M-M-R®II** (Measles, Mumps, and Rubella Virus Vaccine Live) (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)
Form:	Lyophilized live virus vaccine
Composition:	Each 0.5 mL dose contains: Live attenuated virus: Measles virus (derived from Ender's Edmonston strain) propagated in chick embryo cell culture not less than 1000 $TCID_{50}$* Mumps virus (Jeryl Lynn™ [B level] strain) propagated in chick embryo cell culture not less than 12,500 $TCID_{50}$* Rubella virus (Wistar RA 27/3 strain) propagated in WI-38 human diploid lung fibroblasts not less than 1000 $TCID_{50}$* *$TCID_{50}$ = tissue culture infectious doses 50% Each 0.5 ml dose is calculated to contain sorbitol (14.5 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.
Route:	Subcutaneous (SC)
Batch Number:	TBD
Other Product 2:	**Prevnar 13®:** Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Pfizer Inc., Philadelphia, PA, USA)

Composition	Each 0.5 mL dose of the vaccine is formulated to contain: *Streptococcus pneumoniae* serotypes 1, 3, 4.5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F 23F saccharides .....approximately 2.2 µg (of each) 6B saccharides..... 4.4 µg Succinate buffer .....295 µg Aluminum as aluminum phosphate adjuvant .....125 µg Excipients: CRM_{197} carrier protein 34 µg Polysorbate 80 100 µg
Form	Suspension for injection
Route	IM
Batch Number	TBD
Other Product 3:	**Hexacima® (**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, Lyon, 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:	TBD
Other Product 4:	**Pentaxim®:** (Diphtheria, Tetanus, Pertussis (Acellular, Component) Poliomyelitis (inactivated) Vaccine, (Adsorbed) and *Haemophilus influenza* type b Conjugate Vaccine (Sanofi Pasteur S.A., France
Form	Powder and suspension for injection

Composition	Each 0.5 mL dose contains, after reconstitution: Diphtheria Toxoid ..... ≥ 30 IU Tetanus toxoid ..... ≥ 40 IU *Bordetella pertussis* antigens: Toxoid (PT) ..... 25 µg Filamentous hemagglutinin (FHA) ..... 25µg Poliomyelitis virus: Type 1 ..... 40 D-antigen units (DU) Type 2 ..... 8 DU Type 3 ..... 32 DU Polysaccharide of *Haemophilus influenzae type b conjugated to tetanus protein* 10 µg Tetanus toxoid (PRP-T) 24 µg Excipients: Saccharose, trometamol, aluminium hydroxide. Hanks' medium without phenol red, acetic acid and / or sodium hydroxide for pH adjustment, formaldehyde, phenoxyethanol, water for injections.
Route	IM
Batch number	TBD
Other Product 5:	**ENGERIX-B®:** [Hepatitis B Vaccine (Recombinant)] (GlaxoSmithKline Biologicals 441 Rixensart, Belgium)
Form:	Suspension for injection
Composition:	Each 0.5-mL pediatric/adolescent dose contains 10 µg of hepatitis B surface antigen adsorbed on 0.25 mg aluminum as aluminum hydroxide. Excipients: Sodium chloride.....9 mg/mL Disodium phosphate dihydrate.....0.98 mg/mL Sodium dihydrogen phosphate dihydrate.....0.71 mg/mL
Form	Suspension for injection
Route	IM
Batch Number:	TBD
Other Product 6:	**RotaTeq®:** (Rotavirus Vaccine, Live, Oral, Pentavalent) (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)
Form	Oral Solution
Composition	Each 2 mL dose contains the following 5 live reassortant rotaviruses: G1 serotype .....2.2 x 10^6 infectious units G2 serotype .....2.8 x 10^6 infectious units G3 serotype .....2.2 x 10^6infectious units G4 serotype .....2.0 x 10^6infectious units P1A(8).....2.3 x 10^6infectious units The reassortants are suspended in a buffered stabilizer solution. Each 2 mL vaccine dose also contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum.

Route	Oral (PO)
Batch Number:	TBD
Screening Criteria	For Mexico, there are no screening criteria other than the inclusion and exclusion criteria. For the Russian Federation, in accordance with local practices for the conduct of clinical trials, 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 CBC and blood chemistry. These subjects will also provide a urine sample for urinalysis. The results of CBC and biochemistry laboratory tests as well as urine chemistry tests, performed for the subject in terms of routine practice, can be used, if the tests were done within 7 days before and in this case no additional samples should be taken. The 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) Infants 2 months of age (60 to 89 days of age) on the day of the first study visit.* 2) Born after a full-term pregnancy, with an estimated gestation age ≥ 37 weeks and a birth weight ≥ 2.5 kg. 3) Informed consent form has been signed and dated by the parent(s) or guardian(s), as required by local regulations.† 4) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures. 5) In good health as determined by medical history and physical assessment. 6) ***For the Russian Federation:*** The subject's parents are able to verbally report or provide written documentation that the subject's mother was hepatitis B antigen-negative during pregnancy with the subject. * "2 months" means from the 2nd month after birth to the day before the 3rd month after birth (2 months to 2 months 29 days); "60 days" means from the 60th day after birth to the day before the 90th day after birth (60 to 89 days). †In the Russian Federation, as per local regulations, only the subject's parent(s) are entitled to sign an informed consent form. 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 at the time of study enrollment or 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 preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks before and/or following any trial vaccination except for influenza vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccination. 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 (ie, meningitis polysaccharide or meningitis conjugate vaccine containing serogroups A, C, Y, or W; or meningococcal B serogroup-containing vaccine). 4) Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), poliovirus, rotavirus, *Streptococcus pneumoniae*, measles, mumps, rubella, and / or varicella.

	5) ***For Mexico:*** More than 1 previous dose of hepatitis B vaccine. 6) Receipt of immune globulins, blood or blood-derived products since birth. 7) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth. 8) Family history of congenital or hereditary immunodeficiency until the immune competence of the potential vaccine recipient is demonstrated. 9) Individuals with blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems. 10) Individuals with active tuberculosis. 11) History of any *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically. 12) History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and /or rotavirus infection / disease. 13) At high risk for meningococcal infection during the trial (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) 14) History of intussusception. 15) History of any neurologic disorders, including seizures (febrile and non-febrile) and progressive neurologic disorders. 16) History of Guillain-Barré syndrome. 17) Known systemic hypersensitivity to any of the vaccine components or to latex, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances, including neomycin, gelatin, and yeast. 18) Verbal report of thrombocytopenia contraindicating intramuscular vaccination in the Investigator's opinion. 19) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion. 20) Receipt of oral or injectable antibiotic therapy within 72 hours of the first blood draw. 21) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion. 22) Any condition which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives. 23) Moderate or severe acute illness/infection (according to Investigator 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. 24) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study. *For the Russian Federation, febrile illness is defined as temperature ≥ 37°C. A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
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 or Menveo® and for the antigens contained in the routine pediatric 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 exact binomial distribution (Clopper-Pearson method) for percentages. For geometric mean titers (GMTs) and geometric mean concentrations (GMCs), 95% CIs of point estimates will be calculated using normal approximation, assuming that they are log-normally distributed. ***Primary Objective*** Descriptive analyses on meningococcal serogroups A, C, Y, and W measured by hSBA for Groups 1, 2, and 3 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine or Menveo® will be computed on the following parameter: • Percentage of subjects with titer ≥ 1:8 and 95% CI The 95% CI will be computed using the exact binomial distribution (Clopper-Pearson method). ***Secondary Objectives*** Descriptive analyses on meningococcal serogroups A, C, Y, and W measured by hSBA, for Groups 1, 2, and 3, before the first vaccination, 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine or Menveo® (Dose 2 of MenACYW conjugate vaccine and Dose◦3 of Menveo®) and 30 days after the last vaccination in the second year of life will include but not limited to the following: • GMT and 95% CI • Titer distribution and 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-infant vaccination, and 95% CI • Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-12 month vaccination, and 95% CI • Percentage of subjects with hSBA vaccine seroresponse* and 95% CI *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. Descriptive analysis on meningococcal serogroups A, C, Y, and W measured by rSBA before the first vaccination, 30 days after the last vaccination of the infant series (Dose 2 of the MenACYW conjugate vaccine and Dose 3 of Menveo®), and 30 days after the last vaccination of the second year of life with MenACYW conjugate vaccine or Menveo® in a subset of subjects (100 subjects per group in Groups 1 and 3, and 50 subjects in Group 2) will include but not limited to the following parameters:

- 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* and 95% CI

*rSBA vaccine seroresponse is defined as:

- A post-vaccination rSBA titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8,
- A post-vaccination titer ≥ 4 times the pre-vaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8

The analyses on the concomitant vaccines will include GMT and titer distribution or GMC, and RCDC, as well as percentage of subjects with:

The Russian Federation:

- 30 days after vaccination with MMR vaccine at 12 months of age
  - Anti-measles antibody concentrations (serostatus cutoff 225 mIU/mL
  - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL).
  - Anti-Rubella antibody concentrations (serostatus cutoff: 10 IU/mL)
- Before the first vaccination with Pentaxim®
  - Anti-pertussis (PT and FHA) antibody concentrations
- 30 days after the last vaccination with Pentaxim® at 6 months of age
  - Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU/mL and 1.0 IU/mL
  - Anti-pertussis (PT and FHA) antibody concentrations (vaccine response)
  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations and ≥ 0.15 µg/mL and 1.0 µg/mL
- 30 days after vaccination with ENGERIX-B®† at 6 months of age
  - Anti-HBs antigen ≥ 10 mIU /mL and 100 mIU / mL

†In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead. Further details will be provided in the CSR.

Mexico:

- 30 days after vaccination with M-M-R®II at 12 months of age
  - Anti-measles antibody concentrations (serostatus cutoff: 225 mIU/mL)
  - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
  - Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)
- 30 days after vaccination with Prevnar 13® at 6 months of age and the last vaccination with Prevnar 13® at 12 months of age
  - Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and 1.0 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Before the first vaccination with Hexacima® vaccine:
  - Anti-pertussis (PT and FHA) antibody concentrations

	• 30 days after the last vaccination with Hexacima® vaccine at 12 months of age
	  • Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
	  • Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
	  • Anti-pertussis (PT and FHA) antibody concentrations vaccine response
	  • Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
	  • Anti-PRP antibody concentrations and ≥ 0.15 μg / mL and 1.0 μg / mL
	  • Anti-HBs antigen antibody concentrations ≥ 10 mIU / mL and 100 mIU / mL
	• Before the first vaccination with RotaTeq®
	  • Anti-rotavirus serum IgA antibody concentrations
	• 30 days after the last vaccination with RotaTeq®
	  • Anti-RV IgA ≥ 3-fold and ≥ 4-fold antibody titers rise from baseline
	Observational Objectives
	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).

	Sample Size Calculation The sample size of this study was chosen to provide immunogenicity and safety data; it is not intended for the purposes of hypothesis testing. No formal sample size calculations will be performed. Though there are no statistically powered hypotheses, the overall study cohort (n=525) will provide a probability of approximately 95% of observing any AE with a true incidence of 0.57%. The overall MenACYW conjugate vaccine cohort (n=350) will provide a probability of approximately 95% of observing any AE with a true incidence of 0.85%. In a treatment arm with n=200, there is a probability of approximately 95% of observing any AE with a true incidence of 1.5%. In a treatment arm with n=150, there is a probability of approximately 95% of observing any AE with a true incidence of 2%.

Table of Study Procedures (1/4)

Phase III Trial, Group 1 (Mexico): 6 Visits, 4 Vaccination Visits, 4 Telephone Calls, 3 Blood Samples, 11 Months Duration Per Subject for Subjects Randomized to Receive MenACYW Conjugate Vaccine

Visit / Telephone Call	**Visit 1**	**TC1***	**Visit 2**	**Visit 3**	**TC2***	**Visit 4**	**TC3†**	**Visit 5**	**TC4***	**Visit 6**
Approximate Subject Age	**2 months‡**	**-**	**4 months**	**6 months**	**-**	**7 months**	**-**	**12 months**	**-**	**13 months**
Trial timelines (days, months)	D0	V01 +8 days	V01 + 60 days	V02 + 60 days	V03 + 8 days	V03 + 30 days	V05 -14 days	V04 +5 months	V05 +8 days	V05 + 30 days
Time windows (days)	NA	+2 days	+14 days	+14 days	+2 days	+14 days	+2 days	+14 days	+2 days	+14 days
Informed consent form signed and dated	X									
Inclusion/exclusion criteria	X									
Collection of demographic data	X									
Medical history§ (including history of maternal immunization against tetanus)	X									
Physical examination and temperature	X**		X††	X††				X††		
Review of temporary contraindications for blood sampling (BL) ‡‡§§	X					X				X
BL (6 mL)	BL0001					BL0002				BL0003
Review of warnings and precautions and / or contraindications for vaccinations	X		X	X				X		
Review conditions for withdrawal***	X		X	X				X		
Contact IRT system for randomization / allocation of subject number / vaccine assignment	X									
Contact IRT system for vaccine dose number for all vaccines to be given			X	X				X		
Vaccination with MenACYW conjugate vaccine	**X**			**X**				**X**		
Prevnar 13® vaccination†††	**X**		**X**	**X**				**X**		

Visit / Telephone Call	Visit 1	TC1*	Visit 2	Visit 3	TC2*	Visit 4	TC3†	Visit 5	TC4*	Visit 6
Approximate Subject Age	**2 months‡**	**-**	**4 months**	**6 months**	**-**	**7 months**	**-**	**12 months**	**-**	**13 months**
RotaTeq® vaccination†††	**X**		**X**	**X**						
Hexacima® vaccination†††	**X**		**X**	**X**				**X**		
M-M-R®II vaccinations†††								**X**		
Immediate surveillance (30 min)	X		X	X				X		
Diary Card (DC):										
Provided	DC1		DC2	DC3		DC4		DC5		
Reviewed			DC1	DC2		DC3		DC4		DC5
Collected			DC1	DC2		DC3		DC4		DC5
Telephone call		X			X		X		X	
Recording of solicited injection site and systemic reactions	X		X	X				X		
Recording of unsolicited AEs		Reported from D0 to D30 after each vaccination visit								
Reporting of SAEs / AESIs‡‡‡	To be reported throughout the study period									
Collection of reportable concomitant medications	To be reported throughout the study period									
Trial termination record										X

Abbreviations: V: Visit; TC: telephone call; D: Day; IRT: interactive response technology; AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest

*This call is made 8 days after the respective vaccinations. If Day 8 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 SAEs (including AESIs) not yet reported and will remind the subject's parent/guardian to continue using the diary card, to bring the diary card to the study center at the next visit, and confirm the date and time of the next visit.

†This call is made 14 days before V05 to remind the subject's parent / guardian of the forthcoming visit. If the subject's participation is discontinued due to withdrawal of / guardian consent or for other reasons, the staff will check over the phone to see if the subject received any medications or treatments or experienced any parental SAEs (including AESIs) that have not yet been reported to the study personnel and will make arrangements to retrieve the diary card.

‡"2 months" means from the 2nd month after birth to the day before the 3rd month after birth (2 months to 2 months 29 days).

§Medical history to include history of maternal immunization against tetanus.

**Physical examination to be performed as per routine standard of care. Temperature needs to be measured before each vaccination and recorded in the source documents. As a reminder, a temperature ≥38.0ºC is a temporary contraindication. The vaccine should not be administered until the condition has resolved or the febrile event has subsided.

††Physical examination should be performed on the basis of relevant medical history at the time of the visit, according to the investigator's clinical judgment. Temperature needs to be measured before each vaccination and recorded in the source documents. As a reminder, a temperature ≥38.0°C is a temporary contraindication. The vaccine should not be administered until the condition has resolved or the febrile event has subsided

‡‡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. 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

§§If vaccines are to be administered at the same visit, blood sample will be drawn prior to vaccinations.

***Conditions for withdrawal are listed in Section 5.2.8 of the protocol.

†††Routine vaccines should be administered in accordance with available official recommendations in Mexico.

‡‡‡AESIs will be collected throughout the trial, as SAEs, to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality.

Table of Study Procedures (2/4)

Phase III Trial, Group 2 (Mexico): 6 Visits, 4 Vaccination Visits, 5 Telephone Calls, 3 Blood Samples, 11 Months Duration Per Subject for Subjects Randomized to Receive Menveo Vaccine

Visit / Telephone Call (TC)	**Visit 1**	**TC1***	**Visit 2**	**TC2***	**Visit 3**	**TC3***	**Visit 4**	**TC4†**	**Visit 5**	**TC5***	**Visit 6**
Approximate Subject Age	**2 months‡**	**-**	**4 months**	**-**	**6 months**	**-**	**7 months**	**-**	**12 months**	**-**	**13 months**
Trial timelines (days, months)	D0	V01 +8 days	V01+60 days	V02 +8 days	V02 +60 days	V03 +8 days	V03 +30 days	V05 -14 days	V04 +5 months	V05 +8 days	V05 +30 days
Time windows (days)	NA	+2 days	+14 days	+2 days	+14 days	+2 days	+14 days	+2 days	+14 days	+2 days	+14 days
Informed consent form signed and dated	X										
Inclusion/exclusion criteria	X										
Collection of demographic data	X										
Medical history§	X										
Physical examination and temperature	X**		X††		X††				X††		
Review of temporary contraindications for blood sampling (BL) ‡‡ §§	X						X				X
BL (6 mL)	BL0001						BL0002				BL0003
Review of warnings and precautions and / or contraindications for vaccinations	X		X		X				X		
Review conditions for withdrawal***	X		X		X				X		
Contact IRT system for randomization / allocation of subject number / vaccine assignment	X										
Contact IRT system for vaccine dose number for all vaccines to be given			X		X				X		
Vaccination with Menveo®	**X**		**X**		**X**				**X**		

Visit / Telephone Call (TC)	**Visit 1**	**TC1***	**Visit 2**	**TC2***	**Visit 3**	**TC3***	**Visit 4**	**TC4†**	**Visit 5**	**TC5***	**Visit 6**
Approximate Subject Age	**2 months‡**	**-**	**4 months**	**-**	**6 months**	**-**	**7 months**	**-**	**12 months**	**-**	**13 months**
Prevnar 13® vaccination†††	**X**		**X**		**X**				**X**		
RotaTeq® vaccination†††	**X**		**X**		**X**						
Hexacima® vaccination†††	**X**		**X**		**X**				**X**		
M-M-R®II vaccinations†††									**X**		
Immediate surveillance (30 min)	X		X		X				X		
Diary Card (DC):											
Provided	DC1		DC2		DC3		DC4		DC5		
Reviewed			DC1		DC2		DC3		DC4		DC5
Collected			DC1		DC2		DC3		DC4		DC5
Telephone call		X		X		X		X		X	
Recording of solicited injection site and systemic reactions	X		X		X				X		
Recording of unsolicited AEs	Collected from D0 to D30 after each vaccination visit										
Reporting of SAEs / AESIs§§§	To be reported throughout the study period										
Collection of reportable concomitant medications	To be reported throughout the study period										
Trial termination record											X

Abbreviations: V: Visit; TC: telephone call; D: Day; IRT: interactive response technology; AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest

*This call is made 8 days after the respective vaccinations. If Day 8 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 SAEs (including AESIs) not yet reported and will remind the subject's parent/guardian to continue using the diary card, to bring the diary card to the study center at the next visit, and confirm the date and time of the next visit

†This call is made 14 days before V05 to remind the subject's parent / guardian of the forthcoming visit. If the subject's participation is discontinued due to withdrawal of / guardian consent or for other reasons, the staff will check over the phone to see if the subject received any medications or treatments or experienced any parental SAEs (including AESIs) that have not yet been reported to the study personnel and will make arrangements to retrieve the diary card.

