NCT number: NCT03547271

Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers in Europe

Phase III, partially modified double-blind, randomized, parallel-group, active-controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Nimenrix® when administered as a 3-dose series concomitantly with routine pediatric vaccines to healthy infants and toddlers in Europe

Clinical Study Protocol, Amendment 5

Health Authority File Number:	EudraCT #: 2017-004731-36
WHO Universal Trial Number (UTN):	U1111-1183-6653
Study Code:	MET58
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular (IM)
Indication For This Study:	MenACYW conjugate vaccine administered to healthy infants and toddlers
Manufacturer:	Same as Sponsor
Coordinating Investigator	This is a multi-center trial with multiple investigators. Investigators and study sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Sponsor's Responsible Medical Officer:	[redacted]

Pharmacovigilance Global Safety Officer:	[redacted]
Clinical Trial Managers:	[redacted]
Version and Date of the Protocol:	Version 7.0 dated 03 February 2022

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History of Protocol Versions

Previous versions of the protocol

Version	Date	Comments
1.0	29 March 2018	Protocol updated in response to comments provided by the Health Authorities
2.0	09 July 2018	**Original version of the protocol approved by Health Authorities and Ethics Committees**
3.0	25 June 2019	**Protocol Amendment 1 – Version approved by Health Authorities and Ethics Committees**
4.0	22 January 2020	**Protocol Amendment 2 - Version approved by Health Authorities and Ethics Committees**
5.0	14 April 2020	**Protocol Amendment 3 - Version approved by Health Authorities and Ethics Committees**
6.0	18 June 2021	**Protocol Amendment 4 - Version approved by Health Authorities and Ethics Committees**

*Version in bold font have been approved by the Independent Ethics Committee(s) (IEC[s]) / Institutional Review Board(s) (IRB[s]) and used in the study.

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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 Study:	Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers in Europe
Development Phase:	Phase III
Coordinating Investigator:	This is a multi-center trial with multiple investigators.
Study Sites:	This will be a multi-center, multinational study with approximately 50 sites in Europe. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Q4 2018 to Q4 2023
Study Design, Schedule of Study Procedures, and Methodology:	A Phase III, partially modified double-blind (open-label for some of the vaccines / study groups), randomized, parallel-group, active-controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Nimenrix® (Meningococcal group A, C, W-135, and Y conjugate vaccine) when administered as a 3-dose series concomitantly with routine pediatric vaccines to healthy infants and toddlers in Europe. Licensed pediatric vaccines administered concomitantly with the study vaccines will be the following: • DTaP-IPV-HB-Hib (combined Diphtheria, Tetanus, acellular Pertussis, Hepatitis B, Inactivated Poliovirus and *Haemophilus influenzae* type b conjugate vaccine; hexavalent vaccine) • Prevenar 13® (pneumococcal 13-valent conjugate vaccine; PCV13) • Synflorix® (pneumococcal 10-valent conjugate vaccine; PCV10) • M-M-RVAXPRO® (measles, mumps, rubella vaccine; MMR vaccine) <u>Vaccinations</u> Approximately 1652 healthy infants aged 2 months* at enrollment will be randomized as follows depending on the pneumococcal vaccines that will be administered in the respective countries. * "2 months" refers to infants aged 6 to 12 weeks (≥ 42 to ≤ 89 days) at enrollment. **Countries where the pneumococcal vaccination administered will be PCV10 (**Czech Republic, Romania, Sweden, Finland, and Poland): 1432 subjects will be randomized in a 1:1 ratio to one of the following 2 groups: • Group 1: MenACYW conjugate vaccine (2+1 regimen) + PCV10 + Hexavalent vaccine + MMR vaccine (n=716) • Group 2: Nimenrix® (2+1 regimen) + PCV10 + Hexavalent vaccine + MMR vaccine (n=716)

	Countries where the pneumococcal vaccination administered will be PCV13 (Italy and Spain)**:** 220 subjects will be randomized in a 1:1 ratio to one of the following 2 groups: • Group 3: MenACYW conjugate vaccine (2+1 regimen) + PCV13 + Hexavalent vaccine + MMR vaccine (n=110) • Group 4: MenACYW conjugate vaccine (3+1 regimen) + PCV13 + Hexavalent vaccine + MMR vaccine (n=110) Subjects in Groups 1, 2, and 3 will receive either 3 doses of MenACYW conjugate vaccine or 3 doses of Nimenrix® administered concomitantly with routine vaccines at 2 months of age (Visit 1), 4 months of age (Visit 2), and 12 to 18 months of age (Visit 4). The hexavalent vaccines and the pneumococcal vaccines (PCV10 or PCV13) will be administered in a 2+1 regimen (ie, 2 doses in infancy and 1 final dose in the second year of life). Subjects in Group 4 will receive 4 doses of MenACYW conjugate vaccine with routine pediatric vaccines at 2 months of age (Visit 1), 4 months of age (Visit 2), 6 months of age (Visit 3; MenACYW conjugate vaccine only), and 12 to 18 months of age (Visit 5; MenACYW conjugate vaccine and routine vaccines). The hexavalent vaccine and PCV13 will be administered in a 2+1 regimen, concomitantly with the 1st and 2nd doses in infancy and the 4th dose of MenACYW conjugate vaccine. The 3rd dose of MenACYW conjugate vaccine will be administered alone, without any other routine pediatric vaccines. In all 4 vaccine groups, the MMR vaccine may be preferably administered concomitantly with the other vaccines at 12 to 18 months of age. If not, the subject will receive a licensed Measles, Mumps and Rubella vaccine with a gap of at least 4 weeks before any study vaccines or after the end of the study (ie, after the subject will have completed the last study procedure at the last study visit). When administered outside the study visit, the licensed Measles, Mumps and Rubella vaccine will be sourced by the health care system, according to the national immunization program. Subjects in Finland, Sweden or Poland may receive the licensed rotavirus vaccine concomitantly with study vaccines at study vaccination visits Visit 1 and Visit 2. If not, the rotavirus vaccine can be administered with a time interval of at least 2 weeks before or 2 weeks after Visit 1 and/or Visit 2. The rotavirus vaccines will be sourced by the study sites and administered as per local standard practices. Safety data will be collected after its administration when done concomitantly with the study vaccine. No immunogenicity data will be evaluated after its administration. Subjects in Spain, Czech Republic, and Poland will be offered 2 doses of the Meningococcal B vaccine (Bexsero®) when parents are willing to vaccinate their child within the second year of life. This vaccine is a non-study vaccine to be administered as per local standard practices at additional optional visits after the end of the trial (ie, after the subject will have completed the last study procedure at the last study visit). This vaccine will be outside the scope of the study evaluations. No immunogenicity and safety data will be collected after its administration. The Meningococcal B vaccine (Bexsero®) will be reimbursed by the Sponsor.