‡"2 months" means from the 2nd month after birth to the day before the 3rd month after birth (2 months to 2 months 29 days).

§Medical history to include history of maternal immunization against tetanus.

**Physical examination to be performed as per routine standard of care. Temperature needs to be measured before each vaccination and recorded in the source documents. As a reminder, a temperature ≥38.0ºC is a temporary contraindication. The vaccine should not be administered until the condition has resolved or the febrile event has subsided.

††Physical examination should be performed on the basis of relevant medical history at the time of the visit, according to the investigator's clinical judgment. Temperature needs to be measured before each vaccination and recorded in the source documents. As a reminder, a temperature ≥38.0°C is a temporary contraindication. The vaccine should not be administered until the condition has resolved or the febrile event has subsided.

‡‡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. 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.

§§If vaccines are to be administered at the same visit, blood sample will be drawn prior to vaccinations.

***Conditions for withdrawal are listed in Section 5.2.8 of the protocol.

†††Routine vaccines should be administered in accordance with available official recommendations in Mexico.

§§§AESIs will be collected throughout the trial, as SAEs, to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality.

Table of Study Procedures (3/4)

Phase III Study, Group 3 (Russian Federation): 7 or 8 Visits, 5 Vaccination Visits, 5 Telephone Calls, 3 Blood Samples, 11 Months Duration per Subject for Subjects Randomized to Receive MenACYW Conjugate Vaccine

Visit / Telephone Call	**V0**	**V01**	**TC1***	**V02**	**TC2***	**V03**	**V04**	**TC3***	**V05**	**TC4†**	**V06**	**TC5***	**V07**
Approximate Subject Age	**2 months‡**	**2 months**	**-**	**3 months**	**-**	**4.5 months**	**6 months**	**-**	**7 months**	**-**	**12 months**	**-**	**13 months**
Trial timeline (days, months)		Day 0 + 1 day	V01 +8 days	V01 +30 days	V02 +8 days	V02 +45 days	V03 +45 days	V04 +8 days	V04 +30 days	V06 -14 days	V05 +5 months	V06 +8 days	V06 +30 days
Time windows (days)	NA	+4 days	+2 days	+14 days	+2 days	+14 days	+14 days	+2 days	+14 days	+2 days	+14 days	+ 2 days	+14 days
Informed consent form signed and dated	X	X											
Inclusion / exclusion criteria	X	X											
Collection of demographic data	X	X											
Medical history§	X	X											
Urine Sample, (8 mL)**	X												X
Physical examination & temperature	X	X††		X‡‡		X‡‡	X‡‡				X‡‡		
Review of temporary contraindications for Blood Sampling (BL)§§***	X								X				X

Visit / Telephone Call	**V0**	**V01**	**TC1***	**V02**	**TC2***	**V03**	**V04**	**TC3***	**V05**	**TC4†**	**V06**	**TC5***	**V07**
Approximate Subject Age	**2 months‡**	**2 months**	**-**	**3 months**	**-**	**4.5 months**	**6 months**	**-**	**7 months**	**-**	**12 months**	**-**	**13 months**
BL	BL0001 6 mL†††								BL0002 6 mL‡‡‡				BL0003 6 mL†††
Review of warnings and precautions and / or contraindications to vaccinations		X		X		X	X				X		
Review conditions for withdrawal§§§		X		X		X	X				X		
Contact IRT system for randomization / allocation of subject number / vaccine assignment		X											
Contact IRT system for vaccine dose number for all vaccines to be given				X		X	X				X		
Vaccination with MenACYW conjugate vaccine				**X**			**X**				**X**		
ENGERIX B®**††† vaccination**							**X**						
Prevnar 13® vaccination†††		**X**				**X**							
Pentaxim® vaccination†††				**X**		**X**	**X**						
MMR vaccination†††											**X**		

Visit / Telephone Call	**V0**	**V01**	**TC1***	**V02**	**TC2***	**V03**	**V04**	**TC3***	**V05**	**TC4†**	**V06**	**TC5***	**V07**
Approximate Subject Age	**2 months‡**	**2 months**	**-**	**3 months**	**-**	**4.5 months**	**6 months**	**-**	**7 months**	**-**	**12 months**	**-**	**13 months**
Immediate surveillance (30 minutes)		X		X		X	X				X		
Telephone Call			X		X			X		X		X	
Diary Card (DC):													
Provided		DC1		DC2		DC3	DC4		DC5		DC6		
Reviewed				DC1		DC2	DC3		DC4		DC5		DC6
Collected				DC1		DC2	DC3		DC4		DC5		DC6
Collection of reportable medications	To be reported throughout the study period												
Recording of solicited injection-site and systemic reactions		X		X		X	X				X		
Recording of unsolicited AEs	Collected from D0 to D30 after each vaccination visit												
Reporting of SAEs / AESIs‡‡‡‡	To be reported throughout the study period												
Trial Termination													X

Abbreviations: V: Visit; TC: telephone call; D: Day; IRT: interactive response technology; AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest

*This call is made 8 days after the respective vaccinations. If Day 8 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 SAEs (including AESIs) not yet reported and will remind the subject's parent/guardian to continue using the diary card, to bring the diary card to the study center at the next visit, and confirm the date and time of the next visit

†This call is made 14 days before V06 to remind the subject's parent(s) of the forthcoming visit. If the subject's participation is discontinued due to withdrawal of parental / guardian consent or for other reasons, the staff will check over the phone to see if the subject received any medications or treatments or experienced any SAEs (including AESIs) that have not yet been reported to the study personnel and will make arrangements to retrieve the diary card.

‡"2 months" means from the 2nd month after birth to the day before the 3rd month after birth (2 months to 2 months 29 days).
§ Medical history to include history of maternal immunization against tetanus.

** 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.

††Physical examination to be performed as per routine standard of care. Temperature needs to be measured before each vaccination and recorded in the source documents.

‡‡ Physical examination should be performed on the basis of relevant medical history at the time of the visit, according to the investigator's clinical judgment. Temperature needs to be measured before each vaccination and recorded in the source documents. As a reminder, a temperature ≥37.0˚C in the Russian Federation is a temporary contraindication. The vaccine should not be administered until the condition has resolved or the febrile event has subsided.

§§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. 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.

*** If vaccines are to be administered at the same visit, blood sample will be drawn prior to vaccinations.

††† 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 and Visit 7. In this case, the blood sample volume collected at Visit 0 and Visit 7 will be 4 mL.

‡‡‡The minimal blood volume required for study immunogenicity objectives is 4 mL at Visit 0 and Visit 7 and 6 mL at Visit 5.

§§§Conditions for withdrawal are listed in Section 5.2.8 of the protocol.

****In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead. Further details will be provided in the CSR.

††††Routine vaccines should be administered in accordance with official recommendations in the Russian Federation. In the event M-M-R®II combination vaccine cannot be supplied or is unavailable in the Russian Federation, locally licensed MMR or MM+R vaccines will be administered instead. Further details will be provided in the CSR.

‡‡‡‡AESIs will be collected throughout the trial, as SAEs, to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality.

Table of Study Procedures (4/4)

Phase III Study, Group 4 (Russian Federation): 7 or 8 Visits, 5 Vaccination Visits, 5 Telephone Calls, 3 Blood Samples, 11 Months Duration per Subject for Subjects Randomized to Receive Routine Pediatric Vaccines

Telephone Call	**V0**	**V01**	**TC1***	**V02**	**TC2***	**V03**	**V04**	**TC3***	**V05**	**TC4***	**V06**	**TC5†**	**V07**
Approximate Subject Age	**2 months‡**	**2 months**	**-**	**3 months**	**-**	**4.5 months**	**6 months**		**7 months**	**-**	**12 months**	**-**	**13 months**
Trial timeline (days, months)		Day 0 + 1 day	V01 +8 days	V01 +30 days	V02 +8 days	V02 +45 days	V03 +45 days	V04 +8 days	V04 +30 days	V06 -14 days	V05 +5 months	V06 +8 days	V06 +30 days
Time windows (days)	NA	+4 days	+2 days	+14 days	+2 days	+14 days	+14 days	+2 days	+14 days	+2 days	+14 days	+2 days	+14 days
Informed consent form signed and dated	X	X											
Inclusion / exclusion criteria	X	X											
Collection of demographic data	X	X											
Medical history§	X	X											
Urine Sample (8mL)**	X												X
Physical examination & temperature	X	X††		X		X‡‡	X‡‡				X‡‡		
Review of temporary contraindications for Blood Sampling (BL)§§***	X							X					X
BL	BL0001 6 mL†††								BL0002 6 mL‡‡‡				BL0003 6 mL†††
Review of warnings and precautions and / or contraindications to vaccinations		X		X		X	X				X		
Review conditions for withdrawal§§§		X		X		X	X				X		
Contact IRT system for randomization / allocation of subject number / vaccine assignment		X											

Telephone Call	**V0**	**V01**	**TC1***	**V02**	**TC2***	**V03**	**V04**	**TC3***	**V05**	**TC4***	**V06**	**TC5†**	**V07**
Approximate Subject Age	**2 months‡**	**2 months**	**-**	**3 months**	**-**	**4.5 months**	**6 months**		**7 months**	**-**	**12 months**	**-**	**13 months**
Contact IRT system for vaccine dose number for all vaccines to be given				X		X	X				X		
ENGERIX B® vaccination**†††† **							**X**						
**Prevnar 13® vaccination†††† **		**X**				**X**							
**Pentaxim® vaccination†††† **				**X**		**X**	**X**						
**MMR vaccination†††† **											**X**		
Immediate surveillance (30 minutes)		X		X		X	X				X		
Telephone Call			X		X			X		X		X	
Diary Card (DC):													
Provided		DC1		DC2		DC3	DC4		DC5		DC6		
Reviewed				DC1		DC2	DC3		DC4		DC5		DC6
Collected				DC1		DC2	DC3		DC4		DC5		DC6
Collection of reportable concomitant medications	To be reported throughout the study period.												
Recording of solicited injection and systemic reactions		X		X		X	X				X		
Recording of Unsolicited AEs	Collected from D0 to D30 after each vaccination visit												
Reporting of SAEs / AESIs‡‡‡‡	To be reported throughout the study period												
Trial Termination													X

Abbreviations: V: Visit; TC: telephone call; D: Day; NA: not applicable; IRT: interactive response technology; AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest

*This call is made 8 days after the respective vaccinations. If Day 8 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 SAEs (including AESIs) not yet reported and will remind the subject's parent/guardian to continue using the diary card, to bring the diary card to the study center at the next visit, and confirm the date and time of the next visit.

†This call is made 14 days before V06 to remind the subject's parent(s) of the forthcoming visit. If the subject's participation is discontinued due to withdrawal of parental / guardian consent or for other reasons, the staff will check over the phone to see if the subject received any medications or treatments or experienced any SAEs (including AESIs) that have not yet been reported to the study personnel and will make arrangements to retrieve the diary card.

‡"2 months" means from the 2nd month after birth to the day before the 3rd month after birth (2 months to 2 months 29 days).

§Medical history to include history of maternal immunization against tetanus.

** 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.

††Physical examination to be performed as per routine standard of care. Temperature needs to be measured before each vaccination and recorded in the source documents.

‡‡Physical examination should be performed on the basis of relevant medical history at the time of the visit, according to the investigator's clinical judgment. Temperature needs to be measured before each vaccination and recorded in the source documents. As a reminder, a temperature ≥37.0˚C in the Russian Federation is a temporary contraindication. The vaccine should not be administered until the condition has resolved or the febrile event has subsided.

§§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. 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.

***If vaccines are to be administered at the same visit, blood sample will be drawn prior to vaccinations.

†††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 and Visit 7. In this case, the blood sample volume collected at Visit 0 and Visit 7 will be 4 mL.

‡‡‡The minimal blood volume required for study immunogenicity objectives is 4 mL at Visit 0 and Visit 7 and 6 mL at Visit 5.

§§§Conditions for withdrawal are listed in Section 5.2.8 of the protocol.

****In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead. Further details will be provided in the CSR.

††††Routine vaccines should be administered in accordance with available official recommendations in the Russian Federation. In the event M-M-R®II combination vaccine cannot be supplied or is unavailable in the Russian Federation, locally licensed MMR or MM+R vaccines will be administered instead. Further details will be provided in the CSR.

‡‡‡‡AESIs will be collected throughout the trial, as SAEs, to ensure that the events are communicated to the Sponsor in an expedited manner and followed up until the end of the follow-up period or resolution, as per the assigned causality.

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List of Abbreviations

µg	microgram
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BL	blood sampling
CBC	complete blood count
CDM	Clinical Data Management
CO_2	carbon dioxide
COFEPRIS	Comision Federal para la Proteccion contra Riesgos Sanitarios (Federal Commission for Protection against Sanitary Risks)
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CRO	contract research organization
CTA	Clinical Trial Agreement
CTL	Clinical Team Leader
D	day
dil	dilution
DNA	deoxyribonucleic acid
DOD	delta optical density
DT	diphtheria toxin
DTaP	diphtheria, tetanus, pertussis [acellular component]
DU	D-antigen units
E	envelope
ECL	elecrochemiluminiscent
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid

EIA	Enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
gp	glycoprotein
GPO MBP	Government Pharmaceutical Organization - Mérieux Biological Products
GPV	Global PharmacoVigilance
HBs	hepatitis B surface [antigen]
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
HRP	horseradish peroxidase
hSBA	serum bactericidal assay using human complement
ICF	informed consent form
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
IMD	invasive meningococcal disease
IME	important medical event
IMP	Investigational Medicinal Product
IND	investigational new drug (application)
IOM	Institute of Medicine
IRB	Institutional Review Board
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IU	international units
JL	Jeryl-Lynn®

LCLS	last contact, last subject
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MMR	measles, mumps, and rubella vaccine
MSD	MesoScale Discovery
MIT	mouse inoculation test
NIC	National Immunization Calendar
NIMP	Non-Investigational Medicinal Product
NIP	National Immunization Program
NSAID	non-steroidal anti-inflammatory drug
OD	optical density
PA	Pennsylvania
PCV13	pneumococcal 13-valent conjugate vaccine
PFU	plaque-forming units
PnPS	pneumococcal capsular polysaccharide
PO	orally
PPAS	per-protocol analysis set
PPM	parts per million
prM	premembane
PRNT	plaque reduction neutralization test
PRP	polyribosyl-ribitol phosphate
PS	polysaccharide
PT	pertussis toxoid / toxin
PV	Pharmacovigilance
RCDC	reverse cumulative distribution curve
RIA	Farr-type radio immunoassay
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
RV5	pentavalent rotavirus vaccine

SAE	serious adverse event
SafAS	safety analysis set
SAP	Statistical Analysis Plan
SC	subcutaneous
SCID	Severe Combined Immunodeficiency Disease
SMT	Safety Management Team
TBD	to be determined
TC	telephone call
TCC	tissue culture control
TCID	tissue culture infectious dose
TMF	trial master file
TT	tetanus toxoid
U	units
ULOQ	upper limit of quantitation
WHO	World Health Organization
WT	wild-type
VZV	varicella zoster virus

1 Introduction

1.1 Background

This study (MET33) will describe the immunogenicity and safety of a 3-dose series of the quadrivalent Meningococcal Polysaccharide (PS) (Serogroups A, C, Y, and W) Tetanus toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in children starting immunization at 2 months of age in the Russian Federation and Mexico. The purpose of the MET33 study is to demonstrate that the safety profile and immunogenicity of the 3-dose series of MenACYW conjugate vaccine is similar to that of a 4-dose series of Menveo® when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in Mexico, and to demonstrate that the safety profile and immunogenicity of MenACYW conjugate vaccine is similar when given concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the Russian Federation.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *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 different meningococcal serogroups have been classified based on the immunochemistry of the capsular 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 remains the main cause of epidemics in the world and is especially dominant in Africa and Asia. Serogroup W has been observed in Africa, as well as the United Kingdom, in residents who participated in the Hajj pilgrimage to the Kingdom of Saudi Arabia (4) (6) (7) and more recently inChile (8), Turkey (9) (10), China (11) (12), Argentina (13), Brazil (14) (15), and 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 the frequency with which it causes sporadic cases has gradually increased in the US and more recently in Canada and Europe (17) (18) (19). The Y 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 5-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 England and Wales between 2007-2009 (25) and in Sweden during 2005 – 2012 (26) (27). Nearly 50% of all IMD in Sweden was caused by serogroup Y in 2012 (26). Similarly, an increase in the proportion of IMD caused by serogroup Y has been observed in other Nordic countries, accounting for 31% in Norway in 2009 – 2010 (28) and 38% in Finland in 2010 (29).

In the US, the incidence rate of IMD was 0.14 per 100,000 in all ages; 0.83 per 100,000 in infants less than 1 year; 0.62 per 100,000 in toddlers 1 year of age; 0.27 per 100,000 in children 2 to 4 years of age; and 0.02 per 100,000 in children 5 to 17 years of age in 2013. The age specific incidence rate per 100,000 was 0.08 in adults 50 to 64 years of age, 0.03 in adults 65 to 74 years of age, 0.14 in adults 75 to 84 years of age, and 0.43 in adults 85 years of age and older in 2013 (30).

Reporting of IMD is mandatory in the Russian Federation; however, due to a lack of local typing facilities, the number of reported cases is likely an underestimate. Overall the incidence of IMD, across all regions is 0.3 to 0.8 / 100,000, with up to 59% of cases reported in children under the age of 5 years (31) The serogroups reported in Russia include A, B, C, and W; MenW clonal complex (cc)11 was first detected in Moscow in 2007, with the number of cases increasing in 2014 to 2015. Currently, the national vaccine strategy targets only those groups considered to be at-risk. The primary barriers to vaccination include limited pharmacoeconomic data, a lack of public awareness, and the underestimation of the disease burden (32).

The true burden of IMD in Mexico is unknown. Despite its classification as a reportable disease, only a fraction of isolates are submitted to the national reference library. In general, the number of reported IMD cases has increased since 2002, but incidence remain low ranging from 0.01 to 0.04 per 100,000 in the 2010–2014 period. Following an outbreak of IMD in the Metropolitan area, serogroup C emerge as the prevalent strain, with cases IMD related to serogroup B and C also reported (32).