	Note: To perform an appropriate description of the safety of MenACYW conjugate vaccine and Nimenrix® in Groups 1 and 2, MenACYW conjugate vaccine and Nimenrix® will be administered in a modified double-blind manner in these 2 groups. The MenACYW conjugate vaccine in Groups 3 and 4 and all other concomitant vaccines in all vaccine groups will be administered in an open-label manner. Given that the meningococcal vaccines in Groups 3 and 4 have different vaccination schedules in the number of vaccines administered and timing of their administration, these vaccines will be administered in an open-label manner. Other concomitant vaccines in all groups will be administered in an open-label manner to ensure the subjects received appropriate vaccines as per local standard of care. <u>Blood sampling</u> All subjects will provide 4 blood samples. Subjects in Groups 1, 2, and 3 will provide blood samples for immunogenicity assessment as follows: • at baseline (pre-primary vaccination 1, Day 0) • 30 days (+21 days) after the 2nd dose of MenACYW conjugate vaccine / Nimenrix® • prior to the 3rd dose (toddler dose) of MenACYW conjugate vaccine/ Nimenrix® • 30 days (+21 days) after the 3rd dose (toddler dose) of MenACYW conjugate vaccine / Nimenrix® Subjects in Group 4 will provide blood samples for immunogenicity assessment as follows: • at baseline (pre-primary vaccination 1, Day 0) • 30 days (+21 days) after the 3rd dose of MenACYW conjugate vaccine • prior to the 4th dose (toddler dose) of MenACYW conjugate vaccine • 30 days (+21 days) after the 4th dose (toddler dose) of MenACYW conjugate vaccine <u>Collection of safety data</u> • All subjects will be followed for safety from Day 0 to the last study visit. • All subjects will be observed for 30 minutes after each vaccination and any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited systemic AEs in the electronic case report book (CRB). • The subject's parent / legally acceptable representative will record information in a diary card about solicited reactions from Day 0 to Day 7 after each vaccination and unsolicited AEs will be recorded from Day 0 to Day 30 after each vaccination. • 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 / legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the study. • Study site staff will contact subjects' parent / legally acceptable representative by telephone on 8 days (+2 days) after each vaccination visit to identify the occurrence of any SAEs not yet reported and to remind them to complete the diary card after each vaccination visit and bring it back to the subsequent visit so that it can be reviewed at the study site.

	• Staff will also contact subjects' parent / legally acceptable representative by telephone 5 months after the last visit in infancy and at least 14 days before Visit 4 (Groups 1, 2, and 3) or Visit 5 (Group 4). This contact is to identify the occurrence of any SAEs not yet reported, but also to remind them that routine vaccinations will be provided in the context of this study and that they should bring back the diary card to the subsequent visit so that it can be reviewed at the study site. If the subject does not want to continue in the study, the information recorded on the diary card will be reviewed during this call, and the diary card will be retrieved by the site.
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 independent ethics committees (IECs) / institutional review boards (IRBs), or the governing regulatory authorities in the countries where the study is taking place. 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 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. 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 / legally acceptable representatives and should assure appropriate subject therapy and/or follow-up.
Primary Objective:	To demonstrate the non-inferiority of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of a 3-dose series of MenACYW conjugate vaccine compared to a 3-dose series of Nimenrix® when each vaccine is administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) to infants and toddlers from 6 weeks to 18 months old (Group 1 versus Group 2)
Primary Endpoint:	Antibody titers (geometric mean titers [GMTs]) against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using human complement (hSBA) in Groups 1 and 2, 30 days after the booster dose (third dose/toddler dose) of MenACYW conjugate vaccine or Nimenrix® when administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) to infants and toddlers from 6 weeks to 18 months of age (Group 1 versus Group 2)
Secondary Objectives:	1) To demonstrate the non-inferiority of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of 2 doses in infancy of MenACYW conjugate vaccine compared to 2 doses in infancy of Nimenrix® when each vaccine is administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) (Group 1 versus Group 2) 2) To describe the antibody responses against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine is administered in a 3-dose series concomitantly with the routine pediatric vaccines (Group 3) 3) To describe the antibody responses against the antigens of the routine pediatric vaccines administered in a 3-dose series concomitantly with MenACYW conjugate vaccine or Nimenrix® (Groups 1, 2, and 3)

	4) To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by hSBA when MenACYW conjugate vaccine or Nimenrix® is administered in a 3-dose series concomitantly with PCV10 and other routine pediatric vaccines (Groups 1 and 2) 5) To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by hSBA when MenACYW conjugate vaccine is administered in a 4-dose series concomitantly with PCV13 and other routine pediatric vaccines (Group 4) 6) To describe the antibody responses against the antigens of the routine pediatric vaccines administered with MenACYW conjugate vaccine administered in a 4-dose series concomitantly (Group 4)
Secondary Endpoints:	Secondary immunogenicity endpoints will include at least the following: 1) Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y assessed at 30 days after Dose 2 of MenACYW conjugate vaccine or Nimenrix® measured by hSBA, when administered concomitantly with routine pediatric vaccines (Group 1 versus Group 2) 2) Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA in Group 3 at the following time points: • Day 0 (before Dose 1 of MenACYW conjugate vaccine) In addition, the following endpoints will be assessed: - Antibody titers ≥ 1:4 and titers ≥ 1:8 • 30 days after Dose 2 of MenACYW conjugate vaccine in infancy, and before and 30 days after the booster dose (Dose 3) In addition, the following endpoints will be assessed: - Antibody titers ≥ 1:4 and titers ≥ 1:8 - Post-vaccination titers ≥ 4 times the latest pre vaccination titers - 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 at least 4-fold greater than the pre vaccination titer. 3) Antibody titers or concentrations against the antigens of hexavalent vaccine (DTaP-IPV-HB-Hib) in Groups 1, 2, and 3 at the following time points: • Day 0 (before Dose 1) - Anti-pertussis antibody concentrations (pertussis toxin [PT], filamentous hemagglutinin [FHA]) • 30 days after Dose 2 in infancy - Antibody concentrations/titers for all antigens - Anti-tetanus antibody concentrations ≥ 0.01 international units (IU)/ milliliter (mL) and ≥ 0.1 IU/mL - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8 - Anti-polyribosyl-ribitol phosphate (PRP) antibody concentrations ≥ 0.15 µg/mL

	- Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as: ▪ If the pre-primary vaccination concentration is < 4 × lower level of quantitation (LLOQ), post-primary vaccination concentration ≥ 4 × LLOQ ▪ If the pre-primary vaccination concentration is ≥ 4 × LLOQ, post-primary vaccination concentration ≥ pre-primary vaccination concentration - Anti-hepatitis B surface antigen (HBsAg) antibody concentrations ≥ 10 milli International units (mIU)/mL and ≥ 100 mIU/mL • Before and 30 days after the booster dose (Dose 3): - 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-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8 - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL - Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as: ▪ If the pre-booster vaccination concentration is < 4 × LLOQ, post-booster vaccination concentration ≥ 4 × pre-booster concentration ▪ If the pre-booster vaccination concentration is ≥ 4 × LLOQ, post-booster vaccination concentration ≥ 2 × pre-booster concentration - Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL Antibody concentrations against the antigens of PCV10 in Groups 1 and 2, 30 days after Dose 2 in infancy and 30 days after the booster dose (Dose 3): - Anti-pneumococcal antibody concentrations for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F - Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F Antibody concentrations against the antigens of PCV13 in Group 3, 30 days after Dose 2 in infancy and 30 days after the booster dose (Dose 3): - Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F - Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F Antibody concentrations against the antigens of MMR vaccine 30 days after the MMR vaccine injection* - Antibody concentrations for all antigens - Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL) - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL) - Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL) *when the MMR vaccine has been administered concomitantly with the study vaccines 4) Antibody titers against meningococcal serogroups A, C, W, and Y measured by hSBA in Groups 1 and 2, as detailed for the Secondary Endpoints 2 (similar time points and endpoints)

	5) Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA in Group 4 on Day 0 (before Dose 1 of MenACYW conjugate vaccine), 30 days after Dose 3 in infancy, and before and 30 days after the booster dose (Dose 4) at the following timepoints: • Day 0 (before Dose 1 of MenACYW conjugate vaccine) In addition, the following endpoints will be assessed: - Antibody titers ≥ 1:4 and titers ≥ 1:8 • 30 days after Dose 3 of MenACYW conjugate vaccine in infancy, and before and 30 days after the booster dose (Dose 4) In addition, the following endpoints will be assessed: - Antibody titers ≥ 1:4 and titers ≥ 1:8 - Post-vaccination titers ≥ 4 times the latest pre vaccination titers - 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 at least 4-fold greater than the pre vaccination titer
	6) For Group 4, antibody titers or concentrations against the antigens of DTaP-IPV-HB-Hib vaccine before and 30 days after the booster dose (Dose 4), antibody concentrations against the antigens of PCV13 vaccine 30 days after the booster dose (Dose 4), and antibody concentrations against the antigens of MMR vaccine 30 days after vaccination* *when the MMR vaccine has been administered concomitantly with the study vaccines The timepoints are: Antibody titers or concentrations against the antigens of hexavalent vaccine (DTaP-IPV-HB-Hib): • Pre-booster dose - Anti-pertussis antibody concentrations anti-PT, anti-FHA • 30 days after the booster dose (Dose 4): - 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-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8 - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL - Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as: ▪ If the pre-booster vaccination concentration is < 4 × LLOQ, post-booster vaccination concentration ≥ 4 × pre-booster concentration ▪ If the pre-booster vaccination concentration is ≥ 4 × LLOQ, post-booster vaccination concentration ≥ 2 × pre-booster concentration

	Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL Antibody concentrations against the antigens of PCV13 in Group 4, 30 days after the booster dose (Dose 4): - Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F - Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F Antibody concentrations against the antigens of MMR vaccine 30 days after the MMR vaccine injection† - Antibody concentrations for all antigens - Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL) - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL) - Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL) †when the MMR vaccine has been administered concomitantly with the study vaccines
Observational Objectives:	***Immunogenicity*** To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using rabbit complement (rSBA) in a subset of subjects when MenACYW conjugate vaccine or Nimenrix® is administered concomitantly with routine pediatric vaccines (all groups) ***Safety*** To describe the safety profile of MenACYW conjugate vaccine and Nimenrix® when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers
Observational Endpoints:	***Immunogenicity*** • Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by rSBA in a subset of subjects in all groups‡ at Day 0 (before Dose 1) (all groups), 30 days after Dose 2 (Groups 1, 2, and 3) or 30 days after Dose 3 (Group 4) in infancy, and before and 30 days after the booster dose (in all groups) In addition, the following endpoints will be assessed for all groups: - Antibody titers ≥ 1:8, and titers ≥ 1:128 - Post-vaccination titers ≥ 4 times the latest pre vaccination titers - 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 (‡) The rSBA subset will comprise: - Group 1 and Group 2: 100 subjects in each group - Group 3 and Group 4: 50 subjects in each group The rSBA subset will include subjects from all countries except Poland.

	The following endpoints will be used for all subjects for the evaluation of safety: • Unsolicited systemic AEs reported in the 30 minutes after each vaccination, including occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken, relationship to the product administered, and whether the event caused termination from the study. • Solicited (prelisted in the subject's diary card and CRB) injection site and systemic reactions starting any time from Day 0 (day of vaccination) through Day 7 after each vaccination, including occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction caused termination from the study. • Unsolicited non-serious AEs reported up to 30 days after each vaccination, including occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to the product administered, and whether the event caused termination from the study. • SAEs (including AESIs) reported throughout the study, ie, from Visit 1 (first vaccination) to the last study visit (Visit 5 for Groups 1, 2, and 3 and Visit 6 for Group 4, occurring 30 days [+21 days] after the last vaccination), including occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to the product administered, whether the event caused termination from the study, outcome, elapsed time from last administration (if less than 24 hours), relationship to study procedures, and seriousness criterion.
Planned Sample Size:	Approximately a total of 1652 subjects are planned to be enrolled (with an estimated dropout rate from the Per-Protocol Analysis Set [PPAS] of 26.2%): • Group 1: n=716 enrolled, 528 evaluable • Group 2: n=716 enrolled, 528 evaluable • Group 3: n=110 enrolled, 88 evaluable • Group 4: n=110 enrolled, 88 evaluable Approximately 20% of subjects 6 to 8 weeks of age (≥ 42 to ≤ 59 days) should be enrolled in Groups 1 and 2 to provide safety and immunogenicity data for this population of age, as described below: • Group 1 and Group 2: approximately 144 subjects in each group • Group 3 and Group 4: approximately 22 subjects in each group
Duration of Participation in the Study:	The duration of each subject's participation in the study will be approximately 11 to 17 months.
Investigational Product:	**MenACYW conjugate vaccine:** Meningococcal Polysaccharide (Serogroups A, C, W, and Y) 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:	To be determined
Control Product:	**Nimenrix®:** Meningococcal group A, C, W-135, and Y conjugate vaccine (Pfizer Limited, Sandwich, United Kingdom)
Form:	Powder and solvent for solution for injection in a pre-filled syringe
Composition:	After reconstitution, each 0.5 mL dose contains: *Neisseria meningitidis* group A polysaccharide* ..... 5 µg *Neisseria meningitidis* group C polysaccharide* ..... 5 µg *Neisseria meningitidis* group W-135 polysaccharide* ..... 5 µg *Neisseria meningitidis* group Y polysaccharide* ..... 5 µg *conjugated to tetanus toxoid protein carrier ..... 44 µg The vaccine also contains the excipients: sucrose, trometamol, sodium chloride, water for injections
Route:	IM
Batch Number:	To be determined
Other Product 1:	**DTaP-IPV-HB-Hib:** Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed) (Sanofi Pasteur SA, Marcy L'Etoile, France) (licensed products: **Hexyon®, Hexacima®**), referred to as **hexavalent vaccine** in the protocol
Form:	Suspension for injection
Composition:	Each 0.5 mL dose* is formulated to contain the following components: Diphtheria Toxoid.....not less than 20 IU† Tetanus Toxoid.....not less than 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 *Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al3+) †As lower confidence limit (p=0.95) ‡Produced on Vero cells §Or equivalent antigenic quantity determined by a suitable immunochemical method **Produced in yeast *Hansenula polymorpha* cells by recombinant deoxyribonucleic acid (DNA) technology The vaccine also contains the excipients: disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, water for injections. The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin, and polymyxin B, which are used during the manufacturing process.
Route:	IM
Batch Number:	To be determined

Other Product 2:	**Synflorix®:** Pneumococcal polysaccharide conjugate vaccine (adsorbed) (GlaxoSmithKline Biologicals SA, Rixensart, Belgium), referred to as **PCV10**
Form:	Suspension for injection
Composition:	Each 0.5 mL dose is formulated to contain the following: Pneumococcal polysaccharide serotype 1*† ..... 1 µg Pneumococcal polysaccharide serotype 4*† ..... 3 µg Pneumococcal polysaccharide serotype 5*† ..... 1 µg Pneumococcal polysaccharide serotype 6B*† ..... 1 µg Pneumococcal polysaccharide serotype 7F*† ..... 1 µg Pneumococcal polysaccharide serotype 9V*† ..... 1 µg Pneumococcal polysaccharide serotype 14*† ..... 1 µg Pneumococcal polysaccharide serotype 18C*‡ ..... 3 µg Pneumococcal polysaccharide serotype 19F*§ ..... 3 µg Pneumococcal polysaccharide serotype 23F*† ..... 1 µg * adsorbed on aluminum phosphate ..... 0.5 mg Al3+ † conjugated to protein D (derived from non-typable *Haemophilus influenzae*) carrier protein ..... 9-16 µg ‡ conjugated to tetanus toxoid carrier protein ..... 5-10 µg § conjugated to diphtheria toxoid carrier protein ..... 3-6 µg The vaccine also contains the excipients: sodium chloride, water for injections.
Route:	IM
Batch Number:	To be determined
Other Product 3:	**Prevenar 13®:** Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Pfizer Limited, Sandwich, United Kingdom), referred to as **PCV13**
Form:	Suspension for injection
Composition:	Each 0.5 mL vaccine dose is formulated to contain the following: Pneumococcal polysaccharide serotype 1 ..... 2.2 µg Pneumococcal polysaccharide serotype 3 ..... 2.2 µg Pneumococcal polysaccharide serotype 4 ..... 2.2 µg Pneumococcal polysaccharide serotype 5 ..... 2.2 µg Pneumococcal polysaccharide serotype 6A ..... 2.2 µg Pneumococcal polysaccharide serotype 6B ..... 4.4 µg Pneumococcal polysaccharide serotype 7F ..... 2.2 µg Pneumococcal polysaccharide serotype 9V ..... 2.2 µg Pneumococcal polysaccharide serotype 14 ..... 2.2 µg Pneumococcal polysaccharide serotype 18C ..... 2.2 µg Pneumococcal polysaccharide serotype 19A ..... 2.2 µg Pneumococcal polysaccharide serotype 19F ..... 2.2 µg Pneumococcal polysaccharide serotype 23F ..... 2.2 µg The pneumococcal polysaccharides are conjugated to CRM_{197} carrier protein and adsorbed on aluminum phosphate (0.125 mg aluminum). The vaccine also contains the excipients: sodium chloride, succinic acid, Polysorbate 80, water for injections.
Route:	IM
Batch Number:	To be determined