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 including 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 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 < 40 years of age; and MET32, a Phase I/II study in toddlers.

The formulation has been evaluated in around 7115 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in 10 completed studies: 4 Phase II studies, MET39, MET44, MET50, conducted in the USA, and MET54 conducted in Finland, and 6 Phase III studies, MET35, MET43, MET49 and MET56, conducted in the USA, MET51 conducted in EU region (Spain,

Germany, Hungary and Finland), and MET57 conducted in Thailand, South Korea, Russia, and Mexico. The vaccine is currently approved under the brand name MenQuadfi® for use as single dose in ages 12 months and older in the European Union (under centralised procedure[a]), Iceland, Liechtenstein, Norway, Australia, Canada, UK, Brazil, and Argentina. The vaccine is also approved for use as single dose in ages 2 years and older in the USA.

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. The relevant Phase II studies are discussed below.

1.2.1.1 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® (pneumococcal conjugate vaccine) or PREVNAR 13® (pneumococcal 13-valent conjugate vaccine [PCV13]), Pentacel® (diphtheria, tetanus, pertussis [acellular, component]-poliovirus [inactivated]//*Haemophilus influenzae* type b [DTaP-IPV//Hib]), ROTARIX® (monovalent rotavirus vaccine [RV1]) or RotaTeq® (pentavalent rotavirus vaccine[RV5]), hepatitis B vaccine, and M-M-R®II vaccine (measles, mumps, and rubella vaccine [MMR]).

Immunogenicity

After the infant series consisting of 1, 2, or 3 doses of MenACYW conjugate vaccine, protective serum bactericidal assay using human complement (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.

[a] European Union countries include Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden.

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, one 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 vaccine- related SAEs during this study.

1.2.1.2 Study MET54 (Phase II)

MET54 was a Phase II, randomized, open-label, active-controlled, multi-center study conducted in Europe (Finland). 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 serum bactericidal assay using baby rabbit complement (rSBA) and human complement (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 adverse reactions (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 safety findings were identified with administration of the MenACYW conjugate vaccine. The MenACYW conjugate vaccine was well tolerated and immunogenic. Single dose of the MenACYW conjugate vaccine demonstrated excellent potential to be an alternative vaccine option for toddlers receiving meningococcal vaccination for the first time.

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 the MenACYW conjugate vaccine. However, based on the data generated from previous studies, the immunogenicity profile of the MenACYW conjugate vaccine in different age groups shows that the majority of subjects developed 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 further evaluation of the MenACYW conjugate vaccine in humans.

Subjects who receive Menveo® will likely be protected against meningococcal disease caused by *N. meningitidis* serogroups A, C, Y, and W.

As with any vaccine, MenACYW conjugate vaccine and Menveo® may not protect 100% of individuals against the diseases they are designed to prevent.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine or Menveo® 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 when administered to infants / toddlers. There may be a rare possibility of an allergic reaction, which could be severe. There may also be a risk of febrile convulsion in some children who experience high fever. There may be other risks for MenACYW conjugate vaccine or Menveo® that are not yet known.

In a previous study with MenACYW conjugate vaccine (MET32), 1 SAE of reactive arthritis reported in a toddler was considered by the Investigator to be related to the investigational vaccine. The subject developed right knee inflammation the day after receiving MenACYW conjugate vaccine, given by intramuscular (IM) injection in the right deltoid. The subject recovered after treatment with ibuprofen and antibiotics. Results of the reactive arthritis investigations performed as part of the workup were not indicative of any specific diagnosis. A point of further consideration was the monoarticular nature of the inflammation in this subject; reactive arthritis would typically be present clinically in a polyarticular fashion. Importantly, no similar cases have been reported following the administration of MenACYW conjugate vaccine in any other completed trials.

Guillain-Barré syndrome 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 (33). A retrospective cohort study carried out in the US using healthcare claims data found no evidence of increased Guillain-Barré syndrome risk associated with the use of that vaccine. The study was able to exclude all but relatively small incremental risks (34).

A review by the Institute of Medicine (IOM) found inadequate evidence to accept or reject a causal relationship between tetanus toxoid containing vaccines and Guillain-Barré syndrome (35). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (36). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (37).

No occurrences of Guillain-Barré syndrome, 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 Investigator's Brochure for MenACYW conjugate vaccine, the investigational labeling for Menveo®, and the package inserts for the routine pediatric vaccines for additional information regarding potential risks (38).

1.4 Rationale for the Study

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 > 56 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. Compared to a previous Sanofi Pasteur meningococcal conjugate vaccine, Menactra®, 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 titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response. The program targets licensure of the MenACYW conjugate vaccine in many countries in North America, Europe, Latin America, Africa, the Middle East, and Asia Pacific.

The MenACYW conjugate vaccine is designed to cover broader age groups than those covered by Menomune® -A/C/Y/W-135 and Menactra®. Menactra® has been very successful since its licensure in 2005; however, it is not licensed in Europe and is not indicated in persons 8 months of age or younger or 56 years of age and older. While Menomune® -A/C/Y/W-135 and Menactra® are currently licensed in different parts of the world, the MenACYW conjugate vaccine is being developed by Sanofi Pasteur to ultimately replace Menomune® -A/C/Y/W-135 and Menactra® in the global market as a quadrivalent meningococcal conjugate vaccine indicated in infants/toddlers, children, adolescents, adults, and older adults > 56 years of age. Meningococcal PS vaccines have 2 important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) PS alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of PS vaccines in infants and children has been shown to be improved by conjugating the PS to protein carriers. 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 (Ig) G 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.

MenACYW conjugate vaccine is being developed for the infant/toddler population in the international region as a 3-dose series. This Phase III study (MET33) will generate data to primarily support the licensing of the MenACYW conjugate vaccine in the 2 international countries being targeted in the study and also in other countries outside of the US and EU with an infant/toddler indication from 6 weeks of age. The purpose of the MET33 study is to describe the safety profile and immunogenicity of the MenACYW conjugate vaccine and the comparator Menveo® when administered with routine pediatric vaccines given to healthy infants and toddlers.

2 Study Objectives

2.1 Primary Objectives

1) To describe the vaccine seroprotection (antibody titer ≥1:8) to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine or Menveo® measured by serum bactericidal assay using human complement (hSBA), for Groups 1 and 2, when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico

2) To describe the vaccine seroprotection (antibody titer ≥1:8) to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by hSBA, for Group 3, when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation

The endpoints for the primary objectives are presented in Section 9.1.

2.2 Secondary Objective

1) To describe the hSBA vaccine seroresponse to the antigens (meningococcal serogroups A, C, Y, and W) for Groups 1 and 2, 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®), when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico
2) To describe the hSBA vaccine seroresponse to the antigens (meningococcal serogroups A, C, Y, and W) for Group 3, 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine), when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation
3) To describe the immunogenicity profile of routine pediatric vaccines when administered concomitantly with MenACYW conjugate vaccine (Groups 1 and 3), Menveo® (Group 2), or when administered alone (Group 4)
4) To describe the hSBA antibody responses against meningococcal serogroups A, C, Y, and W when MenACYW conjugate vaccine and Menveo® are administered concomitantly with routine pediatric vaccines in Mexico and the Russian Federation (Groups 1, 2, and 3)
5) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine and Menveo® measured by serum bactericidal assay using baby rabbit complement (rSBA) before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®), when administered concomitantly with routine pediatric vaccines in a subset of subjects (100 subjects per group in Groups 1 and 3, and 50 subjects in Group 2) in Mexico
6) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series (Dose 2 of MenACYW conjugate vaccine), when administered concomitantly with routine pediatric vaccines in a subset of subjects (100 subjects in Group 3) in the Russian Federation
7) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine and Menveo® measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life, when administered concomitantly with routine pediatric vaccines in a subset of subjects (100 subjects in Group 1, and 50 subjects in Group 2) in Mexico
8) To describe the antibody titers to the antigens (meningococcal serogroups A, C, Y, and W) present in MenACYW conjugate vaccine measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life, when administered concomitantly with routine pediatric vaccines in a subset of subjects (100 subjects in Group 3) in the Russian Federation

The endpoints for the secondary objectives are presented in Section 9.2.

2.3 Observational Objectives

Safety

1) To describe the safety profile of MenACYW conjugate vaccine and Menveo® when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Mexico (Group 1 vs Group 2).
2) To describe the safety profile of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the Russian Federation (Group 3)
3) To describe the safety profile of routine pediatric vaccines in healthy infants and toddlers in Mexico (Groups 1 and 2) and the Russian Federation (Groups 3 and 4)

The endpoints for the observational objectives are presented in Section 9.3.

3 Investigators and Study Organization

This study will be conducted in approximately 14 centers in Mexico and the Russian Federation. The Principal Investigators and any sub-investigators at the individual sites may be coordinated by 1 Coordinating Investigator in each country. Details of the study centers, the Investigators at each center, and the Coordinating Investigators are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal Safety Management Team (SMT) will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns.

The Sponsor's Responsible Medical Officer (RMO) (the RMO, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is Olga Lyabis, MD, PhD, MSc, 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 (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 IECs or IRBs.

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 study. 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 the Sponsor will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All SAEs occurring during the study that are related to the product administered will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

This is a Phase III, open-label, randomized, parallel-group, active-controlled, multi-center study to describe the immunogenicity and safety of a 3-dose immunization schedule of MenACYW conjugate vaccine or a 4-dose immunization schedule of a licensed quadrivalent meningococcal conjugate vaccine (Menveo® [Meningococcal {Groups A, C, Y and W-135} Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine]) when administered concomitantly with routine pediatric vaccines (Prevnar 13®, Hexacima®, RotaTeq®, and M-M-R®II) in healthy infants and toddlers aged 2 to 12 months in Mexico, and to describe the immunogenicity and safety of a 3-dose immunization schedule of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines (Prevnar 13®, Pentaxim®, ENGERIX-B®, and MMR) in healthy infants and toddlers aged 2 to 12 months in the Russian Federation.

A total of 525 subjects will be enrolled. Approximately 300 healthy, meningococcal-vaccine naïve infants aged 2 months will be randomized in a 2:1 ratio in Mexico, and 225 healthy, meningococcal-vaccine naïve infants aged 2 months will be randomized in a 2:1 ratio in the Russian Federation into the following groups:

Mexico

Group 1: MenACYW conjugate vaccine at 2, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age

Group 2: Menveo® at 2, 4, 6, and 12 months of age + routine pediatric vaccines at 2, 4, 6, and 12 months of age

The Russian Federation

Group 3: MenACYW conjugate vaccine at 3, 6, and 12 months of age + routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age

Group 4: Routine pediatric vaccines at 2, 3, 4.5, 6, and 12 months of age

All subjects in Groups 1 and 2 will receive either MenACYW conjugate vaccine or Menveo® concomitantly with the following routine pediatric vaccines in accordance with available official recommendations ***in Mexico***:

- Prevnar 13® (pneumococcal 13-valent conjugate vaccine [PCV13]) at 2, 4, 6, and 12 months of age*
- Hexacima® (DTaP-IPV-HB-Hib) at 2, 4, 6, and 12 months of age
- RotaTeq® (pentavalent rotavirus vaccine [RV5]) 2, 4, and 6 months of age
- MMR (measles, mumps, rubella [MMR] vaccine) at 12 months of age

All subjects in Group 3 will receive MenACYW conjugate vaccine concomitantly with the following routine pediatric vaccines; and all subjects in Group 4 will receive the following routine pediatric vaccines alone in accordance with the National Immunization Calendar (NIC) recommendations in ***the Russian Federation***:

- Prevnar 13® (pneumococcal 13-valent conjugate vaccine [PCV13]) at 2 and 4.5 months of age*
- Pentaxim® (DTaP-Hib-IPV) at 3, 4.5, and 6 months of age†
- ENGERIX-B® (hepatitis B vaccine) at 6 months of age‡
- MMR vaccine at 12 months of age§

* No immunogenicity endpoints will be measured for this vaccine in the Russian Federation. The PCV13 routine vaccine recommended at 15 months of age in the Russian Federation is considered as out of scope for this study and will not be provided by the Sponsor but procured by the sites as per their standard practices.

† The 4th dose of Pentaxim®, which is administered at 18 months of age, is considered out of the scope of the study, and it will not be provided by the Sponsor but procured by the sites as per their standard practices. Subjects will be instructed to receive it for completion of the Pentavalent series as per the NIC of the Russian Federation.

‡ In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead. Further details will be provided in the CSR.

§ In the event M-M-R®II combination vaccine cannot be supplied or is unavailable in the Russian Federation, locally licensed MMR or MM+R vaccines will be administered instead. Further details will be provided in the CSR.

Note about Screening / Enrollment Visits

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

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.

Blood sampling

Subjects will provide blood samples for immunogenicity assessments according to the following schedules:

Mexico

Groups 1 and 2:

- A blood sample at baseline (before the first study vaccination at Visit 1)

- A blood sample 30 days (+14 days) after the 2nd dose of MenACYW conjugate vaccine or 3rd dose of Menveo® (Visit 4)
- A blood sample 30 days (+14 days) after the 3rd dose of MenACYW conjugate vaccine or the 4th dose of Menveo® (Visit 6)

The Russian Federation

Group 3:

- A blood sample at baseline (before the first study vaccination, at Visit 0)
- A blood sample 30 days (+14 days) after the 2nd dose of MenACYW conjugate vaccine (Visit 5)
- A blood sample 30 days (+14 days) after the 3rd dose of MenACYW conjugate vaccine (Visit 7)

Group 4:

- A blood sample at baseline (before the first study vaccination, at Visit 0)
- A blood sample 30 days (+14 days) after the 1st dose of ENGERIX B® and 3rd dose of Pentaxim® vaccines (Visit 5)
- A blood sample 30 days (+14 days) after the 1st dose of MMR vaccine (Visit 7)

Upon completion of all study procedures and termination from the trial, study participants should receive the remainder of the recommended toddler vaccines from their health care provider, according to the respective available official recommendations for each country.

For the Russian Federation only:

In accordance with local practice of conduct of clinical trials in Russian Federation, 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) and at Visit 7.

The additional biological analyses have been implemented for subjects enrolled at sites in the Russian Federation per local practices of conduct of clinical trials only and were not implemented to address any concern of the Sponsor regarding safety issues.

Clinical laboratory evaluations of MenACYW conjugate vaccine were performed in the Phase I studies (MET28 and MET32) with no findings considered to be of clinical relevance. Throughout the clinical development, no concerns in terms of abnormal blood count or blood chemistry parameters reported as AEs have been observed.

The same type of biological analysis was performed in the frame of another MenACYW phase III study in toddlers in Russia (MET57), no abnormalities in biological parameters were identified.

5.1.2 Justification of the Study Design

The MET33 study is part of an ongoing development program that focuses on demonstrating that the safety profile of the MenACYW conjugate vaccine is similar to that of licensed quadrivalent

meningococcal conjugate vaccines, and that the immunogenicity of the MenACYW conjugate vaccine is non-inferior to licensed comparators in direct comparison trials. MET33 is a pivotal Phase III safety study in which the vaccine candidate will be evaluated in healthy infants / toddlers receiving concomitantly licensed routine pediatric vaccines in the Russian Federation and in Mexico. This study was initially designed to evaluate the safety profile of MenACYW conjugate vaccine following a 3-dose series of the MenACYW conjugate vaccine or a 4-dose series of the licensed comparator Menveo® in the countries selected. The comparator product (Menveo®) was licensed in Russia in 2016, based on 2 randomized, active controlled immunogenicity studies in participants aged 2 months to 65 years, inclusive, that were conducted in North America, Latin America, and Australia (39) (40) (41). The immunogenicity of the vaccine in children aged 2 to 16 months was evaluated after subjects received a series of 4 doses of Menveo® vaccine coadministered with routine vaccinations at either 2, 4, 6, and 12 months of age or at 2, 4, 6, and 16 months of age. The results demonstrated that concomitant administration of Menveo® vaccine with routine planned vaccines for children aged 2 to 23 months did not cause immune intereference. An increase in reactogenicity or a change in the safety profile of routine vaccinations was not observed.

However, Menveo® is currently not available at a national level in the Russian Federation; it was never imported or produced within the country, with no access to the health and market sectors. No other comparator is available in the Russian Federation for use in this trial. It is crucial to evaluate the potential impact for clinically relevant immunological interference and safety of any new vaccine with current routine infant and toddler vaccinations. This current multinational study will assess and describe the safety profile of a 3-dose series of the MenACYW conjugate vaccine when given concomitantly with routine vaccinations in a treatment cohort in the Russian Federation, and will evaluate the safety profile of MenACYW conjugate vaccine following a 3-dose series of the MenACYW conjugate vaccine or a 4-dose series of the licensed comparator Menveo® in Mexico. Enrollment in the study will start at 2 months of age in Mexico and in the Russian Federation.

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: Pentaxim®, Prevnar® or Prevnar 13®, RotaTeq® or ROTARIX®, and ENGERIX-B®[a] or RECOMBIVAX HB®. All subjects received M-M-R®II and VARIVAX® at 12 months. A total of 457 subjects completed the study. The immunogenicity and safety 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

[a] In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead.

concomitantly with MenACYW conjugate vaccine and the vaccine was safe and well tolerated regardless of the number of doses administered during the first year of life.

Given that the meningococcal vaccines used in this study have different schedules, appearances and preparation methods, the study has an open-label design.

5.1.3 Study Plan

Vaccination

Subjects in Mexico will receive either MenACYW conjugate vaccine or Menveo®, with routine pediatric vaccines according to the vaccination schedule shown in Table 5.1.

Subjects in the Russian Federation will receive either MenACYW conjugate vaccine or routine pediatric vaccines alone, according to the vaccination schedule shown in Table 5.2.

Blood sampling

Subjects will provide blood samples for immunogenicity assessments at the following time points:

Mexico

Subjects in Groups 1 and 2: Visit 1 (pre-vaccination), Visit 4, and Visit 6 (see Table 5.1)

Russian Federation

Groups 3 and 4: Visit 0 (pre-vaccination), Visit 5, and Visit 7 (see Table 5.2)

For sites in the Russian Federation only:

Subjects enrolled at sites in the Russian Federation will also provide additional blood sample, (depending on local laboratory needs) for CBC and blood chemistry testing at Visit 0 (Screening visit) and at Visit 7 in accordance with local regulations. Total blood volume collected will be approximately 6 mL per blood draw at Visit 0, Visit 5, and Visit 7. See Table 5.2.
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 and Visit 7. In this case, the blood sample volume collected at Visit 0 and Visit 7 will be 4 mL.

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 7 per Health Authority request and in accordance with local regulations.

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.