Other Product 4:	**M-M-RVAXPRO®:** Measles, mumps, and rubella vaccine (live) (Merck Sharp & Dohme B.V., Haarlem, The Netherlands), referred to as **MMR vaccine**
Form:	Powder and solvent for suspension for injection
Composition:	Each 0.5 mL dose is formulated to contain the following: Measles virus* Enders' Edmonston strain (live, attenuated) .....not less than 1x103 cell culture infection dose 50% ($CCID_{50}$)† Mumps virus* Jeryl Lynn™ [Level B] strain (live, attenuated) .....not less than 12.5x103 $CCID_{50}$† Rubella virus‡ Wistar RA 27/3 strain (live attenuated) .....not less than 1x103 $CCID_{50}$† * produced in chick embryo cells †50% cell culture infectious dose ‡ produced in WI-38 human diploid lung fibroblasts The vaccine contains the following excipients: sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolyzed gelatin, Medium 199 with Hank's salts, Minimum Essential Medium Eagle, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH), water for injections. The vaccine may also contain traces of recombinant human albumin.
Route:	IM
Batch Number:	To be determined
Inclusion Criteria:	An individual must fulfill all of the following criteria to be eligible for study enrollment: 1) Aged ≥ 42 to ≤ 89 days on the day of the first study visit 2) Healthy infants as determined by medical history, physical examination and judgment of the Investigator 3) Informed consent form has been signed and dated by the parent(s) or other legally acceptable representative 4) Subject and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures 5) Covered by health insurance according to local regulations
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 study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure 2) Receipt of any vaccine in the 4 weeks preceding the first study vaccination or planned receipt of any vaccine in the 4 weeks before and/or following any study vaccination except for influenza vaccination and rotavirus vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. This exclusion criterion does not apply to subjects in Finland, Sweden or Poland who plan to receive the licensed rotavirus vaccine concomitantly with study vaccines at study vaccination visits V1 and V2
	3) Receipt or planned receipt during the study period vaccination against meningococcal disease with either the study vaccine or another vaccine (ie, mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W or Y; or meningococcal B serogroup-containing vaccine)

4) Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), poliovirus, *Streptococcus pneumoniae*, measles, mumps, or rubella. Previous vaccination against hepatitis B when administered to risk groups, as per local recommendation.
5) Receipt of immune globulins, blood or blood-derived products since birth
6) 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
7) Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated
8) Individuals with blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems
9) Individuals with active tuberculosis
10) History of *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically
11) History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, measles, mumps, rubella, and of *Haemophilus influenzae* type b, and / or *Streptococcus pneumoniae* infection or disease.
12) At high risk for meningococcal infection during the study (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)
13) Individuals with underlying conditions predisposing them to invasive pneumococcal disease (specifically, but not limited to, subjects with sickle cell disease or human immunodeficiency virus [HIV] infection)
14) History of any neurologic disorders, including seizures and progressive neurologic disorders
15) History of Guillain-Barré syndrome
16) Known systemic hypersensitivity to any of the vaccine components, or history of a severe allergic reaction (eg, anaphylaxis) to the vaccine(s) used in the study or to a vaccine containing any of the same substances including neomycin, streptomycin, polymyxin B, glutaraldehyde, formaldehyde, and gelatin
17) Verbal report of thrombocytopenia, contraindicating intramuscular vaccination in the investigator's opinion
18) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the investigator's opinion
19) Chronic illness (including, but not limited to, cardiac disorders, congenital heart disease, chronic lung disease, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases) that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion
20) Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives
21) 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.

	22) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw 23) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study 24) Infants born preterm (by less than 37 weeks of gestation) requiring specific immunization schedule for routine childhood vaccines and/or specific care at the time of vaccination, as per national recommendations
Statistical Methods:	Main immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed on the Full Analysis Set (FAS) according to randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS). **Primary Objective:** Non-inferiority of MenACYW conjugate vaccine (Group 1) compared to Nimenrix® (Group 2) in terms of hSBA antibody titers after a 3-dose series to infants and toddlers will be tested. For each of the 4 serogroups (A, C, W, and Y), GMTs 30 days after a 3-dose series vaccination will be used to compare Group 1 and Group 2 with the following individual hypotheses: H_0 *(Null hypothesis)*: • $GMT_{MenACYW} / GMT_{Nimenrix} \leq 1/1.5$ (or $GMT_{Nimenrix} / GMT_{MenACYW} \geq 1.5$) H_1 *(Alternative hypothesis)*: • $GMT_{MenACYW} / GMT_{Nimenrix} > 1/1.5$ (or $GMT_{Nimenrix} / GMT_{MenACYW} < 1.5$) The statistical methodology will be based on the use of the 2-sided 95% confidence interval (CI) of the ratio of post-vaccination GMTs between Group 1 and Group 2. The CI will be calculated using a normal approximation of log-transformed titers. Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected. For each serogroup, the 2-sided 95% CI of the GMT ratio Group 1 (MenACYW) / Group 2 (Nimenrix) should lie above 1/1.5. The PPAS will be used as the main analysis. **Secondary Objectives** If the primary objective is met, non-inferiority of MenACYW conjugate vaccine (Group 1) compared to Nimenrix® (Group 2) in terms of hSBA antibody titers ≥ 1:8 after a 2-dose series in infants will be tested (Secondary Objective 1). For each of the 4 serogroups (A, C, W, and Y), the percentages of subjects who achieve an hSBA titer ≥ 1:8 30 days after the 2 dose administered in infancy will be used to compare responses between Group 1 and Group 2 with the following individual hypotheses: • H_0 *(Null hypothesis)*: $p(_{MenACYW}) - p(_{Nimenrix}) \leq -10\%$ • H_1 *(Alternative hypothesis)*: $p(_{MenACYW}) - p(_{Nimenrix}) > -10\%$ where $p(_{MenACYW})$ and $p(_{Nimenrix})$ are the percentages of subjects who achieve an hSBA titer ≥ 1:8 in the MenACYW conjugate vaccine group and the Nimenrix® group, respectively.

Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages is > -10%, the non-inferiority will be demonstrated. The CI of the difference in percentages will be computed using the Wilson score method without continuity correction.

The PPAS will be used as the main analysis.

The statistical analyses for the Secondary Objectives 2, 3, 4, 5, 6 and 7 will be descriptive.

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.

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).

Calculation of Sample Size:

Approximately a total of 1652 subjects will be enrolled.