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

Table 5.1: Vaccination and BL schedule: Mexico (Groups 1 and 2)

Visit (V)	V01	V02	V03	V04	V05	V06*
Subject Age	**2 months**	**4 months**	**6 months**	**7 months**	**12 months***	**13 months**
Group 1	**MenACYW†** Prevnar 13® Hexacima® RotaTeq® **BL0001** (Pre-Vaccination)	Prevnar 13® Hexacima® RotaTeq®	**MenACYW†** Prevnar 13® Hexacima® RotaTeq®	**BL0002**	**MenACYW†** Prevnar 13® Hexacima® M-M-R®II	**BL0003**
Group 2	**Menveo®** Prevnar 13® Hexacima® RotaTeq® **BL0001** (Pre-Vaccination)	**Menveo®** Prevnar 13® Hexacima® RotaTeq®	**Menveo®** Prevnar 13® Hexacima® RotaTeq®	**BL0002**	**Menveo®** Prevnar 13® Hexacima® M-M-R®II	**BL0003**

*Per the current National Immunization Program (NIP) and Health Authority recommendations in Mexico, the varicella vaccine is administered at or after 12 months of age; it is not administered within the scope of the study. However, VARIVAX® vaccine will be provided by the Sponsor as a benefit vaccine as per standard practices and the current recommendations of the NIP in Mexico. The study personnel / Investigator will be responsible for administering this vaccine at V6 after the last blood sample (BL0003) of the study. No endpoints will be measured for this vaccine, even if it is administered at V6 of the study.

†MenACYW conjugate vaccine

Table 5.2: Vaccination, BL, and urinalysis schedule: the Russian Federation (Groups 3 and 4)

Visit (V)	V0	V01	V02	V03	V04	V05	V06	V07
Subject Age	**2 months**	**2 months**	**3 months**	**4.5 months**	**6 months**	**7 months**	**12 months**	**13 months**
Group 3	**BL0001** (6 mL) **UA** (8 mL)	Prevnar 13®†	**MenACYW*** Pentaxim®‡	Prevnar 13®† Pentaxim®‡	**MenACYW*** Pentaxim®‡ ENGERIX-B®§	**BL0002** (6 mL)	**MenACYW*** MMR**	**BL0003** (6 mL) **UA** (8 mL)
Group 4	**BL0001** (6 mL) **UA** (8 mL)	Prevnar 13®†	Pentaxim®‡	Prevnar 13®† Pentaxim®‡	Pentaxim®‡ ENGERIX-B®§	**BL0002** (6 mL)	MMR**	**BL0003** (6 mL) **UA** (8 mL)

V: Visit, UA: Urinalysis

*MenACYW conjugate vaccine

† No immunogenicity endpoints will be measured for this vaccine in the Russian Federation. The PCV13 routine vaccine recommended at 15 months of age in the Russian Federation is considered as out of scope for this study and will not be provided by the Sponsor but procured by the sites as per their standard practices.

‡The 4th dose of Pentaxim®, which is administered at 18 months of age, is considered out of the scope of the study, and it will not be provided by the Sponsor but procured by the sites as per their standard practices. Subjects will be instructed to receive it for completion of the Pentavalent series as per the NIC of the Russian Federation recommendation.

§In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead. Further details will be provided in the CSR.

** In the event M-M-R®II combination vaccine cannot be supplied or is unavailable in the Russian Federation, locally licensed MMR or MM+R vaccines will be administered instead. Further details will be provided in the CSR.

Table 5.3: Schedule of antigen testing: Mexico (Groups 1 and 2)

Visit (V)	V01	V02	V03	V04	V05	V06
Subject Age	**2 months**	**4 months**	**6 months**	**7 months**	**12 months**	**13 months**
Trial Timeline	**D0**	**V01 + 60 days**	**V02 + 60 days**	**V03 + 30 days**	**V04 + 150 to 180 days**	**V05 + 30 days**
BL (5 mL)	**BL0001**			**BL0002**		**BL0003**
Group 1	Meningococcal Serogroups (A, C, Y, W)* Pertussis (PT, FHA) RV IgA	—	—	Meningococcal Serogroups (A, C, Y, W) PCV13 RV IgA		Meningococcal Serogroups (A, C, Y, W) PCV13 Hib (PRP) Pertussis (PT, FHA) HepB Polio (types 1, 2, 3) Tetanus Diphtheria M-M-R®II

Group 2	Meningococcal Serogroups (A, C, Y, W) Pertussis (PT, FHA) RV IgA	—	—	Meningococcal Serogroups (A, C, Y, W) PCV13 RV IgA		Meningococcal Serogroups (A, C, Y, W) PCV13 Hib (PRP) Pertussis (PT, FHA) HepB Polio (types 1, 2, 3) Tetanus Diphtheria M-M-R®II

PT: pertussis toxin; FHA: filamentous hemagluttinin; Hib: *Haemophilus influenzae* type B; PRP: polyribosyl-ribitol phosphate; HepB: hepatitis B; PCV13: pneumococcal 13-valent conjugate vaccine; M-M-R®II: measles, mumps, and rubella

*Antibody responses to meningococcal serogroups (A, C, Y, and W) will be measured by rSBA before the first vaccination (Visit 1), 30 days after the final vaccination in the infant series, and 30 days after the last vaccination in the entire 3- or 4- dose vaccine schedule in a subset of subjects (100 subjects per group in Groups 1, 3, and 5 and 50 subjects per group in Groups 2, 4, and 6.)

Table 5.4: Schedule of antigen testing: the Russian Federation (Groups 3 and 4)

Visit (V)	V0	V01	V02	V03	V04	V05	V06	V07
Subject Age	**2 months**	**2 months**	**3 months**	**4.5 months**	**6 months**	**7 months**	**12 months**	**13 months**
Trial Timeline		**D0**	**V01+30 days**	**V02 + 45 days**	**V03 + 45 days**	**V04 + 30 days**	**V05 + 5 months**	**V06 + 30 days**
BL	**BL0001 (6 mL)**					**BL0002 (6 mL)**		**BL0003 (6 mL)**
Group 3	Meningococcal Serogroups (A, C, Y, W)* Pertussis (PT, FHA)	—		—		Meningococcal Serogroups (A, C, Y, W) Hib (PRP) Pertussis (PT, FHA) HepB Polio (types 1, 2, 3) Tetanus Diphtheria PCV13		Meningococcal Serogroups (A, C, Y, W) MMR‡
Group 4	Pertussis (PT, FHA)	—	—	—	—	Pertussis (PT, FHA) HepB Polio (types 1, 2, 3) Tetanus Diphtheria PCV13		MMR

PT: pertussis toxin; FHA: filamentous hemagluttinin; Hib: *Haemophilus influenzae* type B; PRP: polyribosyl-ribitol phosphate; HepB: hepatitis B; PCV13: pneumococcal 13-valent conjugate vaccine; M-M-R®II: measles, mumps, and rubella

*Antibody responses to meningococcal serogroups (A, C, Y, and W) will be measured by rSBA before the first vaccination, 30 days after the final vaccination in the infant series, and 30 days after the last vaccination in the entire 3- or 4- dose vaccine schedule in a subset of subjects (100 subjects per group in Groups 1, 3, and 50 subjects per group in Groups 2.)

Collection of Safety Data

All subjects will be followed for safety from Visit 1 to the last study visit.

- 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 (eCRF).
- The subject's parent / guardian will record information in a diary card about solicited injection-site reactions and solicited systemic reactions from D0 to D7 after each vaccination and unsolicited AEs will be recorded from D0 after each vaccination until the subject returns for the next study visit.
- Serious AEs (including AEs of special interest [AESIs]) will be recorded in a diary card throughout the study. The subject's parent / guardian will be asked to notify the site immediately about any potential SAEs at any time during the trial.
- A member of the study staff will contact subject's parent / guardian by telephone 8 days (+2 days) after each vaccination visit to identify the occurrence of any SAE (including AESIs) not yet reported and to remind them to complete the diary card after each vaccination visit, and to bring it back to the next study visit.
- The completed diary cards will be collected and reviewed with the subject's parent / guardian at subsequent visits.
- A member of the study staff will contact the subject's parent / guardian by telephone 14 days (+2 days) before the first study visit of the subject's second year of life to identify the occurrence of any SAE not yet reported and to remind them to complete the diary card and to bring it back to the next study visit so it can be reviewed at the study site.

5.1.4 Visit Procedures

Mexico

Visit 1 (Day 0): Inclusion, Blood Sampling (BL), and Vaccination

1) Give the parent / guardian information about the study, obtain written informed consent, and give him/her a signed copy.
2) Check inclusion and exclusion criteria for eligibility.
3) Collect demographic data.
4) Obtain verbal medical history about the subject, including ongoing medications and history of maternal immunization against tetanus.
5) Conduct a physical examination
6) Measure temperature. If the temperature is ≥38°C, postpone vaccination until the condition is resolved.
7) Contact IRT system for randomization / allocation of subject number / vaccine assignment

8) Review temporary contraindications for blood sampling. Ensure the subject has not had any antibiotics within the previous 72 hours (3 days).

9) Collect 6-mL blood sample (BL0001) (see Section 7.1 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 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) Review warnings and precautions to vaccinations.

11) Administer the appropriate study vaccines per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately[a].

- Meningococcal vaccine: inject IM into the anterolateral area of the thigh (preferably the right thigh).[b,c]
- Prevnar 13®: inject IM into the anterolateral thigh (preferably the left thigh).[b]
- Hexacima®: inject IM into the anterolateral area of the thigh (preferably the left thigh).[b]
- RotaTeq®: administer PO per instructions in the package insert.

12) Keep the subject under observation for 30 minutes and record any AE in the source document.

13) Give the parent / guardian a diary card (DC1), a thermometer, and a ruler, and go over the instructions for their use.

14) Remind the parent / guardian to expect a telephone call 8 days after Visit 1 and to bring back the diary card when they return for Visit 2 at a specified date and time.

15) Remind the parent / guardian to notify the site in case of an SAE.

16) Complete the CRFs for this visit.

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[a] Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the CRF. If the initial vaccines are administered in the wrong limbs, this should be corrected for subsequent injections.

[b] The only other vaccine that can be administered with the meningococcal vaccine in the right thigh is ENGERIX-B®. Do not administer Pentaxim® or PREVNAR 13® in the right thigh.

[c] Multiple injections given in the same extremity should be separated as far as possible preferably 2.54 cm to 3.81 cm apart with a minimum of 2.54 cm. Keep the subject under observation for 30 minutes and record any AR in the source document.

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

Note: If Day 8 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 has occurred that has not yet been reported, 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 the next visit.
   Notify the site in case of an SAE.

Visit 2 (60 [+14] days after Visit 1): Collection of Safety Information and Vaccination

1) If the diary card information from D0 to D07 (DC1) has not yet been obtained, obtain it at this time. Collect and review the pages of the diary card with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review warnings and precautions to vaccinations.
3) Review contraindications to subsequent vaccinations.
4) Review conditions for withdrawal.
5) Contact IRT system for dose number for all vaccines to be given.
6) Administer the appropriate study vaccine per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately.

   For subjects in Group 2 only:

   - Meningococcal vaccine: inject IM into the anterolateral area of the thigh (preferably the right thigh).[a,b]

   For subjects in Groups 1 and 2:

   - Prevnar 13®: inject IM into the anterolateral area of the thigh (preferably the left thigh).

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[a] The only other vaccine that can be administered with the meningococcal vaccine in the right thigh is ENGERIX-B®. Do not administer Pentaxim® or PREVNAR 13® in the right thigh.

[b] Multiple injections given in the same extremity should be separated as far as possible preferably 2.54 cm to 3.81 cm apart with a minimum of 2.54 cm. Keep the subject under observation for 30 minutes and record any adverse reaction (AR) in the source document.

- Hexacima®: inject IM into the anterolateral area of the thigh (preferably the left thigh).[b]
- RotaTeq®: administer PO per instructions in the package insert.

7) Give the parent / guardian a diary card (DC2).
8) Remind the parent / guardian to expect a telephone call 8 days after Visit 2 and to bring back the diary card when they return for Visit 3 at a specified date and time.
9) Remind the parent / guardian to notify the site in case of an SAE.
10) Complete the relevant CRFs for this visit.

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

Refer to steps in Telephone Call 1.

Visit 3 (60 [+14] days after Visit 2): Collection of Safety Information and Vaccination

1) If the diary card information from D0 to D07 (DC2) has not yet been obtained, obtain it at this time. Collect and review the pages of the diary card with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review warnings and precautions to vaccinations.
3) Review contraindications to subsequent vaccinations.
4) Review conditions for withdrawal.
5) Contact IRT system for dose number for all vaccines to be given.
6) Administer the appropriate study vaccine per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately.
    - Meningococcal vaccine: inject IM into the anterolateral area of the thigh (preferably the right thigh).[a,b]
    - Hexacima®: inject IM into the anterolateral area of the thigh (preferably the left thigh).
    - Prevnar 13®: inject IM into the anterolateral area of the thigh (preferably the left thigh).[b]
    - RotaTeq®: administer PO per instructions in the package insert.

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[a] The only other vaccine that can be administered with the meningococcal vaccine in the right thigh is ENGERIX-B®. Do not administer Pentaxim® or PREVNAR-13® in the right thigh.

[b] Multiple injections given in the same extremity should be separated as far as possible preferably 2.54 cm to 3.81 cm apart with a minimum of 2.54 cm. Keep the subject under observation for 30 minutes and record any AR in the source document.

7) Keep the subject under observation for 30 minutes and record any AE in the source document.
8) Give the parent / guardian a diary card (DC3).
9) Remind the parent / guardian to expect a telephone call 8 days after Visit 3 and to bring back the diary card when they return for Visit 4 at a specified date and time.
10) Remind the parent / guardian to notify the site in case of an SAE.
11) Complete the relevant CRFs for this visit.

Telephone Call 2 (Group 1) (8 [+2] days after Visit 3) / Telephone Call 3 (Group 2) (8 [+2] days after Visit 3)

Refer to steps in Telephone Call 1.

Visit 4 (30 [+14] days after Visit 3): Collection of Safety Information and Blood Sampling

1) If the diary card information from D0 to D07 (DC3) has not yet been obtained, obtain it at this time. Collect and review the pages of the diary card with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review temporary contraindications to blood sampling
3) Collect 6-mL blood sample (BL0002) (see Section 7.1 for detailed instructions regarding the handling of blood samples).
4) Give the parent / guardian a diary card (DC4).
5) Remind the parent / guardian to bring back the diary card when they return for Visit 5 at a specified date and time.
6) Remind the parent / guardian to notify the site in case of an SAE.
7) Complete the relevant CRFs for this visit.

Telephone Call 3 (Group 1) (14 [+ 2] days before Visit 5) / Telephone Call 4 (Group 2) (14 [+ 2] days before Visit 5)

1) Contact the subjects' parent/ guardian by telephone within 14 days before V05 to remind them about the forthcoming study visit.
2) If the subject participation in the study is discontinued:
    a. Review the diary card including any AEs, medications, or therapy that occurred since the last visit.
    b. Ask the subject's parent / guardian if the subject has experienced any SAE in the time since vaccination that has not been reported to the study personnel. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
    c. Make arrangements to retrieve the diary card.

Visit 5 (5 months [+14 days] after Visit 4): Collection of Safety Information and Vaccination

1) If the diary card information from D0 to D07 (DC4) has not yet been obtained, obtain it at this time. Collect and review the pages of the diary card with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review the subject's relevant health history with parent / guardian, including any AEs, medications, or therapy that occurred since vaccination.
3) Review warnings and precautions to vaccinations.
4) Review contraindications to subsequent vaccinations.
5) Review conditions for withdrawal.
6) Contact IRT system for dose number for all vaccines to be given.
7) Administer the appropriate study vaccine per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately:
    - Meningococcal vaccine: inject IM into the anterolateral area of the thigh (preferably the right thigh).[a,b]
    - Prevnar 13®: inject IM into the anterolateral thigh (preferably the left thigh).[a]
    - M-M-R®II inject SC into the outer aspect of the upper arm (preferably the left arm)
    - Hexacima®: inject IM into the anterolateral area of the upper thigh (preferably the left thigh)
8) Keep the subject under observation for 30 minutes and record any AE in the source document.
9) Give the parent / guardian a diary card (DC5).
10) Remind the parent / guardian to expect a telephone call 8 days after Visit 5 and to bring back the diary card when they return for Visit 6 at a specified date and time.
11) Remind the parent / guardian to notify the site in case of an SAE.
12) Complete the relevant CRFs for this visit.

[a] The only other vaccine that can be administered with the meningococcal vaccine in the right thigh is ENGERIX-B®. Do not administer Pentaxim® or PREVNAR-13® in the right thigh.

[b] Multiple injections given in the same extremity should be separated as far as possible preferably 2.54 cm to 3.81 cm apart with a minimum of 2.54 cm. Keep the subject under observation for 30 minutes and record any AR in the source document.

Telephone Call 4 (Group 1) (8 [+2] days after Visit 5) / Telephone Call 5 (Group 2) (8 [+2] days after Visit 5)

Refer to steps in Telephone Call 1.

Visit 6 (30 [+14 days] days after Visit 5): Collection of Safety Information, Blood Sampling, and Trial Termination

1) If the diary card information from D0 to D07 (DC5) has not yet been obtained, obtain it at this time. Collect and review the pages of the diary card with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review temporary contraindications to blood sampling
3) Collect 6-mL blood sample (BL0003) (see Section 7.1 for detailed instructions regarding the handling of blood samples).
4) Remind the parent / guardian to notify the site in case of an SAE.
5) Complete the trial termination record.

The Russian Federation

Visit 0: Inclusion, Allocation of Subject's number, Urinalysis, and Blood Sampling:

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 the parent(s) 1 signed original as per local regulations and practice[a].
2) Check inclusion and exclusion criteria for eligibility.
3) Collect demographic data.
4) Obtain verbal medical history about the subject, including ongoing medications and history of maternal immunization against tetanus.
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, 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) Take the subject's temperature by the axillary route.
7) Contact the IRT system for randomization /allocation of subject number / vaccine assignment.

[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 responsibility of a guardian will not be included in the study.

The signature of only 1 of the parents will be required on the ICF.

8) Obtain the first 6 mL blood sample[a] (see Section 7.1 for detailed instructions regarding the handling of blood samples). If attempts to obtain the first blood draw are unsuccessful (after attempts as per local regulations / practice), then Visit 0 can be rescheduled to a later date at which point inclusion reasonable /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) Obtain a urine sample (approximately 8 mL).[b]
10) Collect reportable concomitant medications information.
11) Complete relevant source documentation and CRF pages for the visit.
12) Confirm subject's eligibility based on the results of the baseline testing of CBC, blood chemistry, and urinalysis.

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 (1 [+4] days after Visit D0): Randomization, Inclusion, and Vaccination

Steps 1 through 4 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 5 through 10 for all subjects

Visit 1 (1 [+4] days after Visit Day 0): Inclusion, Blood Sampling (BL), and Vaccination:

4) Review warnings and precautions to vaccinations.
5) Review contraindications to vaccination
6) Contact the IRT system for randomization / allocation of subject number / vaccine assignment
7) Administer the appropriate study vaccines per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately[c].

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[a] 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 4 mL.

[b] 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.

[c] Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the CRF. If the initial vaccines are administered in the wrong limbs, this should be corrected for subsequent injections.

- ***Groups 3 and 4:*** Prevnar 13®: inject IM into the anterolateral area of the thigh (preferably the left thigh)[a]

8) Keep the subject under observation for 30 minutes and record any AE in the source document.
9) Give the parent a diary card (DC1), a thermometer, and a ruler, and go over the instructions for their use.
10) Remind the parent to expect a telephone call 8 days after Visit 1 and to bring back the diary card when they return for Visit 2 at a specified date and time.
11) Remind the parent to notify the site in case of an SAE.
12) Complete the relevant CRFs for this visit.

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

Note: If Day 8 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 has occurred that has not yet been reported, follow the instructions in Section 10 for reporting it.
2) Remind the parent 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 the next visit.

   Notify the site in case of an SAE.

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

1) If the diary card information from D0 to D07 (DC1) has not yet been obtained, obtain it at this time. Collect and review the pages of the diary card with the parent(s), including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting. Review warnings and precautions to vaccinations.
2) Review warnings and precautions for vaccinations
3) Review contraindications to subsequent vaccinations.
4) Review conditions for withdrawal.

[a] Multiple injections given in the same extremity should be separated as far as possible preferably 2.54 cm to 3.81 cm apart with a minimum of 2.54 cm. Keep the subject under observation for 30 minutes and record any AR in the source document.

5) Contact IRT system for dose number for all vaccines to be given.
6) Administer the appropriate study vaccine per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately.
    - ***For Group 3 only:*** Meningococcal vaccine: inject IM into the anterolateral area of the thigh (preferably the right thigh).[a,]
    - ***For Groups 3 and 4:*** Pentaxim®: inject IM into the anterolateral area of the thigh (preferably the left thigh).[b]
7) Keep the subject under observation for 30 minutes and record any AE in the source document.
8) Give the parent(s) a diary card (DC2).
9) Remind the parent(s) to expect a telephone call 8 days after Visit 2 and to bring back the diary card when they return for Visit 3 at a specified date and time.
10) Remind the parent(s) to notify the site in case of an SAE.
11) Complete the relevant CRFs for this visit.

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

Refer to steps in Telephone Call 1.

Visit 3 (45 [+14] days after Visit 2): Collection of Safety Information and Vaccination

1) If the diary card information from D0 to D07 (DC2) has not yet been obtained, obtain it at this time. Review the subject's relevant medical history with the parent, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review warnings and precautions to vaccinations.
3) Review contraindications to subsequent vaccinations.
4) Review conditions for withdrawal.
5) Contact IRT system for dose number for all vaccines to be given.

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[a] The only other vaccine that can be administered with the meningococcal vaccine in the right thigh is ENGERIX-B®. Do not administer Pentaxim® or PREVENAR 13® in the right thigh.

[b] Multiple injections given in the same extremity should be separated as far as possible preferably 2.54 cm to 3.81 cm apart with a minimum of 2.54 cm. Keep the subject under observation for 30 minutes and record any AR in the source document.

6) Administer the appropriate study vaccine per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately.
    - Prevnar 13®[a]: inject IM into the anterolateral area of the thigh (preferably the right thigh).
    - Pentaxim®: inject IM into the anterolateral area of the thigh region (preferably the left thigh).
7) Keep the subject under observation for 30 minutes and record any AEs in the source document.
8) Give the parent(s) a diary card.
9) Remind the parent to return for Visit 4 at a specified date and time.
10) Remind the parent(s) to notify the site in case of an SAE.
11) Complete the relevant CRFs for this visit.

Visit 4 (45 [+14] days after Visit 3): Collection of Safety Information and Vaccination

1) Obtain the diary card information from D0 to D07 (DC3). Review the subject's relevant medical history with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review warnings and precautions to vaccinations.
3) Review contraindications to subsequent vaccinations.
4) Review conditions for withdrawal.
5) Contact IRT system for dose number for all vaccines to be given.
6) Administer the appropriate study vaccine per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately.
    - ***For Group 3 only:*** Meningococcal vaccine: inject IM into the anterolateral area of the thigh (preferably the right thigh).[b]
    - ***For Groups 3 and 4:***

      Pentaxim®: inject IM into the anterolateral area of the thigh (preferably the left thigh).

      ENGERIX B®: inject IM into the middle third of the anterolateral thigh region.

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[a] No endpoints will be measured for this vaccine, as it is considered out of scope for this study.

[b] The only other vaccine that can be administered with the meningococcal vaccine in the right thigh is ENGERIX-B®. Do not administer Pentaxim® or PREVENAR 13® in the right thigh.

7) Keep the subject under observation for 30 minutes and record any AE in the source document.
8) Give the parent(s) a diary card (DC4)
9) Remind the parent(s) to expect a telephone call 8 days after Visit 3 and to bring back the DC when they return for Visit 5 at a specified date and time.
10) Remind the parent(s) to notify the site in case of an SAE.
11) Complete the relevant CRFs for this visit.

Telephone Call 3 (8 [+2] days after Visit 4)

Refer to steps in Telephone Call 1.

Visit 5 (30 days [+14] days after Visit 4): Collection of Safety Information and Blood Sampling

1) Obtain the diary card information from D0 to D07 (DC4). Review the subject's relevant medical history with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review temporary contraindications for blood sampling. Ensure the subject has not had any antibiotics within the previous 72 hours (3 days).
3) Collect 6 mL blood sample (BL0002) (see Section 7.1 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 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
4) Give the parent(s) a diary card (DC5)
5) Remind the parent(s) to return for Visit 6 at a specified date and time.
6) Complete the relevant CRFs for this visit.

Telephone Call 4 (Visit 6 - 14 [+ 2 days])

1) Contact the subjects' parent/ guardian by telephone within 14 days before Visit 6 to remind them about the forthcoming study visit.
2) If the subject's participation in the study is discontinued:
   a. Review the diary card including any AEs, medications, or therapy that occurred since the last visit.
   b. Ask the subject's parents(s) if the subject has experienced any SAE in the time since vaccination that has not been reported to the study personnel. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
   c. Make arrangements to retrieve the diary card.

Visit 6 (5 months [+14 days] after Visit 5): Collection of Safety Information and Vaccination

1) If the diary card information from D0 to D07 (DC5) has not yet been obtained, obtain it at this time. Review the subject's relevant medical history with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review the subject's relevant medical history with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination.
3) Review warnings and precautions to vaccinations.
4) Review contraindications to subsequent vaccinations.
5) Review conditions for withdrawal.
6) Contact IRT system for dose number for all vaccines to be given.
7) Administer the appropriate study vaccine per Operating Guidelines. Each vaccine should be administered in an assigned location and documented appropriately.
    - ***For Group 3 only:*** Meningococcal vaccine: inject IM into the anterolateral area of the thigh (preferably the right thigh).[a, b]
    - ***For Groups 3 and 4:*** MMR[b]
8) Keep the subject under observation for 30 minutes and record any AE in the source document.
9) Give the parent(s) (DC6).
10) Remind the parent(s) to expect a telephone call 8 days after Visit 3 and to bring the completed diary card when they return for Visit 7 at a specified date and time.
11) Remind the parent(s) to notify the site in case of an SAE.
12) Complete the relevant CRFs for this visit.

Telephone Call 5 (8 [+2] days after Visit 6)

Refer to steps in Telephone Call 1.

Visit 7 (30 [+14] days after Visit 6: Collection of Safety Information, Blood Sampling, and Trial Termination

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[a] The only other vaccine that can be administered with the meningococcal vaccine in the right thigh is ENGERIX-B®. Do not administer Pentaxim® or PREVENAR 13® in the right thigh.

[b] Multiple injections given in the same extremity should be separated as far as possible preferably 2.54 cm to 3.81 cm apart with a minimum of 2.54 cm. Keep the subject under observation for 30 minutes and record any AR in the source document.

1) If the diary card information from D0 to D07 (DC6) has not yet been obtained, obtain it at this time. Collect and review the pages of the diary card with the parent, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review temporary contraindications to blood sampling
3) Collect 6 mL blood sample[a] (BL0003) (for CBC, blood chemistry, and immunogenicity assessment [see Section 7.1 for detailed instructions regarding the handling of blood samples]) and 8 mL urine sample for urinalysis.
4) Remind the parent to notify the site in case of an SAE.

5.1.5 Planned Study Calendar

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

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject): 18 October 2018 to 26 January 2022

Planned inclusion period - FVFS to FVLS (first visit, last subject): 18 October 2018 to 18 December 2020

Planned primary vaccination period: 18 October 2018 to 14 December 2021

Planned end of study: 26 January 2022

Planned date of final clinical study report: 23 June 2023

5.2 Enrollment and Retention of Study 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 (eg, 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.

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[a] 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 7. In this case, the blood sample volume collected at Visit 7 will be 4 mL.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject and / or a parent and / or a guardian[a] voluntarily confirms his or her willingness to participate in a particular study. 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 parent / guardian must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

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 prior to the form being used.

If new information becomes available that may be relevant to the parent's / guardian's willingness to continue participation in the study, 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.

In Mexico

Informed consent forms will be provided in duplicate, or a photocopy of the signed consent will be made. The original will be kept by the Investigator, and the copy 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

Informed consent forms are provided in duplicate (in 2 originals). One of the signed, original forms will be kept by the Investigator, and 1 signed, original form will be kept by the subject's parent(s).

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 1 of the parents will be required on the ICF.

5.2.3 Screening Criteria

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

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[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 responsibility of a guardian will not be included in the study.

The signature of only 1 of the parents will be required on the ICF.

For the Russian Federation, in accordance with local practices for the conduct of clinical trials, 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 CBC and blood chemistry. These subjects will also provide a urine sample for urinalysis. The results of CBC and biochemistry laboratory tests as well as urine chemistry tests, performed for the subject in terms of routine practice, can be used, if the tests were done within 7 days before and in this case no additional samples should be taken.

The 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 to be eligible for study enrollment:

1) Infants 2 months of age (60 to 89 days of age) on the day of the first study visit. [a]
2) Born after a full-term pregnancy with an estimated gestation age ≥ 37 weeks and a birth weight ≥ 2.5 kg
3) Informed consent form has been signed and dated by the parent(s) or guardian(s), as required by local regulations[b]
4) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures
5) In good health as determined by medical history and physical assessment.

For the Russian Federation:

6) The subject's parent(s) are able to verbally report or provide written documentation that the subject's mother was hepatitis B antigen-negative during pregnancy with the subject.

5.2.5 Exclusion Criteria

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

1) Participation at the time of study enrollment or 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.

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[a] "2 months" means from the 2nd month after birth to the day before the 3rd month after birth (2 months to 2 months 29 days); "60" days means from the 60th day after birth to the day before the 90th day after birth (60 to 89 days).

[b] 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.

2) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks before and/or following any trial vaccination except for influenza vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccination. 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 (ie, meningitis polysaccharide or meningitis conjugate vaccine containing serogroups A, C, Y, or W; or meningococcal B serogroup-containing vaccine).
4) Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, poliovirus, rotavirus, *Streptococcus pneumoniae*, measles, mumps, rubella, and / or varicella.
5) ***For Mexico:*** More than 1 previous dose of hepatitis B vaccine.
6) Receipt of immune globulins, blood or blood-derived products since birth.
7) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth.
8) Family history of congenital or hereditary immunodeficiency until the immune competence of the potential vaccine recipient is demonstrated.
9) Individuals with blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
10) Individuals with active tuberculosis
11) History of any *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically.
12) History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and /or rotavirus infection/disease.
13) At high risk for meningococcal infection during the trial (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).
14) History of intussusception.
15) History of any neurologic disorders, including seizures (febrile and nonfebrile) and progressive neurologic disorders.
16) History of Guillain-Barré syndrome.

17) Known systemic hypersensitivity to any of the vaccine components or to latex, 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, including neomycin, gelatin, and yeast[a].
18) Verbal report of thrombocytopenia contraindicating IM vaccination in the Investigator's opinion.
19) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination in the Investigator's opinion.
20) Receipt of oral or injectable antibiotic therapy within 72 hours of the first blood draw.
21) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion[b].
22) Any condition which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives.
23) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38°C[c]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
24) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.

If the subject has a primary physician who is not the Investigator, the site must contact this physician with the subject's parent's / guardian's consent to inform him / her of the subject's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

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 (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the subject is or has been followed by a physician or conditions/illnesses 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 (electronic) case report book (CRB). The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

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[a] The components of all study vaccines are listed in Section 6.1.1 and in the Investigator's Brochure

[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.

[c] For the Russian Federation, febrile illness is defined as temperature ≥ 37°C. A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

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 in lieu of a diagnosis 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 study.

For the Russian Federation Only

Any clinically significant abnormal results of the Visit 0 CBC, blood chemistry, or urinalysis according to Investigator's 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, and urinalysis 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

5.2.7.1 Temporary Contraindications

Should a subject experience one of the conditions listed below, the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the Table of Study Procedures.

- Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38°C[a]). The vaccine should not be administered until the condition has resolved or the febrile event has subsided.
- Planned receipt of any vaccine in the 4 weeks before or after any study vaccination except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any

[a] For the Russian Federation, febrile illness is defined as temperature ≥ 37°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

5.2.7.2 Definitive Contraindications[a]

The following AEs constitute absolute contraindications to subsequent vaccination with any of the study vaccines. If a subject should experience any of these events during the study, that subject is not to receive any additional study vaccines but should continue in the study and be followed up for safety only as per protocol up to 6 months after the last vaccination received.

MenACYW conjugate vaccine:

1) History of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine.
2) History of Guillain-Barré syndrome within 6 weeks after vaccination with a tetanus toxoid-containing vaccine
3) Severe allergic reaction (eg, anaphylaxis) after a previous dose of vaccine, any component of the vaccine, or any other tetanus toxoid or meningococcal-containing vaccine.

Menveo® (Mexico only):

4) Severe allergic reaction (eg, anaphylaxis) after a previous dose of Menveo®, any component of this BL vaccine, or any other CRM197, diphtheria toxoid or meningococcal-containing vaccine is a contraindication to administration of Menveo®.

M-M-R®II (Mexico only):

5) Hypersensitivity to any component of the vaccine, including gelatin.
6) Anaphylactic or anaphylactoid reactions to neomycin.
7) Active untreated tuberculosis.
8) Patients receiving immunosuppressive therapy. (This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, eg, for Addison's disease.)
9) Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
10) Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with HIV; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

[a] This list is not definitive and is not the final list of contraindications to vaccination. The investigators at each site should refer to the local package inserts and / or reference safety information for each of the routine pediatric vaccines when making these judgements and decisions.

Prevnar 13® (pneumococcal 13 – valent conjugate vaccine):

For Mexico:

11) Severe allergic reaction (eg, anaphylaxis) to any component of Prevnar 13® or any diphtheria toxoid-containing vaccine.

12) Infants or children with coagulation disorders, premature infants.

For the Russian Federation:

13) Allergic reaction after previous dose of Prevnar 13® or Prevnar® (including, anaphylactic shock, severe generalized allergic reactions).

14) Hypersensitivity to diphtheria toxoid and / or any other component of Prevnar 13®.

Hexacima® (Mexico only) (DTaP-IPV//Hib vaccine):

1) Hypersensitivity to any of the active substances, or to any of the excipients contained in the formula, or to any pertussis-containing vaccine, or after a previous administration of the vaccine or any other vaccine that contains the same components or constituents.
2) Vaccination must be postponed in the case of moderate to high fever and/or in the presence of any acute disease. A mild infection and/or low grade fever does not represent a contraindication.
3) Vaccination with Hexacima® is contraindicated if the infant that experienced an encephalopathy of unknown origin during the 7 days after the administration of any pertussis-containing vaccine (acellular or "whole cell"). Under these circumstances the anti-pertussis vaccination must be suspended and the vaccination against diphtheria, tetanus, hepatits B, poliovirus and Hib must be continued.
4) Uncontrolled neurologic disorder and nervous system or uncontrolled epilepsy: The pertussis-containing vaccines must be stopped until the treatment for this condition has been established, the affection is controlled and the benefit versus the risk of vaccination must be evident.

PENTAXIM®

For the Russian Federation:

1) Evolving encephalopathy with or without convulsions.
2) Encephalopathy of unknown origin within 7 days following a previous dose of any vaccine containing *Bordetella pertussis* antigens (whole-cell or acellular pertussis vaccines).
3) Strong reaction within 48 hours of a previous dose of any vaccine containing pertussis component: fever ≥ 40°C, abnormal prolonged crying syndrome (longer than 3 hours), febrile and afebrile seizures, hypotonic-hyporesponsive syndrome.
4) Hypersensitivity reaction after a previous dose of any vaccine against diphtheria, tetanus, pertussis, polio or *(Haemophilus influenzae* type b) Hib-infection.
5) Hypersensitivity reaction to any component of the vaccine, including glutaraldehyde, neomycin, streptomycin and polymyxin B.

ENGERIX-B® (hepatitis B vaccine)[a]:

For the Russian Federation:

1) Hypersensitivity to any component of the vaccine (and baker's yeast) or manifestations of hypersensitivity reaction, as well as severe reaction (fever > 40°C, swelling and redness > 8 cm in diameter at the site of administration) after previous administration of ENGERIX-B®[b] vaccine.

RotaTeq® (rotavirus vaccine):

For Mexico:

1) Hypersensitivity to any component of the vaccine.
2) Individuals who develop symptoms suggestive of hypersensitivity after receiving a dose of pentavalent rotavirus vaccine (RV5) (RotaTeq®) should not receive further doses of RV5 (RotaTeq®).
3) Individuals with Severe Combined Immunodeficiency Disease (SCID). Cases of gastroenteritis associated with vaccine virus have been reported post-marketing in infants with SCID.

5.2.8 Conditions for Withdrawal

Parents / Guardians will be informed that they have the right to withdraw their child from the study at any time.

A subject may be withdrawn from the study:

1) At the discretion of the Investigator or Sponsor due to safety concerns or significant non-compliance with the protocol (based on the Investigator's judgment), without the subject's permission (withdrawal)
2) At the request of the parent / guardian (dropout)

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

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

Withdrawn subjects will not be replaced.

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[a] HIV infection is not considered as a contraindication for hepatitis B vaccination.

[b] In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed hepatitis B vaccine will be administered instead.

5.2.9 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (ie, 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 CRB and in the source documents.

5.2.10 Classification of Subjects Who Discontinue the Study

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

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.3.2.1. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject's parent / guardian cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.9. The certified letter was sent by the Investigator and returned unsigned, and the parent/guardian did not give any other news and did not bring the child to any following visit.
Protocol Deviation	To be used: In case of significant non-compliance with the protocol (eg, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). If the subject experiences a definitive contraindication that is a protocol deviation. The parent/guardian signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit.
Withdrawal by Subject or Parent / Guardian / Legally Acceptable Representative	To be used: When the parent/guardian indicated unwillingness to continue in the study When the parent/guardian made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the study because of an AE, a protocol deviation, or loss of eligibility, including definitive 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.