For the Primary Objective

With 716 enrolled subjects in Group 1 and in Group 2, the study will have 96.2% power to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, Y hSBA antibody titers (ratio of GMTs in the 2 groups) after a 3-dose series to infants and toddlers 6 weeks to 18 months old, assuming:

- An estimated 26.2% dropout rate from the PPAS (528 subjects evaluable by group),
- a 1-sided alpha level of 2.5%,
- a non-inferiority margin of 1.5 (GMT ratio),
- a standard deviation (SD) of log10-transformed titers of 0.7 for serogroups A and C, 0.5 for serogroup Y, and 0.6 for serogroup W.

Table S1 Power of the study based on the primary objective

Antigen	MenACYW Standard Deviation*	Non-inferiority Margin	Power
A	0.7	1.5	98.3%
C	0.7	1.5	98.3%
Y	0.5	1.5	> 99.9%
W	0.6	1.5	99.7%
Overall			96.2%

Since the hypothesis needs to be met for all serogroups, no alpha adjustment for multiple comparisons is necessary in these calculations.

* SDs are based on the results of the MET39 (NCT01049035) MenACYW 2/4/12 months schedule (Group 3) after booster results. For the power computation, the same SD in the control group (Nimenrix®) is assumed.

For the Secondary Objective

With 716 enrolled subjects in Group 1 and in Group 2, the study will have a > 90% power (Farrington and Manning formula) to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, Y hSBA antibody titers ≥ 1:8 (difference in the percentage of seroprotected subjects in the 2 groups) after 2 doses in infancy at 2 months and 4 months of age, assuming:

- An estimated 26.2% dropout rate from the PPAS (528 subjects evaluable per group)
- A 1-sided alpha level of 2.5%,
- A non-inferiority margin of 10% (percentage difference)

Table S2: Power of the study for the secondary objective

Antigen	Estimated Percentage of hSBA Titer ≥ 1:8 Nimenrix®*	Non-inferiority margin†	Power
A	76%	10%	96.7%
C	94%	10%	> 99.9%
Y	71%	10%	94.7%
W	82%	10%	98.7%
Overall			90%

Since the hypothesis needs to be met for all serogroups, and the secondary objective is to be tested only if the primary objective succeeds, no alpha adjustment for multiple comparisons is necessary in these calculations.

* Percentages of subjects with an hSBA titer ≥ 1:8 are based on the MET39 (NCT01049035) MenACYW 2/4/12 months schedule (Group 3) post dose 2 results using estimates 2% lower than in the MenACYW group. The power is calculated with the assumption that the estimates from the investigational group equal that of the control group corresponding to the estimated percentages in the Nimenrix® group described above.

† A non-inferiority margin of 10% has been widely used in previous studies evaluating the same antigens and in a competitor's study of the same type. Also taking into account the level of the reference rate taken in the Nimenrix® group, it is reasonable to use 10%.

The sample size has been arbitrarily set to 110 subjects in Group 3 and Group 4 as these data are not intended to be used for any hypothesis testing. No formal sample size calculations were performed. In each group, there is more than 95% probability to observe an event with an incidence of 2.7%.

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

Table of Study Procedures - Groups 1, 2, and 3

Phase III study, 5 visits, 3 vaccination visits, 4 telephone calls, 10 vaccine injections, 4 blood collections per subject, 11- to 17-month duration per subject

Visit/Contact	Visit 1	Telephone Call (TC) 1	Visit 2	TC2	Visit 3	TC3	Visit 4	TC4	Visit 5
Age of Subject	2 months (42 to 89 days)						12-18 months*		
Study timelines (days)	Day 0	Visit 1 + 8 days	Visit 1 + 60 days	Visit 2 + 8 days	Visit 2 + 30 days	Visit 3 + 5 months AND Visit 4 – at least 14 days†	Visit 2 + at least 180 days	Visit 4 + 8 days	Visit 4 + 30 days
Time windows (days)		+2 days	+14 days	+2 days	+21 days			+2 days	+21 days
Informed consent form signed and dated	X								
Inclusion/exclusion criteria	X								
Collection of demographic data	X								
Medical history	X								
Physical examination (including temperature)‡§	X						X		
Temperature measurement§			X						
Contact interactive response technology (IRT) system for vaccine group randomization	X		X				X		
Review of temporary contraindications for blood sampling**	X				X		X		X
Blood sampling (BL)††	BL0001 (2 or 3 mL)‡‡				BL0002 (3 or 4 mL) ‡‡		BL0003 (5 or 6 mL)‡‡		BL0004 (5 or 6 mL)
Review warnings and precautions to vaccinations	X		X				X		
Review of contraindications to subsequent vaccinations			X				X		

Visit/Contact	Visit 1	Telephone Call (TC) 1	Visit 2	TC2	Visit 3	TC3	Visit 4	TC4	Visit 5
Age of Subject	2 months (42 to 89 days)						12-18 months*		
Study timelines (days)	Day 0	Visit 1 + 8 days	Visit 1 + 60 days	Visit 2 + 8 days	Visit 2 + 30 days	Visit 3 + 5 months AND Visit 4 – at least 14 days†	Visit 2 + at least 180 days	Visit 4 + 8 days	Visit 4 + 30 days
Time windows (days)		+2 days	+14 days	+2 days	+21 days			+2 days	+21 days
Vaccination with MenACYW conjugate vaccine or Nimenrix®	**X**		**X**				**X**		
Vaccination with routine pediatric vaccines§§	**X**		**X**				**X**		
Immediate surveillance (30 minutes)	X		X				X		
Diary card (DC) provided	DC1		DC2		DC3		DC4		
Telephone call		X***		X***		X†††		X***	
Diary card reviewed and collected			DC1		DC2		DC3		DC4
Recording of solicited injection site and systemic reactions‡‡‡	X		X§§§		X§§§				X§§§
Recording of unsolicited adverse events (AEs)	Day 0 to Day 30 after each vaccination visit								
Reporting of serious adverse events (SAEs, including adverse events of special interest [AESIs])****	To be reported throughout the study period								
Collection of reportable concomitant medications	X		X		X		X		X
Study termination record (Completion at End of study)									X

* Visit 4 may occur anytime from the day the subject turns 12 months to the day before the subject turns 19 months of age as long as there is an interval of at least 180 days since Visit 2.

†Staff will contact subjects' parent / legally acceptable representative by telephone 5 months after the last visit in infancy and at least 14 days before Visit 4.

‡ Physical examination should be performed as per standard of care. If a routine examination had been performed within the last week by the Investigator, a sub-investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area.

§Temperature needs to be measured before each vaccination and recorded in the source documents. The route for this study is rectal, oral, or axillary according to local practices, with the rectal route preferred for infants and the axillary route preferred for toddlers.

** Should a subject receive oral or injectable antibiotic therapy within 3 days prior to any 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 appropriately documented that the sample was taken less than 3 days after stopping antibiotic treatment.

†† At Visits 1 and 3, the blood sample volume indicated will be taken from all subjects including those subjects in a subset to assess the antibody response to meningococcal serogroups (A, C, W, and Y) measured by rSBA assay in addition to hSBA assay. At Visits 4 and 5, blood sample volume of 5 mL will be taken from all subjects, except subjects included in the rSBA subset. Blood sample volume of 6 mL will be taken from subjects included in the rSBA subset.

‡‡ Blood sample at Visit 1 and Visit 4 will be drawn before administration of the vaccines. 2 or 3 mL of blood at Visit 1, and 3 or 4 mL of blood at Visit 3 are collected depending on the weight at the study visit

§§ Routine pediatric vaccines: Hexavalent vaccine and PCV10 (Group 1 and Group 2) or PCV13 (Group 3) at Visits 1, 2, and 4. The MMR vaccine may be administered preferably at Visit 4. Subjects in Finland, Sweden or Poland may receive the licensed rotavirus vaccine concomitantly with study vaccines at Visit 1 and Visit 2.