If the subject's status at the end of the study is "Withdrawal by Subject or Parent / Guardian / Legally Acceptable Representative", the site will attempt to contact the subjects parents except if they specified that they do not want to be contacted again and it is documented in the source document.

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 study 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 the Global PharmacoVigilance (GPV) Department (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 Study and Protocol

Any amendments to this study 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. All substantial amendments (eg, those that affect the conduct of the study or the safety of subjects) require IEC / IRB approval, and must also be forwarded to regulatory authorities.

An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. The IECs / IRBs may be informed, as per local regulations.

The Investigator is responsible for ensuring that changes to an approved study, 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 Study

The study may be discontinued if new data about the investigational product resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in the countries where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) (CROs) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subjects' parents/guardians and should assure appropriate subject therapy and/or follow-up.

There will be an internal team at the level of the Sponsor (SMT), which will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The SMT is empowered to recommend a pause in both recruitment and / or further vaccination while it investigates any potential signal or concern.

6 Vaccines Administered

For proper management of the supply and accountability of the products, MenACYW conjugate vaccine will be considered an Investigational Medicinal Product (IMP). All other vaccines will be classified as IMP or non-investigational medicinal products (NIMPs), in accordance with the national laws and regulations of each country.

6.1 Identity of the Investigational Products

Identity of the Investigational Products

6.1.1 Identity of Study Product

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

Form: Liquid solution

Dose: 0.5 milliliter (mL)

Route: IM

Batch number: To be determined (TBD)

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 micrograms (µg)
Serogroup C ..... 10 µg
Serogroup Y ..... 10 µg
Serogroup W ..... 10 µg

Tetanus toxoid protein carrier ..... approximately 55 µg[a]

6.1.1.2 Preparation and Administration

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

[a] Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation.

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. A replacement 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.

The site of IM injection should be prepared with a suitable antiseptic prior to administration of 1 dose (0.5 mL) of MenACYW conjugate vaccine in the thigh (preferably the right thigh). After vaccine administration, 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 each vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

Each 0.5 mL dose is to be injected IM into anterolateral area of the thigh.

6.1.1.3 Dose Selection and Timing

Subjects in Group 1 and Group 2 (Mexico) will receive MenACYW conjugate vaccine administered at 2, 6, and 12 months of age.

Subjects in Group 3 (the Russian Federation) will receive MenACYW conjugate vaccine administered at 3, 6, and 12 months of age.

6.1.2 Identity of Control Product

Menveo®: Meningococcal (Groups A, C, Y and W 135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine (GlaxoSmithKline Vaccines, Srl, Bellaria-Rosia 53018, Sovicille [SI], Italy)

Form: Lyophilized powder and liquid components are combined to produce a Solution for Intramuscular Injection

Dose: 0.5 mL

Route: IM

Batch number: TBD

6.1.2.1 Composition

Each 0.5 mL dose of vaccine contains the following active ingredients:

MenA oligosaccharide	10 µg
MenC oligosaccharide	5 µg
MenY oligosaccharide	5 µg
MenW-135 oligosaccharide	5 µg
CRM_{197} protein	32.7 to 64.1 µg

Other ingredients per 0.5 mL dose: residual formaldehyde ..... < 0.30 µg

6.1.2.2 Preparation and Administration

Menveo® is supplied in 2 vials that must be combined prior to administration: reconstitute the MenA lyophilized conjugate vaccine component with the MenCYW-135 liquid conjugate vaccine component immediately before administration.

See the investigational labeling for Menveo® for precautions and administration instructions.

Each 0.5 mL dose is to be injected IM into the anterolateral thigh area.

6.1.2.3 Dose Selection and Timing

Subjects in Group 2 (Mexico) will receive Menveo® administered at 2, 4, 6, and 12 months of age.

6.2 Identity of Other Products

6.2.1 Identity of Other Product 1

M-M-R®II (Measles, Mumps, and Rubella Virus Vaccine Live) (Merck & Co., Inc., Whitehouse Station, NJ, USA)

Form: Lyophilized live virus vaccine

Dose: 0.5 mL

Route: SC

Batch number: TBD

6.2.1.1 Composition

Each 0.5 mL dose contains live attenuated virus:

Measles virus (derived from Ender's Edmonston strain) propagated in chick embryo cell culture .....not less than 1000 $TCID_{50}$

Mumps virus (Jeryl Lynn™ [B level] strain) propagated in chick embryo cell culture .....not less than 12,500 $TCID_{50}$

Rubella virus (Wistar RA 27/3 strain) propagated in WI-38 human diploid lung fibroblasts .....not less than 1000 $TCID_{50}$

Each 0.5 mL dose is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin (< 0.3 mg), fetal bovine serum (< 1 parts per million [ppm]), other buffer and media ingredients and approximately 25 µg of neomycin.

6.2.1.2 Preparation and Administration

See the M-M-R®II package insert (42) for specific precautions and the procedure for preparing and administering M-M-R®II.

Each 0.5 mL dose is to be injected SC into the outer aspect of upper arm.

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.

6.2.1.3 Dose Selection and Timing

Subjects in Groups 1 and 2 (Mexico) will receive M-M-R®II administered at 12 months of age.

Subjects in Group 3 and 4 (the Russian Federation) will receive MMR administered at 12 months of age.

6.2.2 Identity of Other Product 2

Monosodium L-glutamate 0.5 mg
Sodium **Prevnar 13®:** Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Pfizer Inc, Philadelphia, PA, USA)

Form: Suspension for injection

Dose: 0.5 mL

Route: IM

Batch number: TBD

6.2.2.1 Composition

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

Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides	approximately 2.2 µg of each
6B saccharides	4.4 µg

Excipients:

CRM_{197} carrier protein	34 µg
Polysorbate 80	100 µg
Succinate buffer	295 µg
Aluminum as aluminum phosphate adjuvant	125 µg

6.2.2.2 Preparation and Administration

Prevnar 13® is supplied in a single-dose prefilled syringe.

See the Prevnar 13® package insert (43) for specific precautions and the procedure for preparing and administering Prevnar 13®.

Each 0.5 mL dose is to be injected IM middle section of lower third of the anterolateral region of the right thigh.

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.

6.2.2.3 Dose Selection and Timing

Subjects in Groups 1 and 2 (Mexico) will receive Prevnar 13® administered at 2, 4, 6, and 12 months of age.

Subjects in Groups 3 and 4 (the Russian Federation) will receive Prevnar 13®[a] administered at 2 and 4.5 months of age.

6.2.3 Identity of Other Product 4

Hexacima® (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, Lyon, France); (licensed in Mexico as Hexacima®)

Form: Suspension for injection

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.2.3.1 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

[a] No endpoints will be measured for this vaccine, as it is considered out of scope for this study

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.

6.2.3.2 Preparation and Administration

Hexacima® 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, 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 Hexacima® 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 Hexacima® are detailed in the Package Insert.

6.2.3.3 Dose Selection and Timing

All subjects in Groups 1 and 2 (Mexico) will receive a total of 4 doses of Hexacima®, administered at 2, 4, 6, and 12 months of age.

6.2.4 Identity of other product 5

Pentaxim®: (Diphtheria, Tetanus, Pertussis (Acellular, Component) Poliomyelitis (inactivated) Vaccine, (Adsorbed) and *Haemophilus influenza* type b Conjugate Vaccine (Sanofi Pasteur S.A., France.

Form: Powder and suspension for injection.

Dose: 0.5 mL

Route: IM

Batch number: TBD

6.2.4.1 Composition

Each 0.5 mL dose contains, after reconstitution:

Diphtheria Toxoid .....≥ 30 IU
Tetanus toxoid .....≥ 40 IU

Bordetella pertussis antigens:

Toxoid (PT) .....25 µg
Filamentous hemagglutinin (FHA).....25µg

Poliomyelitis virus:

Type 1 .....40 D-antigen units (DU)
Type 2 ..... 8 DU
Type 3 ..... 32 DU

Polysaccharide of *Haemophilus influenzae type b conjugated to tetanus protein* .....10 µg
Tetanus toxoid (PRP-T).....24 µg

Excipients:

Saccharose, trometamol, aluminium hydroxide. Hanks' medium without phenol red, acetic acid and / or sodium hydroxide for pH adjustment, formaldehyde, phenoxyethanol, water for injections

6.2.4.2 Preparation and Administration

Pentaxim® is supplied as a powder and suspension for injection.

See the Pentaxim® package insert (44) for precautions and the procedure for preparing and administering Pentaxim®.

Each 0.5 mL dose is to be injected IM into the anterolateral area of the thigh.

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.

6.2.4.3 Dose Selection and Timing

Subjects in Groups 3 and 4 (the Russian Federation) will receive Pentaxim® administered at 3, 4.5, and 6 months of age.

6.2.5 Identity of Other Product 6

ENGERIX-B®: (Hepatitis B Vaccine [Recombinant]) (GlaxoSmithKline Biologicals 441 Rixensart, Belgium)

Form: Suspension for injection
Dose: 0.5 mL
Route: IM
Batch number: TBD

6.2.5.1 Composition

Each 0.5 mL pediatric/adolescent dose contains 10 µg of hepatitis B virus surface antigen adsorbed on 0.25 mg aluminum as aluminum hydroxide.

Excipients:

Sodium chloride	9 mg/mL
Disodium phosphate dihydrate	0.98 mg/mL
Sodium dihydrogen phosphate dihydrate	0.71 mg/mL

6.2.5.2 Preparation and Administration

ENGERIX-B® is supplied as 0.5 mL prefilled syringes.

See the ENGERIX-B® package insert (45) for specific precautions and the procedure for preparing and administering ENGERIX-B®.

Each 5 mL dose is to be injected IM middle third of the anterolateral thigh region. 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.

6.2.5.3 Dose Selection and Timing

Subjects in Groups 3 and 4 (the Russian Federation) will receive ENGERIX-B® administered at 6 months of age.

6.2.6 Identity of Other Product 7

RotaTeq®: (Rotavirus Vaccine, Live, Oral, Pentavalent) (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)

Form: Oral solution

Dose: 2 mL

Route: PO

Batch number: TBD

6.2.6.1 Composition

Each 2 mL dose contains the following 5 live reassortant rotaviruses:

G1 serotype	2.2×10^6 infectious units
G2 serotype	2.8×10^6 infectious units
G3 serotype	2.2×10^6 infectious units
G4 serotype	2.0×10^6 infectious units
P1A(8)	2.3×10^6 infectious units

The reassortants are suspended in a buffered stabilizer solution.

Each 2 mL vaccine dose also contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum.

6.2.6.2 Preparation and Administration

RotaTeq® is supplied in a container consisting of a squeezable plastic dosing tube with a twist-off cap, allowing for direct PO administration.

See the RotaTeq® package insert (46) for specific precautions and for the procedure for preparing and administering RotaTeq®.

Each 2 mL dose is to be administered PO, according to the instructions in the package insert.

6.2.6.3 Dose Selection and Timing

Subjects in Groups 1 and 2 (Mexico) will receive RotaTeq® administered at 2, 4, and 6 months of age.

6.3 Product Logistics

6.3.1 Labeling and Packaging

MenACYW conjugate vaccine and Menveo® will be supplied by the Sponsor and will be labeled and packaged in cartons, according to national regulations. The content of the label, and the language in which it is written, will also be in accordance with the local regulatory specifications and requirements. Each carton will have 2 detachable labels to enable identification of the Investigational Products and provide information on the study. The detachable carton labels may be affixed to source documents and the subject's vaccination card. See the Operating Guidelines for additional details.

All other vaccine products will be packaged and labeled according to the regulations of each country. Where permitted by national laws and regulations, the remaining vaccine products will retain their original commercial labels and packaging. Additional labels will be applied, as necessary, in the appropriate language, according to national laws and 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 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 (ie, 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. The Study and Control Products (MenACYW conjugate vaccine or Menveo®) will be stored in a refrigerator at a temperature ranging from +2°C to +8°C and never frozen. All commercially labeled products should be stored according to the manufacturer's instructions. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the study 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 study 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 CRB. If applicable, information may also be entered into the subject's vaccination card.

The Sponsor's monitoring staff will verify the study site's product accountability records against the record of administered doses in the CRBs and the communication from the IRT system.

In case of any expected or potential shortage of product during the study, 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 (eg, because the vial broke or particulate matter was observed in the syringe), the site personnel must either contact the IRT system 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 study 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

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and whose parent / guardian signs the ICF will be randomly assigned in a 2:1 ratio in Mexico, and in a 2:1 ratio in the Russian Federation such that Group 1 will have 200 subjects, Group 2 will have 100 subjects, Group 3 will have 150 subjects, and Group 4 will have 75 subjects.

Site staff will connect to the IRT system, enter the identification and security information, and confirm a minimal amount of data in response to IRT-system prompts. The IRT system will then provide the vaccine assignment and subject number. The full detailed procedures for Group allocation are described in the Operating Guidelines. If a subject who has enrolled is not eligible to participate in the study, then the subject's information will only be recorded on the subject-recruitment log.

Subject numbers that are assigned by the IRT system will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). For example, Subject 840000100005 is the fifth subject enrolled in Center Number 1 in the US (840 being the US country code).

Subject numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT system.

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 study personnel.

The person in charge of product management at the site will maintain accountability records of product delivery to the study 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 but not limited to other therapies (eg, blood products), should be recorded in the source documents. All new medications prescribed for new medical conditions / AEs during study participation should also be recorded in the source documents.

Documentation in the CRB of concomitant medication(s) will be limited to specific categories of medication(s) (Categories 1, 2, and 3 as detailed below). Those will include Category 1, 2, and 3 medications ongoing at the time of inclusion in the study, or started at any time during the subject's participation in the trial. For category 3 medication, the period of reporting in CRB will be restricted to only 3 days (72 hours) prior to each blood sampling time point.

Collection period in source documents

Reportable medications (Category 1, 2, and 3) will be collected in the source documents from the day of first vaccination to the end of the trial. [a]

Categories of Reportable medications and reporting period

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination.

- Category 1: Reportable medications with potential impact on the evaluation of the safety of the study vaccines. For example, antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids (therapy duration less than 2 weeks), and other immune modulators. Category 1 medications do not define the Per-Protocol Analysis Set (PPAS).

Note: Topical steroids (Inhaled, otic, ophthalmic, nasal etc.) should not be captured or reported.

  Category 1 medications will be reported in the CRB from the day of first vaccination to the end of the solicited and unsolicited follow-up period after each vaccination. These medications will also be collected in the CRB for the 30- day period prior to the subsequent doses of the vaccine, wherever applicable (second, third, fourth, etc., in case of a multi-dose schedule with more than a 30-day interval between doses).

- Category 2: Reportable medications with potential impact on immune response of the study vaccines and used to define the Per-Protocol Analysis Set (PPAS). For example:
  - Flu vaccines administered within 14 days pre or post each trial vaccination, including the day of the study vaccination visit

    Any vaccine other than study vaccines (vaccines non-described in the Protocol) within the 28 days (4 weeks) preceding or after the trial vaccination, including the day of the study vaccination visit.
  - 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 immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone

[a] Subjects/ Subject's parents will be required to document all medications received in the Diary Cards. The sites will focus on only recording the medications belonging to the 3 categories in the other source documents.

or equivalent for more than 2 consecutive weeks) within past 3 months, anti-cancer chemotherapy, anti-proliferative drugs such as DNA synthesis inhibitors, or radiation therapy: used in the 6 months preceding the first trial vaccination, and up to the last blood draw.

Category 2 medications will be reported in the CRB during the study period up to the last blood draw.

- Category 3: Systemic (Oral or injectable) antibiotics, as they may interfere with bioassays used for antibody testing when taken before a blood draw. Antibiotics that the subject received within 72 hours preceding each visit for blood draw related to IMP assessment (meningococcal vaccines) and used to define the PPAS. Category 3 medications will be reported in the CRB for the period of 3 days (72 hours) before each blood draw.

Note: Topical antibiotics (Inhaled, otic, ophthalmic, nasal, etc.) should not be captured or reported.

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

- Trade name
- Rationale for the origin of prescription: Whether it was a prophylactic[a] medication. Prophylactic medications will be recorded in the Action Taken section of the AE collection tables
- Medication category (1, 2, or 3)
- Start and stop dates
- Dosage and administration route, homeopathic medication, will not be recorded.

If the subject has received medications other than those listed in Categories 1, 2, and 3, the detailed information will be collected in the source documents only.

Medications given to treat an AE will be captured in the "Action Taken" section of the AE CRB only. No details will be recorded in the concomitant medication CRB unless the medication(s) received belongs to one of the prelisted categories.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

[a] Medication(s) prescribed for preventing AE occurrence (e.g. paracetamol to reduce the risk of fever)

7.1 Sample Collection

7.1.1 Blood Samples

For Immunogenicity

At Visit 0 (Groups 3 and 4) 4 mL of blood will be drawn in tubes provided by or recommended by the Sponsor. At Visits 1, 4, and 6 (for Groups 1 and 2), and at Visits 5 and 7 (Groups 3 and 4), 6 mL of blood will be drawn 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 write 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. Blood is to be taken from the limb opposite to the one that will be used for vaccination, when possible.

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

Blood samples (volume based on local laboratory needs) for CBC and blood chemistry will be collected in a separate tube from the sample for immunogenicity. The CBC and biochemistry tests will be prioritized by the Investigator following their medical judgment and in accordance with the local hospital's standard practice. 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 and Visit 7. The total blood volume will be a maximum of 6 mL for Group 3 and Group 4 at Visits 0, 5 and 7.

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 Visit 0 /Visit 1 and Visit 7. 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.

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.

7.2 Sample Preparation

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

7.2.1 Blood 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 Blood Samples

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 study. 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.

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 United Nations Class 6.2 specifications and the International Air Transport Association 602 packaging instructions.

Samples will be shipped to R&D Global Operations at Sanofi Pasteur. The address is provided in the Operating Guidelines. Samples will be shipped outside of the country only after the approval from 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 R&D Global Operations for at least 25 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested.

For subjects in Mexico only: Depending on local regulations, subjects' parents / guardians will be asked to indicate in the ICF 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 existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

The above paragraph 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 study sites with protocols, ICFs, CRBs, SAE reporting forms, diary cards, and other study documents, as well as with the following study materials: all study vaccines, 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 study.

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. Additional details are provided in the Operating Guidelines.

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.

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:

- Meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:8 measured by hSBA, assessed at 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine or Menveo® in Mexico (Group 1 and Group 2)
- Meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:8 measured by hSBA assessed at 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine in the Russian Federation (Group 3)

9.1.1.2 Immunogenicity Assessment Methods

All assays will be performed at GCI, Swiftwater, Pennsylvania (PA) or at a qualified contract laboratory for GCI. The assay method to be used is summarized below. Laboratory technicians conducting the immunogenicity assays will be blinded to the group to which each subject was assigned.