*** This call is made 8 days to 10 days after the respective vaccinations. If Day 08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE (including any AESI) not yet reported, and will remind the subject's parent / legally acceptable representative to continue using the diary card, 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 5 months after Visit 3 and at least 14 days before Visit 4. During this telephone call, the staff will find out whether the subject experienced any SAE (including any AESI) not yet reported, will remind the subject's parent / legally acceptable representative that routine vaccinations will be provided in the context of this study and that they should bring back the diary card to the study center at the next visit, and will confirm the date and time of the next visit.

‡‡‡ Solicited injection site and systemic reactions will be recorded from Day 0 through Day 7 after each vaccination visit.

§§§ Solicited injection site and systemic reactions will be recorded during the review and collection of DC1, DC2 and DC4 at Visits 2, 3 and 5.

****AESIs will be collected throughout the study 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 - Group 4

Phase III study, 6 visits, 4 vaccination visits, 5 telephone calls, 11 vaccine injections, 4 blood collections per subject, 11- to 17-month duration per subject

Visit/Contact	Visit 1	Telephone Call (TC) 1	Visit 2	TC2	Visit 3	TC3	Visit 4	TC4	Visit 5	TC5	Visit 6
Age of Subject	2 months (42 to 89 days)								12-18 months*		
Study timelines (days)	Day 0	Day 08	Visit 1 + 60 days	Visit 2 + 8 days	Visit 2 + 60 days	Visit 3 + 8 days	Visit 3 + 30 days	Visit 4 + 5 months AND Visit 5 –at least 14 days†	Visit 3 + at least 180 days	Visit 5 + 8 days	Visit 5 + 30 days
Time windows (days)		+2 days	+14 days	+2 days	+14 days	+2 days	+21 days			+2 days	+21 days
Informed consent form signed and dated	X										
Inclusion/exclusion criteria	X										
Collection of demographic data	X										
Medical history	X										
Physical examination (including temperature)‡§	X								X		
Temperature measurement§			X		X						
Contact IRT system for vaccine group randomization	X		X		X				X		
Review of temporary contraindications for blood sampling**	X						X		X		X

Visit/Contact	Visit 1	Telephone Call (TC) 1	Visit 2	TC2	Visit 3	TC3	Visit 4	TC4	Visit 5	TC5	Visit 6
Age of Subject	2 months (42 to 89 days)								12-18 months*		
Study timelines (days)	Day 0	Day 08	Visit 1 + 60 days	Visit 2 + 8 days	Visit 2 + 60 days	Visit 3 + 8 days	Visit 3 + 30 days	Visit 4 + 5 months AND Visit 5 –at least 14 days†	Visit 3 + at least 180 days	Visit 5 + 8 days	Visit 5 + 30 days
Time windows (days)		+2 days	+14 days	+2 days	+14 days	+2 days	+21 days			+2 days	+21 days
Blood Sampling (BL)††	BL0001 (2 or 3 mL)‡‡						BL0002 (3 or 4 mL) ‡‡		BL0003 (5 or 6 mL)‡‡		BL0004 (5 or 6 mL)
Review warnings and precautions to vaccinations	X		X		X				X		
Review of contraindications to subsequent vaccinations			X		X				X		
Vaccination with MenACYW conjugate vaccine	**X**		**X**		**X**				**X**		
Vaccination with routine pediatric vaccines§§	**X**		**X**						**X**		
Immediate surveillance (30 minutes)	X		X		X				X		
DC provided	DC1		DC2		DC3		DC4		DC5		
Telephone call		X***		X***		X***		X†††		X***	
Diary card reviewed and collected			DC1		DC2		DC3		DC4		DC5

Visit/Contact	Visit 1	Telephone Call (TC) 1	Visit 2	TC2	Visit 3	TC3	Visit 4	TC4	Visit 5	TC5	Visit 6
Age of Subject	2 months (42 to 89 days)								12-18 months*		
Study timelines (days)	Day 0	Day 08	Visit 1 + 60 days	Visit 2 + 8 days	Visit 2 + 60 days	Visit 3 + 8 days	Visit 3 + 30 days	Visit 4 + 5 months AND Visit 5 –at least 14 days†	Visit 3 + at least 180 days	Visit 5 + 8 days	Visit 5 + 30 days
Time windows (days)		+2 days	+14 days	+2 days	+14 days	+2 days	+21 days			+2 days	+21 days
Recording of solicited injection site and systemic reactions‡‡‡	X		X§§§		X§§§		X§§§		X		X§§§
Recording of unsolicited AEs	From Day 0 to Day 30 after each vaccination visit										
Reporting of SAEs, including AESIs****	To be reported throughout the study period										
Collection of reportable concomitant medications	X		X		X		X		X		X
Study termination record (Completion at End of study)											X

* Visit 5 may occur anytime from the day the subject turns 12 months to the day before the subject turns 19 months of age as long as there is an interval of at least 180 days since Visit 3.

†Staff will contact subjects' parent / legally acceptable representative by telephone 5 months after the last visit in infancy and at least 14 days before Visit 5.

‡Physical examination should be performed as per standard of care. If a routine examination had been performed within the last week by the Investigator, a sub-investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area.

§Temperature needs to be measured before each vaccination and recorded in the source documents. The route for this study is rectal, oral, or axillary according to local practices, with the rectal route preferred for infants and the axillary route preferred for toddlers.

** Should a subject receive oral or injectable antibiotic therapy within 3 days prior to any 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 appropriately documented that the sample was taken less than 3 days after stopping antibiotic treatment.

†† At Visits 1 and 4, the blood sample volume indicated will be taken from all subjects including those subjects in a subset to assess the antibody response to meningococcal serogroups (A, C, W, and Y) measured by rSBA assay in addition to hSBA assay. At Visits 5 and 6, blood sample volume of 5 mL will be taken from all subjects, except subjects included in the rSBA subset. Blood sample volume of 6 mL will be taken from subjects included in the rSBA subset.

‡‡ Blood sample at Visit 1 and Visit 5 will be drawn before administration of the vaccines. 2 or 3 mL of blood are collected at Visit 1, and 3 or 4 mL of blood are collected at Visit 4 depending on the weight at the study visit.

§§ Routine pediatric vaccines: Hexavalent vaccine and PCV13 at Visits 1, 2, and 5. The MMR vaccine may be administered preferably at Visit 5.

*** This call is made 8 days to 10 days after the respective vaccinations. If Day 08 falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE (including any AESI) not yet reported, and will remind the subject's parent / legally acceptable representative 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 5 months after Visit 4 and at least 14 days before Visit 5. During this telephone call, the staff will find out whether the subject experienced any SAE (including any AESI) not yet reported, will remind the subject's parent / legally acceptable representative that routine vaccinations will be provided in the context of this study and that they should bring back the diary card to the study center at the next visit, and will confirm the date and time of the next visit.

‡‡‡ Solicited injection site and systemic reactions will be recorded from Day 0 through Day 7 after each vaccination visit.

§§§ Solicited injection site and systemic reactions will be recorded during the review and collection of DC1, DC2, DC3 and DC5 at Visits 2, 3, 4 and 6.

****AESIs will be collected throughout the study 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

List of Abbreviations

µg	Microgram
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
AR	adverse reaction
BL	blood sampling
CCID	cell culture infection dose
CDM	Clinical Data Management
CI	confidence interval
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CRM	cross-reacting material
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	Day
DC	diary card
DNA	deoxyribonucleic acid
DOD	delta optical density
DTaP	diphtheria, tetanus, and acellular pertussis
EDC	electronic data capture
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 & 3
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GDPR	Global Data Protection Regulation
GMC	geometric mean concentration

GMT	geometric mean titer
GPV	Global Pharmacovigilance
HB	hepatitis B
HBsAg	hepatitis B surface antigen
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HPV	human papilloma virus
HRP	horseradish peroxidase
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IM	intramuscular(ly)
IMD	invasive meningococcal disease
IME	important medical event
IOM	Institute of Medicine
IPV	inactivated polio vaccine
IRB	Institutional Review Board
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IU	International unit
LCLS	last contact, last subject
LLOQ	lower limit of quantitation
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
mIU	milli International unit
mL	Milliliter
MMR	measles, mumps, rubella
NSAID	non-steroidal anti-inflammatory drug
OD	optical density
PCV10	pneumococcal conjugate vaccine (10-valent, adsorbed)
PCV13	pneumococcal conjugate vaccine (13-valent, adsorbed)
PHE	Public Health England
PPAS	per-protocol analysis set
PRP	polyribosylribitol phosphate
PRN	pertactin

PS	Polysaccharides
PT	pertussis toxoid / toxin
PV	Pharmacovigilance
rDNA	recombinant deoxyribonucleic acid
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SmPC	Summary of Product Characteristics
SMT	Safety Management Team
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Tetanus
TC	telephone call
TCC	tissue culture control
TMF	trial master file
TT	tetanus toxoid
ULOQ	upper limit of quantitation
US	United States
VCR	vaccination coverage rate
WHO	World Health Organization

1 Introduction

1.1 Background

This is a study using MenACYW conjugate vaccine (MenQuadfi®) against invasive meningococcal disease (IMD).

This study (MET58) will compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Nimenrix® when administered as a 3-dose series concomitantly with routine pediatric vaccines to infants and toddlers in Europe.

IMD is a serious illness caused by the bacterium *Neisseria meningitidis (N. meningitidis)*, a Gram-negative diplococcus found exclusively in humans. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). At least 12 different meningococcal serogroups have been classified based on the immunochemistry of the capsular polysaccharides (PS). Some strains are more likely than others to cause infection (1) (2) (3) . Worldwide, most cases of meningococcal disease are caused by serogroups A, B, C, X, Y, and W (2) (3) (4). Serogroup B is responsible for endemic disease and some outbreaks, while serogroup C is responsible for large outbreaks (5). Serogroup A 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 in Chile (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 United States (US) during the last five-year period: a prolonged outbreak of serogroup B on a university campus in Ohio from 2008 – 2010 and 2 universities in New Jersey and California in 2013 (21) (22).

The epidemiology of *N. meningitidis* can be described as complex, unpredictable, geographically variable, and changing over time. Meningococcal disease occurs worldwide in both endemic and epidemic forms with seasonal variation. In Europe, the incidence rate of IMD has remained stable over the last 5 to 10 years, with the highest peak occurring in the population less than 4 years of age and a smaller peak in the 15 to 19 year old group. The highest incidence rate in Europe is caused by serogroup B, followed by C (23) (24). 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 (25). A gradual increase in serogroup Y IMD has also been recently reported in England and Wales between 2007-2009

(26) and in Sweden during 2005 – 2012 (27) (28). Nearly 50% of all IMD in Sweden was caused by serogroup Y in 2012 (27). 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 (29) and 38% in Finland in 2010 (30).

The goal for MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, W, and Y 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 (31 countries under centralized procedure[a]), Australia, Canada, the United Kingdom, Brazil, Argentina, and Chile. 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. Available study results are presented in the Investigator's Brochure. 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

[a] Countries under centralized procedure 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, United Kingdom (Northern Ireland) (remaining part after Brexit) and other European Economic Area countries – Iceland, Liechtenstein, and Norway.

vaccine concomitantly with routine pediatric vaccines. The routine pediatric vaccines administered concomitantly with MenACYW conjugate vaccine at various schedules included Prevnar® (pneumococcal 7-valent 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 [HB] vaccine, M-M-R® II vaccine (measles, mumps, and rubella vaccine [MMR]), and VARIVAX® (varicella vaccine).

Immunogenicity

After the primary 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.

No interaction was demonstrated between the routine vaccines and MenACYW conjugate vaccine, compared to when the routine vaccines were given without MenACYW conjugate vaccine in the control groups.

Safety

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

No deaths occurred within 30 days. There were 2 subjects in Group 4 who died during the study, 1 as a result of hypoxic ischemic encephalopathy which started 96 days after the 6-month vaccination and 1 as a result of non-accidental head trauma 36 days after the 12-month vaccination. These events were considered by the Investigator as unrelated to study vaccine. There were 2 other subjects who discontinued the study due to a serious adverse event (SAE) and the receipt of intravenous immunoglobulin treatment: 1 subject in Group 2 with Kawasaki disease, 106 days after the 6-month vaccination; and 1 subject in Group 3 with middle lobe pneumonia and Kawasaki disease, 50 and 52 days, respectively, after the 4-month vaccinations. One other subject in Group 4 was discontinued due to a non-serious adverse event (AE) (viral rash 1 day after the 6-month vaccinations). None of these AEs leading to discontinuation were considered by the Investigator as related to the vaccine. There were no 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, W, and Y) were evaluated by serum bactericidal assay using baby rabbit complement (rSBA) and hSBA. MenACYW conjugate vaccine immune responses evaluated by rSBA and hSBA were generally comparable to Nimenrix® immune responses with some variation by serogroup.

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]).

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%).

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

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

In countries where vaccination advisory boards or national pediatric associations have recommended the Meningococcal B vaccine although it is not publicly funded (ie Czech Republic, Spain, and Poland), subjects will be offered 2 doses of the Meningococcal B vaccine (Bexsero®) when parents are willing to vaccinate their child within the second year of life. This vaccine is a non-study vaccine to be administered as per local standard practices at additional optional visits after the end of the trial (ie, after the subject will have completed the last study procedure at the last study visit). This vaccine will be outside the scope of the study evaluations. No immunogenicity and safety data will be collected after its administration. The Meningococcal B vaccine (Bexsero®) will be reimbursed by the Sponsor.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine or Nimenrix® 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 Nimenrix® 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 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 (31). 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 (32).

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 (33). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (34). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (34).

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 risk listed here are not exhaustive. Refer to the Investigator's Brochure of the investigational vaccine and to the package inserts for Nimenrix® (35) and concomitant vaccines for additional information regarding potential risks.

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, W, and Y. 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 polysaccharide 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 polysaccharide vaccines have two important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) polysaccharides alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of polysaccharide vaccines in infants and children has been shown to be improved by conjugating the polysaccharides 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 polysaccharide-specific total immunoglobulin G (IgG) and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials including those with the final formulation (MET39 and MET44) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above trials using the final formulation or in the earlier trials.

The purpose of MET58 is to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and the licensed MenACYW conjugate vaccine (Nimenrix®) when administered as a 3-dose series concomitantly with routine pediatric vaccine to healthy infants and toddlers in Europe.

2 Study Objectives

2.1 Primary Objective

To demonstrate the non-inferiority of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of a 3-dose series of MenACYW conjugate vaccine compared to a 3-dose series of Nimenrix® when each vaccine is administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) to infants and toddlers from 6 weeks to 18 months old (Group 1 versus Group 2)

The endpoint for the primary objective is presented in Section 9.1.2.1.