Antibodies to meningococcal antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in hSBA. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. Serogroup-specific meningococcal bacteria along with human complement are added to the serum dilutions and allowed to incubate. After this incubation period, an agar overlay medium is added to the serum/complement/bacteria mixture, allowed to harden, and then incubated overnight at 37°C with 5% carbon dioxide (CO_2). Bacterial colonies present in the wells are then counted. The endpoint titer is determined by the reciprocal serum dilution yielding ≥ 50% killing as compared to the mean of the complement control wells. The lower limit of quantitation (LLOQ) of the hSBA assay is a titer of 1:4.

This method will be performed on all samples collected from Groups 1, 2, and 3.

9.1.2 Safety

There are no primary objectives for safety.

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:

1) Meningococcal serogroups A, C, Y, and W antibody titers measured by hSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine or Menveo® (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo® in Mexico (Group 1 and Group 2) (vaccine seroresponse[a])
2) Meningococcal serogroups A, C, Y, and W antibody titers measured by hSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine (Dose 2 of MenACYW conjugate vaccine) in the Russian Federation (Group 3) (vaccine seroresponse)
3) The following serological endpoints will be described for Mexico (Groups 1 and 2):

- Day 0 (before the first vaccinations with Hexacima® and RotaTeq®):
  - Anti-pertussis antibody concentrations (PT and FHA)
  - Anti-rotavirus serum immunoglobulin (Ig) A antibody concentrations
- 30 days after the 6-months vaccinations with Prevnar 13® and RotaTeq®:
  - Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
  - Anti-pneumococcal antibody concentrations (PCV13) ≥ 0.35 µg/mL and 1.0 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
  - Anti-rotavirus serum IgA antibody concentrations
  - Anti-rotavirus serum IgA antibody concentrations with ≥3-fold and ≥4-fold rise over baseline

[a] hSBA vaccine seroresponse for serogroups A, C, W, and Y 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 ≥ 4-fold greater than the pre-vaccination titer.

- 30 days after the 12-months vaccinations with M-M-R®II, Prevnar 13®, and Hexacima®:
  - Antibody concentrations/titers for all antigens
  - Anti-pneumococcal antibody concentrations (PCV13) ≥ 0.35 µg / mL and 1.0 µg / mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
  - Anti-measles antibody concentrations (serostatus cutoff 225 mIU / mL)
  - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units / mL)
  - Anti-rubella antibody (serostatus cutoff: 10 IU / mL)
  - Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-pertussis (PT and FHA) vaccine response[a]
  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations and ≥ 0.15 µg / mL and 1.0 µg / mL
  - Anti-HBs concentrations ≥ 10 mIU / mL and 100 mIU / mL

<u>The following serological endpoints will be described for the Russian Federation (Groups 3 and 4):</u>

- Day 0 (before the first vaccination with Pentaxim®):
  - Anti-pertussis antibody concentrations (PT and FHA)
- 30 days after the 6-months vaccinations with Pentaxim® and ENGERIX-B®:
  - Antibody concentrations/titers for all antigens
  - Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-pertussis (PT and FHA) vaccine response
  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations and ≥ 0.15 µg / mL and 1.0 µg / mL
  - Anti-HBs concentrations ≥ 10 mIU / mL and 100 mIU / mL
- 30 days after the 12-months vaccination with MMR:
  - Antibody concentrations for measles, mumps and rubella

[a] Pertussis vaccine response definition:

- If the pre-vaccination concentration is >= 4 x LLOQ, then the post-vaccination concentration is >= pre-vaccination concentration
- If the pre-vaccination concentration is < 4 x LLOQ, then the post-booster vaccination concentration is >= 4 x LLOQ

- Anti-measles antibody concentrations (serostatus cutoff 225 mIU / mL)
- Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units / mL)
- Anti-rubella antibody (serostatus cutoff: 10 IU / mL)

4) The following serological endpoints will be assessed for Groups 1, 2, and 3:

- D0 (before first vaccination) for Group 1, Group 2, and Group 3:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
- 30 days after the 6-month vaccination (after the 2nd dose) with MenACYW conjugate vaccine for Group 1 and Group 3:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and reverse cumulative distribution curves (RCDCs)
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
- 30 days after the 6-month vaccination (after the 3rd dose) with Menveo vaccine for Group 2:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and RCDCs
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
- 30 days after the 12-month vaccination (after the 3rd dose) with MenACYW conjugate vaccine for Group 1 and Group 3:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and RCDCs
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
  - hSBA meningococcal serogroups A, C, Y, and W vaccine seroresponse
- 30 days after the 12-month vaccination (after the 4th dose) with Menveo vaccine for Group 2:
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers
  - Titer distribution and RCDCs
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W antibody titers ≥ 4-fold rise from pre-vaccination (D0) to post-vaccination
  - hSBA meningococcal serogroups A, C, Y, and W vaccine seroresponse

5) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with

MenACYW conjugate vaccine or Menveo® (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®) in Mexico (Group 1 and Group 2)

6) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine (Dose 2 of MenACYW conjugate vaccine) in the Russian Federation (Group 3)
7) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA, before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine or Menveo® in Mexico (Group 1 and Group 2)
8) Meningococcal serogroups A, C, Y, and W antibody titers measured by rSBA before the first vaccination (Visit 1) and 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine in the Russian Federation (Group 3)

9.2.1.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the secondary endpoints are the same as those presented in Section 9.1.1.2.

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

Antibodies to Meningococcal Antigens (rSBA Method)

Functional meningococcal antibody activity against serogroups A, C, Y, and W will be measured in an SBA utilizing baby rabbit complement. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. Serogroup-specific meningococcal bacteria along with baby rabbit complement are added to the serum dilutions and allowed to incubate. After this incubation period, 10 microliters (µL) of the serum/complement/bacteria mixture is removed and added to a blood agar plate using the tilt method, and then incubated overnight at 37°C with 5% CO_2. Bacterial colonies present on the blood agar plate are then counted. The bactericidal titer of each sample is expressed as the final reciprocal dilution yielding ≥ 50% killing as compared to the T60[a] (average number of bacteria in each control well after incubation) colony-forming unit.

The LLOQ of the rSBA assay is a titer of 1:4.

This method will be performed on all samples collected from a subset of subjects (100 subjects per group in Groups 1 and 3, and 50 subjects in Group 2).

Anti-Measles Antibodies

The purpose of the Bulk Measles IgG EIA (Enzyme Immunoassay) is to detect total IgG antibody to measles virus before and after vaccination with a measles-containing vaccine. Plates are coated

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

in house 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. Quantitation of the human IgG antibody to measles virus or titer is determined by comparison of the resulting optical density (OD) to a standard curve. The reference standard is a pool of human sera that has been calibrated against the WHO anti-measles reference standard, lot NIBSC 66/202. The concentration of anti-measles antibody in a sample is reported in milli-International Units per milliliter of serum (mIU/mL). The clinical endpoint for the measles assay is 255 mIU/mL and the LLOQ is 60 mIU/mL a sample is reported in milli-International Units per milliliter of serum (mIU/mL). The clinical endpoint for the measles assay is 255 mIU/mL and the LLOQ is 60 mIU/mL.

This method will be performed on BL0003 collected from all subjects in Mexico and in the Russian Federation.

Anti-Mumps Antibodies

The purpose of the mumps enzyme-linked immunosorbent assay (ELISA) is to detect IgG antibody to mumps virus before and after vaccination with a mumps virus-containing vaccine.The assay uses an earlier passage of the Jeryl Lynn® mumps virus (Jeryl Lynn® 135 [JL135],<12 passages) which is considered to be a wild-type (WT)-like strain. The reactivity of the sera to the mumps antigens prepared from uninfected Vero cells (denoted as tissue culture control [TCC] wells) is subtracted from that of JL135-infected Vero cells. 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 antihuman 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 reference standard is an individual human serum. Results for the assay are reported as the concentration of antibody in Mumps antibody units/mL. The clinical endpoint and the LLOQ for the mumps assay is 10 Mumps Ab units/mL.

This method will be performed on BL0003 collected from all subjects in Mexico and in the Russian Federation.

Anti-Rubella Antibodies

The purpose of the Bulk Rubella IgG EIA (Enzyme Immunoassay) is to detect total IgG antibody to rubella virus before and after vaccination with a rubella-containing vaccine. Plates are coated in house 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 plates 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.

Quantitation of the human IgG antibody to rubella virus or titer is determined by comparison of the resulting analysis OD to a standard curve. The reference standard is an individual human serum that has been calibrated against the WHO anti-rubella reference standard. The concentration of anti-rubella antibody in a sample is reported in International Units per milliliter of serum (IU/mL). The clinical endpoint for the rubella assay is 10 IU/mL and the LLOQ is 5 IU/mL

This method will be performed on BL0003 collected from all subjects in Mexico and in the Russian Federation.

Anti-Pneumococcal Antibodies

The pneumococcal capsular PS (PnPS) IgG Electrochemiluminscent (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 antibody (µg / mL) in human serum. The LLOQ for all PnPS serotypes is 0.15 µg/mL.

This method will be performed on BL0002 samples from all groups.

Anti-Diphtheria, Tetanus and Pertussis Antibodies

The DTP (Diphtheria, Tetanus and Pertussis) ECL 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 4 Pertussis antigens: PT, FHA, FIM and 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. 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 LLOQ for Diphtheria is 0.005 IU/mL, the LLOQ for Tetanus is 0.01 IU/mL and the LLOQ for Pertussis antigens is 2.00 EU/mL.

This method will be performed on BL0003 samples collected from all subjects in Mexico. This method will be performed on BL0002 samples collected from all subjects in the Russian Federation. Only PT and FHA Pertussis antigens will be analyzed in this testing.

Anti-Polio (types 1, 2, and 3) Antibodies

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 antibody 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 < 7.0) contained in the medium. In the absence of neutralizing antibody, 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 mouse inoculation test (MIT) measures the functional serum antibody 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 on BL0003 samples collected from all subjects in Mexico. This method will be performed on BL0002 samples collected from all subjects in the Russian Federation.

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

Anti-PRP concentrations will be measured using a Farr-type radioimmunoassay (RIA). Serum levels of anti-Hib Capsular PRP antibody 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 antibody binds to tritiated capsular PS to form antigen-antibody complexes. These complexes are precipitated with ammonium sulfate and collected by centrifugation. The radioactivity is measured in the precipitated pellet, in counts per minute and is proportional to the amount of anti-Hib capsular PS antibody 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, Lot No. 1983 reference standard. The LLOQ of the anti-PRP RIA is 0.06 µg / mL.

This method will be performed on BL0003 samples collected from all subjects in Mexico. This method will be performed on BL0002 samples collected from all subjects in the Russian Federation.

Anti-hepatitis B Antibodies

Anti-hepatitis B antibody will be measured by the commercially available VITROS ECi/ECiQ Immunodiagnostic System using chemiluminescence detection technology. The VITROS ECi

Immunodiagnostic system uses an antibody mediated antigen sandwich formation to detect the presence of anti-HBs antigen total immunoglobulin in human serum. This involves the reaction of anti-HBs antigen in the sample with plasma-derived HBs antigen (ad and ay subtypes) coated onto the wells. A horseradish peroxidase (HRP)-labeled HBs antigen 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 World Health Organization (WHO) First International Reference Preparation for antibody to HBs antigen (1977). The LLOQ is 5 mIU / mL.

This method will be performed on BL0003 samples collected from all subjects in Mexico. This method will be performed on BL0002 samples collected from all subjects in the Russian Federation.

Anti-Rotavirus IgA Antibodies

Anti-rotavirus IgA Antibodies in human serum will be measured by ELISA. Microtiter plates are coated with rabbit anti-rotavirus antibody and then viral lysate (positive wells) or control cell lysate (negative wells) is added. Diluted serum samples (test samples, reference standard, and quality controls) are incubated in the wells. Unbound antibodies are washed from the wells, and enzyme-conjugated anti-human IgA is added. The enzyme conjugate binds to the antigen-antibody complex. Excess conjugate is washed away and a specific colorimetric substrate is added. Bound enzyme catalyzes a hydrolytic reaction, which causes color development. A reference standard assayed on each plate is used to calculate the amount of specific anti-rotavirus IgA antibody in the units assigned by the reference standard (units [U] / mL of serum).

This method will be performed on BL0002 samples collected from all subjects in Mexico.

The priority of titration for subjects receiving MenACYW conjugate vaccine (Group 1) or Menveo® vaccine (Group 2), and DTaP-IPV-HB-Hib, Rotavirus, PCV13 vaccines is as follows: hSBA, anti-PT, anti-FHA, anti-Hep B, anti-PRP, anti-polio 1, 2, and 3, anti-tetanus, and anti-diphtheria, anti-pneumococcal serotypes 1, 3, 5, 6A, 7F, 19A, 4, 6B, 9V, 14, 18C, 19F, and 23F and anti-Rotavirus (IgA).

The priority of titration for subjects receiving MenACYW conjugate vaccine (Group 1) or Menveo® vaccine (Group 2), and DTaP-IPV-HB-Hib Measles, Mumps, Rubella, PCV13 vaccines is as follows: hSBA, anti-PT, anti-FHA, anti-Hep B, anti-PRP, anti-polio (types 1, 2, and 3) anti-tetanus, anti-diphtheria, anti-measles, anti-mumps, anti-rubella, anti-pneumococcal serotypes 1, 3, 5, 6A, 7F, 19A, 4, 6B, 9V, 14, 18C, 19F, and 23F.

For subjects receiving MenACYW conjugate vaccine and DTaP-IPV//Hib vaccine and hepatitis B vaccine (Group 3) the priority of titrations is as follows: hSBA, anti-PT, anti-FHA, anti-PRP, anti-polio 1, 2, and 3, anti-tetanus, anti-diphtheria and anti-HepB.

For subjects receiving DTaP-IPV//Hib and hepatitis B vaccines only (Group 4), the priority of titrations is as follows: anti-PT, anti-FHA, anti-PRP, anti-polio 1, 2, and 3, anti-tetanus, and anti-diphtheria and anti-Hep B.

For subjects receiving PCV-13 vaccine only (Group 4), the priority of titrations is as follows: anti-pneumococcal serotypes 1, 3, 5, 6A, 7F, 19A, 4, 6B, 9V, 14, 18C, 19F, and 23F.

For subjects receiving MenACYW conjugate vaccine, and MMR vaccine (Group 3), the priority of titrations is as follows: hSBA, anti-measles, anti-mumps, anti-rubella.

For subjects receiving MMR vaccine only (Group 4), the priority of titrations is as follows: anti-measles, anti-mumps, anti-rubella.

9.2.2 Safety

There are no secondary objectives for safety.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

There are no observational objectives for immunogenicity in this study.

9.3.2 Safety

9.3.2.1 Safety Definitions

The following definitions are taken from the International Conference on Harmonization 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 in a clinical investigation subject administered a medicinal product and which does not necessarily 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 pre-existing condition
- 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 actions taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the study period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the Investigator 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 (eg, 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 subject / event outcome or action criteria usually associated with events that pose a threat to a subject'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 (IME)

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs 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 IMEs 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, new-onset diabetes, or autoimmune disease.

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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 outpatient 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.

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered ARs.

(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).

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs (including those related to the product administered) that occur within the first 30 minutes after vaccination.

Solicited Reaction:

A solicited reaction is an "expected" AR (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB.

By definition, solicited reactions are to be considered as being related to the product administered.

For injectable vaccines, solicited reactions can either be solicited injection site reactions or solicited systemic reactions.

The assessment of these reactions by the investigator is mandatory.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if vomiting between D0 and D7 is a solicited reaction (ie, prelisted in the protocol and CRB), then a vomiting starting on D7 is a solicited reaction, whereas vomiting starting on D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

An injection site reaction is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions. They are considered to be related to the product administered.

Systemic AE:

Systemic AEs are all AEs that are not injection or administration site reactions. They therefore include systemic manifestations such as vomiting, fever, as well as localized or topical manifestations that are not associated with the vaccination or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Adverse Event of Special Interest (AESI):

An AESI is an event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done.

Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

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, relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination
- Occurrence, time of 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 D07 after each vaccination
- Occurrence, time of 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 D07 after each vaccination
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the trial from D0 to the last study visit

9.3.2.3 Safety Assessment Methods

At each vaccination visit, the Investigator or a delegate will perform a physical examination on the basis of relevant medical history according to the Investigator's clinical judgment and 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 CRB according to the instructions provided by the Sponsor.

9.3.2.3.1 Immediate Post-vaccination Observation Period

Subjects will be kept under observation for 30 minutes after each vaccination to ensure their safety. The post-vaccination observation 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 CRB, as follows:

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes" and details collected).
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination.
- SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in Section 10.

9.3.2.3.2 Reactogenicity (Solicited Reactions from Day 0 to Day 7 After Each Meningococcal Vaccination)

After the first vaccination, subject's parents / guardians will be provided with a 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 (ie, D0 to D7) 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 (eg, medication)

  The action(s) taken by the parent or guardian to treat and/or manage any **solicited reactions** will be classified in the CRB using the following list (all applicable items should be checked):

  None

  Medication

  Health care provider contact

  Hospitalized

  Discontinuation of study vaccination

Whether the AE was related to the investigational product (for injection site events linked to routine pediatric vaccines)

The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.3.2.3.5

Subject's parents / guardians will be contacted by telephone 8 days after vaccination visit, 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, respectively, present the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

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

CRB term (MedDRA lowest level term [LLT])	**Injection site tenderness**	**Injection site erythema**	**Injection site swelling**
(MedDRA preferred term)	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Tenderness	Redness	Swelling
Definition	Pain when the injection site is touched or injected limb mobilized	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 mobilized, 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

CRB term (MedDRA LLT)	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Data analysis term (MedDRA preferred term)	Pyrexia	Vomiting	Crying	Somnolence	Decreased appetite	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥°38.0°C* (≥ 100.4°F)	Vomiting does not include spitting up	Inconsolable crying without a determined 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 **or** ≥ 100.4°F to < 101.3°F	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 **or** > 101.3°F to < 103.1°F	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 **or** > 103.1°F	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 the Russian Federation, febrile illness is defined as temperature ≥ 37°C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

† 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 based on the unit used to measure the temperature and the intensity scale.

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 CRB. The preferred route for this study is axillary. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic thermometers must not be used.

9.3.2.3.3 Unsolicited Adverse Events

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 following vaccination. Local reactions will be collected after all vaccinations. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from the time of vaccination to 30 days after the last vaccination or study visit. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. 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 (eg, outcome, medical history, results of investigations, copy of hospitalization reports in case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion," and this event will be considered an SAE. See Section 10 for further details on SAE reporting.

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

- Start and stop dates[a]
- Intensity of the event:
  - For measurable unsolicited 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).
  - All other unsolicited AEs will be classified according to the following intensity scale:

[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 study will be considered as ongoing at the end of the study.

- Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

- Whether the AE was related to the investigational product (for unsolicited systemic AEs)

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.3.2.3.5.

- Action taken for each AE (eg, medication)

  The action(s) taken by the parent or guardian to treat and/or manage any unsolicited AEs will be classified in the CRB using the following list (all applicable items should be checked):

  None

  Medication

  Health care provider contact

  Hospitalized

  Discontinuation of study vaccination

- Whether the AE was serious

  For each SAE, the investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures)

- Whether the AE caused study discontinuation

9.3.2.3.4 Adverse Events of Special Interest

An AESI is defined as event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done. The following AEs will be captured as AESIs throughout the study:

- Generalized seizures (febrile and non-febrile) (47) (48)
- Kawasaki disease (49) (50)
- Guillain-Barré syndrome (51)
- Idiopathic thrombocytopenic purpura (ITP) (52) (53)

These events have been listed as AESIs based on the feedback received from the European Union regulators.

No safety concerns relating to these AESIs have been identified with the use of MenACYW conjugate vaccine in the completed clinical trials. Because of their medical importance and to ensure expedited communication to the Sponsor, these AESIs are to be considered and collected as SAEs and reported to the Sponsor according to the procedure described in Section 10. Further instructions on the data collection for these events and the relevant definitions will be provided in the Operating Guidelines.

9.3.2.3.5 Assessment of Causality

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

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 AE is incompatible with a causal relationship; or the AE started before the first vaccination (screening phase, if applicable)

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

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

Adverse events likely to be related to the product, whether serious or not, that persist at the end of the study 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 or the date of "chronicity" establishment.

9.3.3 Biological Laboratory 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 7.

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 7) only if they are considered clinically significant, that is:

- 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 (in an order based on Investigator's medical judgement and available blood volume)

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

9.3.3.2 Blood Chemistry (in an order based on Investigator's medical judgement and available blood volume)

- Serum glucose
- Urea
- Bilirubin total
- Direct bilirubin
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase

9.3.3.3 Urinalysis

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

10 Reporting of Serious Adverse Events

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 (eg, medical

records, discharge summary) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF.

10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the study 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 Investigator (licensed physician [MD or DO]) must validate the information entered on the AE CRF by completing the Investigator validation form.

The Investigator must indicate on the AE CRF that the event was serious and must complete the relevant SAE section of this form. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the CTL with relevant SAE information details.

If the EDC system is unavailable, the site must notify the Sponsor, using the paper version of the CRB, as described in the operating guidelines:

The Investigator must complete the paper copies of the AE and send them to the Sponsor by one of the following means:

- By fax, to the following number: +(1) 570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofipasteur.com
- 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 EDC system becomes available, the Investigator must transcribe the information from the paper forms 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 AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (eg, outcome, precise description of medical history, results of the investigation). All relevant information must be included directly in the AE CRF and the appropriate Safety Complementary Information CRFs. An e-mail alert will be sent automatically to the GPV Department and to the CRA. Copies of documents (eg, 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 investigational product(s), other products (eg, a benefit vaccine), 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 administered will be evaluated by the Investigator as described in Section 9.3.2.3.5.

Following this, the Sponsor's Pharmacovigilance (PV) Global Safety Expert will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The causal relationship to study procedures will be also assessed in the CRB.

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Investigators.

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, Olga Lyabis, MD, PhD, MSc, 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 study protocol.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants' parents / guardians 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 / 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 study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study 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 CRBs, 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 instructions will be provided to assist with data entry during the course of the study.

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 study 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 study 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 to track all modifications and ensure database integrity.

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

11.2 Data Management

Management of SAE and Data

During the study, SAE data (reported on the AE and Safety Complementary Information CRFs) will be integrated into the Sponsor's centralized GPV database upon receipt of these forms and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the PV Global Safety Expert 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 from the GPV database cases will be reconciled with that in the clinical database.

Management of Clinical and Laboratory Data

Clinical data, defined as all data reported in the CRB, will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.

During the study, clinical data reported in the CRBs 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 to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. 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.

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.

11.3 Data Review

A blind 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 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 under the responsibility of the Sponsor and all the conventions to be taken.

12.1.1 Hypotheses and Statistical Methods for the Primary Objective

12.1.1.1 Hypotheses

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

12.1.1.2 Statistical Methods

Descriptive analyses on meningococcal serogroups A, C, Y, and W measured by hSBA for Groups 1, 2, and 3, 30 days after the last vaccination in the second year of life with MenACYW conjugate vaccine or Menveo® will be computed on the following parameter:

- Percentage of subjects with titer ≥ 1:8 and 95% CI

The 95% CI will be computed using the exact binomial distribution (Clopper-Pearson method).

12.1.2 Hypotheses and Statistical Methods for the Secondary Objective

12.1.2.1 Hypotheses

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

12.1.2.2 Statistical Methods for Secondary Objectives 1, 2 and 4

Descriptive analyses on meningococcal serogroups A, C, Y, and W measured by hSBA, for Groups 1, 2, and 3, before the first vaccination, 30 days after the last vaccination of the infant series with MenACYW conjugate vaccine or Menveo® (Dose 2 of MenACYW conjugate vaccine and Dose 3 of Menveo®) and 30 days after the last vaccination in the second year of life will include but not limited to the following:

- GMT and 95% CI
- Titer distribution and 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-infant vaccination, and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-12 month vaccination, and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse[a] and 95% CI

In general, categorical variables will be summarized and presented by frequency counts, percentages, and 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 proportions. For GMTs and geometric mean concentrations (GMCs), 95% CIs of point estimates will be calculated using a normal approximation assuming they are log-normally distributed.

12.1.2.3 Statistical Methods for Secondary Objectives 5, 6, 7, 8

Descriptive analysis on meningococcal serogroups A, C, Y, and W measured by rSBA before the first vaccination, 30 days after the last vaccination of the infant series (Dose 2 of the MenACYW conjugate vaccine and Dose 3 of Menveo®), and 30 days after the last vaccination of the second year of life with MenACYW conjugate vaccine or Menveo® in a subset of subjects (100 subjects per group in Groups 1 and 3, and 50 subjects in Group 2) will include but not limited to the following parameters:

- 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[a] and 95% CI

12.1.2.4 Statistical Methods for Secondary Objective 3

The analyses on the concomitant vaccines will include GMT and titer distribution or GMC, and RCDC, as well as percentage of subjects with:

The Russian Federation[b]:

- 30 days after vaccination with MMR vaccine at 12 months of age
  - Anti-measles antibody concentrations (serostatus cutoff: 225: mlIU/mL).
  - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps ab units/mL).
  - Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL).
- Before the first vaccination with Pentaxim®
  - Anti-pertussis (PT and FHA) antibody concentrations
- 30 days after the last vaccination with Pentaxim® at 6 months of age:
  - Anti-tetanus antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-pertussis (PT and FHA) antibody concentrations (vaccine response)
  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations and ≥ 0.15 µg / mL and 1.0 µg / mL
- 30 days after vaccination with ENGERIX-B®[c] at 6 months of age

Mexico:

- 30 days after vaccination with M-M-R®II at 12 months of age
  - Anti-measles antibody concentrations (serostatus cutoff: 225 mIU/mL)
  - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
  - Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)

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[a] rSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as:
- a post-vaccination rSBA 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

[b] Anti-pneumococcal antibody concentrations will not be determined in this study for the Russian Federation.

[c] In the event ENGERIX B® cannot be supplied in the Russian Federation, a locally licensed monovalent hepatitis B vaccine will be administered instead. Further details will be provided in the CSR.

- 30 days after vaccination with Prevnar 13® at 6 months of age and the last vaccination with Prevnar 13® at 12 months of age
  - Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and 1.0 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Before the first vaccination with Hexacima®
  - Anti-pertussis[a] (PT and FHA) antibody concentrations
- 30 days after the last vaccination with Hexacima® vaccine at 12 months of age
  - Anti-tetanus antibody concentrations ≥ 0.1 IU/mL and 1.0 IU/mL
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU / mL and 1.0 IU / mL
  - Anti-pertussis (PT and FHA) antibody concentrations and pertussis vaccine response
  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations and ≥ 0.15 µg / mL and 1.0 µg / mL
  - Anti-HBs antigen concentrations ≥ 10 mIU / mL and ≥ 100 mIU / mL
- Before the first vaccination and 30 days after the last vaccination with RotaTeq® at 6 months of age
  - Anti-RV IgA ≥ 3-fold and ≥ 4-fold antibody titers from baseline to 30 days after last dose

12.1.3 Statistical Methods for the Observational Objectives

12.1.3.1 Hypotheses

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

12.1.3.2 Statistical Methods

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 is defined as:
- If the pre-vaccination concentration is < 4 x LLOQ, then the post-vaccination concentration is ≥ 4 x LLOQ;
- If the pre-vaccination concentration is ≥ 4 x LLOQ, then the post vaccination concentration is ≥ the pre-vaccination concentration

12.1.4 Sensitivity analysis due to COVID-19 pandemic

The impact of COVID-19 pandemic situation on study conduct will be summarized through impact on visit procedures, study completion and major/critical protocol deviations due to COVID-19. The subjects impacted by COVID-19 pandemic situation will be defined as the subjects with at least one major/critical protocol deviation due to COVID-19 or who did not complete the study due to COVID-19. If more than 10% of subjects are impacted as per this definition, the main immunogenicity and safety endpoints will also be summarized in these subjects to assess the impact of COVID-19 situation on study outcome.

12.2 Analysis Sets

12.2.1 Full Analysis Set

There will be 2 full analysis sets (FAS) for this study:

- FAS for infant vaccination (FAS1). The full analysis set 1 (FAS1) is defined as the subset of all randomized subjects who received at least 1 dose of the study vaccine in infancy (<12 months of age) and have a valid post-vaccination serology result in infancy. All subjects will be analyzed according to the treatment group to which they were randomized.
- FAS for 2nd year of life vaccination (FAS2). The full analysis set 2 (FAS2) is defined as the subset of all randomized subjects who received at least 1 dose of the study vaccine in the 2nd year of life (≥12 months of age) and have a valid post-vaccination serology result in the 2nd year of life. All subjects will be analyzed according to the treatment group to which they were randomized.

Immunogenicity analyses will be performed on the FAS for exploratory purposes.

12.2.2 Safety Analysis Set

The safety analysis set (SafAS) is defined as those subjects who have received at least 1 dose of the study vaccine[a] and have any safety data available.

All subjects will have their safety analyzed after each dose according to the vaccine they actually received at that dose. For 'any dose' safety analyses, all subjects will have their safety analyzed according to the vaccine received at the first dose.

Safety data recorded for a vaccine received out of protocol design will be excluded from the analysis (and listed separately).

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[a] for which safety data are scheduled to be collected

12.2.2.1 Overall Safety Analysis Set for Any Dose

The overall safety analysis set (SafAS) is defined as those subjects who have received at least 1 dose of the study vaccines and have any safety data available. All subjects will have their safety analyzed after any dose according to the vaccine received at the first dose.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

12.2.2.2 Safety Analysis Set for Vaccination at 2 Months of Age

The safety analysis set 1 for vaccination at around 2 months of age (SafAS1) is defined as those subjects who have received the study vaccine at Visit 1 around 2 months of age and have any safety data available. All subjects will have their safety analyzed after the Visit 1 dose according to the vaccines they actually received at Visit 1.

Safety data recorded for a vaccine received out of the protocol design at Visit 1 will be excluded from the analysis (and listed separately).

12.2.2.3 Safety Analysis Set for Vaccination at 3 Months of Age for Russia Only

The safety analysis set 2 (SafAS2) is defined as those subjects who have received the study vaccine at Visit 2 at around 3 months of age for Group 3 and Group 4 in Russia and have any safety data available. Subjects will have their safety analyzed after this dose according to the vaccines they actually received at Visit 2.

Safety data recorded for a vaccine received out of the protocol design at Visit 2 will be excluded from the analysis (and listed separately).

12.2.2.4 Safety Analysis Set for Vaccination at 4 Months of Age for Mexico only

The safety analysis set 3 (SafAS3) is defined as those subjects who have received the study vaccine at Visit 2 around 4 months of age (Group 1 and Group 2) and have any safety data available. Subjects will have their safety analyzed after this dose according to the vaccines they actually received at that visit.

Safety data recorded for a vaccine received out of the protocol design at that visit will be excluded from the analysis (and listed separately).

12.2.2.5 Safety Analysis Set for Vaccination at 4.5 months of Age for Russia Only

The safety analysis set 4 (SafAS4) is defined as those subjects who have received the study vaccine at Visit 3 for Group 3 and Group 4 in Russia at around 4.5 months of age and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccines they actually received at that visit.

Safety data recorded for a vaccine received out of the protocol design at that visit will be excluded from the analysis (and listed separately).

12.2.2.6 Safety Analysis Set for Vaccination at 6 Months of Age

The safety analysis set 5 (SafAS5) is defined as those subjects who have received the study vaccine at Visit 3 (or Visit 4 for Group 3 and Group 4) at around 6 months of age and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccines they actually received at that visit.

Safety data recorded for a vaccine received out of the protocol design at that visit will be excluded from the analysis (and listed separately).

12.2.2.7 Safety Analysis Set for Vaccination at 12 Months of Age

The safety analysis set 6 (SafAS6) is defined as those subjects who have received the study vaccine at Visit 5 (or Visit 6 for Group 3 and Group 4) at around 12 months of age and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccine they actually received at that visit.

Safety data recorded for a vaccine received out of the protocol design at that visit will be excluded from the analysis (and listed separately).

12.2.3 Per-Protocol Analysis Set

The per-protocol analysis set (PPAS) is a subset of the FAS. Immunogenicity analyses will primarily be performed on the per-protocol analysis sets. There will be 2 PPAS corresponding to the 2 FAS:

- PPAS for infant vaccination (PPAS1)
- PPAS for 2nd year of life vaccination (PPAS2)

12.2.4 Per-Protocol Analysis Set 1 (PPAS1)

Serology obtained from the last blood sample of infancy vaccination stage for all antigens will be used for immunogenicity analyses of infant stage of the study.

The subjects presenting with at least one of the following relevant protocol deviations during infancy will be excluded from the PPAS1:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- 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 receive vaccine in the proper time window, according to the Tables of Study Procedures. All infant stage vaccines (including concomitant vaccines) need to be received as scheduled in the Table of Study Procedures.

- Subject did not provide post-dose serology sample during infancy in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy, medication or vaccine

In addition to the reasons listed above, subjects will also be excluded from the PPAS1 if their infancy post vaccination serology sample did not produce a valid test result (ie, results for all antigens are missing).

In the event of a local or NIC with a pandemic influenza or coronavirus vaccine or any other vaccine as needed, subjects who receive 1 or more doses of the pandemic influenza or coronavirus vaccine at any time during the study will not be withdrawn from the study.

12.2.5 Per-Protocol Analysis Set 2 (PPAS2)

Serology obtained from the last blood sample of 2nd year of life for all antigens will be used for immunogenicity analyses of 2nd year of the study.

The subjects presenting with at least one of the following relevant protocol deviations during 2nd year of life will be excluded from the PPAS2:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule including the infant and the 2nd year of the study
- Subject received a vaccine other than the one that he / she was randomized to receive during both the infant and 2nd year of the study
- Preparation and / or administration of vaccine was not done as per-protocol during both the infant and 2nd year of the study
- Subject did not receive vaccine in the proper time window. All 2nd year of life vaccines (including concomitant vaccines) need to be received as scheduled in the Table of Study Procedures.
- Subject did not provide post-dose serology sample during infancy in the proper time window or a post-dose serology sample was not drawn during 2nd year of life
- Subject received a protocol-prohibited therapy, medication or vaccine

In addition to the reasons listed above, subjects will also be excluded from the PPAS2 if their 2nd year of life post vaccination serology sample did not produce a valid test result (ie, results for all antigens are missing).

In the event of a local or NIC recommendation or requirement with a pandemic influenza or coronavirus vaccine or any other vaccine as needed, subjects who receive 1 or more doses of the pandemic influenza or coronavirus vaccine at any time during the study will not be withdrawn from the study.

12.2.6 Populations Used in Analyses

All immunogenicity analyses will be performed on the Per-Protocol Analysis Set (PPAS) including PPAS1 and PPAS2. Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set (FAS), including FAS1 and FAS2, according to randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS and SafAS1 – SafAS6).

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

Missing data will not be imputed. 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 for extreme values, to minimize the numerator and maximizes the denominator:

- If the baseline computed value is < LLOQ and the post-baseline computed value is < LLOQ then the fold-rise is 1
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is ≥ LLOQ then the fold-rise is post-baseline computed value / baseline computed value
- If the baseline computed value is ≥ LLOQ and the post-baseline computed value is < LLOQ then the fold-rise is (LLOQ / 2) / baseline computed value
- If the baseline computed value is < LLOQ and the post-baseline computed value is ≥ LLOQ then the fold-rise is post-baseline computed value / LLOQ

12.3.3 Efficacy

No efficacy data will be collected.

12.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

12.5 Determination of Sample Size and Power Calculation

The sample size of this study was chosen to provide immunogenicity and safety data; it is not intended for the purposes of hypothesis testing. No formal sample size calculations will be performed.

Though there are no statistically powered hypotheses, the overall study cohort (n=525) will provide a probability of approximately 95% of observing any AE with a true incidence of 0.57%. The overall MenACYW conjugate vaccine cohort (n=350) will provide a probability of approximately 95% of observing any AE with a true incidence of 0.85%. In treatment arm with n=200, there is a probability of approximately 95% of observing any AE with a true incidence of 1.5%. In treatment arm with n=150, there is a probability of approximately 95% of observing any AE with a true incidence of 2%.

In case of unexpected situations or any study hold resulting in an unexpected number of unevaluable subjects, total sample size may be increased to replace withdrawn, or unevaluable subjects.

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Study / Good Clinical Practice

The conduct of this study 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 study source documents is to document the existence of subjects and to substantiate the integrity of the study 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 CRB.

The subject pre-screening log should list all individuals contacted by the Investigators to participate in the study, 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 subsequent 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.

Good Documentation Practice should be followed by the Investigator and the site staff managing source documents.

13.3 Confidentiality of Data and Access to Subject Records

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

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

Subjects' race and ethnicity will be collected in this study because these data are required by regulatory agencies.

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 study (ie, 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 study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB 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 study has been received at the site; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the study, 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.

[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.

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

After the start of the study, 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 CRBs. During these visits, the Sponsor/delegate staff will:

Evaluate the quality of the study 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 CRBs and any corresponding answered queries

Determine the number of complete or ongoing issues identified at monitoring visits (eg, 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 CRB, 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 study, 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 Quality Assessment department or by independent auditors to verify that the study 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 study documents during these inspections and audits.

13.4.3 Archiving

The Investigator must keep all study documents after the completion or discontinuation of the study, 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, study 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 study documents upon less than 90 days advance written notification to the Sponsor. In addition, study 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 study 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 study 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 study'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 according to local practice to compensate for the time and travel required for study visits and procedures.

13.7 Publication Policy

Data derived from this study are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the study must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives recognition to the study 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 study 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 study are not to be considered confidential.

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

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15 Signature Page

Signature Page for VV-CLIN-0550216 v5.0
MenQuadTT-MET33-Protocol Amendment 3

Approve & eSign	[redacted]