2.2 Secondary Objectives

1) To demonstrate the non-inferiority of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of 2 doses in infancy of MenACYW conjugate vaccine compared to 2 doses in infancy of Nimenrix® when each vaccine is administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) (Group 1 versus Group 2)
2) To describe the antibody responses against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine is administered in a 3-dose series concomitantly with the routine pediatric vaccines (Group 3)

3) To describe the antibody responses against the antigens of the routine pediatric vaccines administered in a 3-dose series concomitantly with MenACYW conjugate vaccine or Nimenrix® (Groups 1, 2, and 3)
4) To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by hSBA when MenACYW conjugate vaccine or Nimenrix® is administered in a 3-dose series concomitantly with PCV10 and other routine pediatric vaccines (Groups 1 and 2)
5) To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by hSBA when MenACYW conjugate vaccine is administered in a 4-dose series concomitantly with PCV13 and other routine pediatric vaccines (Group 4)
6) To describe the antibody responses against the antigens of the routine pediatric vaccines administered with MenACYW conjugate vaccine administered in a 4-dose series concomitantly (Group 4)

The endpoints for the secondary objectives are presented in Section 9.2.2.1.

2.3 Observational Objectives

Immunogenicity

To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by rSBA in a subset of subjects when MenACYW conjugate vaccine or Nimenrix® is administered concomitantly with routine pediatric vaccines (all groups)

Safety

To describe the safety profile of MenACYW conjugate vaccine and Nimenrix® when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers

The endpoints for the observational objectives are presented in Section 9.3.2.2.

3 Investigators and Study Organization

This study will be conducted in approximately 50 centers in Europe. The Principal Investigators and any sub-investigators at the individual sites will 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.

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

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 Independent Ethics Committees (IECs) or Institutional Review Boards (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 both maintained by the Investigator and the Sponsor together with the composition of the IEC / IRB (the names and qualifications of the members attending and voting at the meetings).

The Investigator or Sponsor will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently (according to national provision) if requested. All SAEs occurring during the study that could be 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, partially modified double-blind (open-label for some of the vaccines / study groups, as detailed in the note below), randomized, parallel-group, active-controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Nimenrix® (Meningococcal group A, C, W-135, and Y conjugate vaccine) when administered as a 3-dose series (ie, 2 doses administered in infancy and 1 dose in the second year of life) concomitantly with routine pediatric vaccines to healthy infants and toddlers in Europe.

Subjects in Groups 1, 2, and 3 will receive either 3 doses of MenACYW conjugate vaccine or 3 doses of Nimenrix® administered concomitantly with routine vaccines at 2 months of age[a] (Visit 1), 4 months of age (Visit 2), and 12 to 18 months of age (Visit 4). The hexavalent vaccines and the pneumococcal vaccines (PCV10 or PCV13) will be administered in a 2+1 regimen (ie, 2 doses in infancy and 1 final dose in the 2nd year of life) mimicking the regimen of MenACYW conjugate vaccine or Nimenrix®.

[a] "2 months" refers to infants aged 6 to 12 weeks (≥ 42 to ≤ 89 days) at enrollment

Subjects in Group 4 will receive 4 doses of MenACYW conjugate vaccine with routine vaccines at 2 months of age[a] (Visit 1), 4 months of age (Visit 2), 6 months of age (Visit 3; MenACYW conjugate vaccine only), and 12 to 18 months of age (Visit 5; MenACYW conjugate vaccine and routine vaccines). The hexavalent vaccine and PCV13 will be administered in a 2+1 regimen, concomitantly to the 1st and 2nd doses in infancy and the 4th dose of MenACYW conjugate vaccine. The 3rd dose of MenACYW conjugate vaccine will be administered alone, without any other routine pediatric vaccines.

In all 4 vaccine groups, the MMR vaccine may be preferably administered concomitantly with the other study vaccines at 12 to 18 months of age. If not, the subject will receive a licensed Measles, Mumps and Rubella vaccine with a gap of at least 4 weeks before any study vaccines or after the end of the study (ie, after the subject will have completed the last study procedure at the last study visit). When administered outside the study visit, the licensed Measles, Mumps and Rubella vaccine will be sourced by the health care system, according to the national immunization program.

Subjects in Finland, Sweden or Poland may receive the licensed rotavirus vaccine concomitantly with study vaccines at study vaccination visits Visit 1 and Visit 2. If not, the rotavirus vaccine can be administered with a time interval of at least 2 weeks before or 2 weeks after Visit 1 and/or Visit 2. The rotavirus vaccines will be sourced by the study sites and administered as per local standard practices. Safety data will be collected after the administration of the rotavirus vaccine concomitantly with the study vaccine. No serological testing will be done for rotavirus immunogenicity.

Subjects in Spain, Czech Republic, and Poland will be offered 2 doses of the Meningococcal B vaccine (Bexsero®) when parents are willing to vaccinate their child within the second year of life. This vaccine is a non-study vaccine to be administered as per local standard practices at additional optional visits after the end of the trial (ie, after the subject will have completed the last study procedure at the last study visit). This vaccine will be outside the scope of the study evaluations. No immunogenicity and safety data will be collected after its administration. The Meningococcal B vaccine (Bexsero®) will be reimbursed by the Sponsor.

5.1.2 Justification of the Study Design

The MET58 study is designed to evaluate the immunogenicity and describe the safety of a 3-dose series (2+1 schedule) of MenACYW conjugate vaccine compared to a 3-dose series of Nimenrix® when administered concomitantly with routine pediatric vaccines to infants and toddlers 6 weeks to 18 months old in Europe. The design of the study has been based on the feedback received from the European Medicines Agency (EMA) as a part of multiple scientific advice documents.

The 2+1 schedule comprises a first infant dose of MenACYW conjugate vaccine or Nimenrix® administered between 6 and 12 weeks of age and the second dose at least 2 months later (between 4 and 5 months of age). The third dose is administered at 12 to 18 months, with a minimum gap of 6 months between the second and third doses. The study will be conducted in European Union (EU) countries where the Sanofi Pasteur tetanus toxoid (TT) - conjugated hexavalent vaccine licensed in Europe (DTaP-IPV-HB-Hib vaccine having different trade names in Europe: Hexyon® in Western Europe, and Hexacima® in Eastern Europe) and PCV10 (Synflorix®) are licensed and could be administered in a 2+1 regimen (ie, 2 doses in infancy and 1 booster dose preferably

between 12 and 15 months of age) mimicking the meningococcal vaccine regimen. Overall, the meningococcal vaccines schedule may fit to the routine immunization schedules in EU countries, knowing its diversity.

Additional vaccine groups (Group 3 and Group 4) will generate data on immunogenicity and safety of MenACYW conjugate vaccine when administered concomitantly with the hexavalent vaccine and PCV13 (Prevenar13®). Data will be also generated with MenACYW conjugate vaccine administered in a 3+1 schedule (Group 4): 3 doses during infancy and a final dose in the second year of life. Although the first and second doses of MenACYW conjugate vaccine in infancy will be administered concomitantly with PCV13 and hexavalent vaccine, the 3rd dose of MenACYW conjugate vaccine in infancy will be administered at least 2 months after the 2nd dose and alone, as there is no routine vaccination at this age in the National Immunization Programs of EU countries participating in MET58. Data generated in Europe with the 3+1 schedule of MenACYW conjugate vaccine will be descriptive only.

In all 4 vaccine groups, the subject will receive a licensed Measles, Mumps and Rubella vaccine either administered concomitantly with the study vaccines at 12 to 18 months of age, or separately with at least a gap of 4 weeks before any study vaccines or after the end of the study (ie, after the subject will have completed the last study procedure at the last study visit). Those clinical data generated would cover any possible integration of the MenACYW conjugate vaccine use in the National Immunization Programs of EU countries and outside the EU.

Despite the fact that this study is being conducted in the EU and is targeting to generate data relevant for the EU population and aligned with EU meningococcal conjugate vaccine schedules, it is also part of the global development program for the MenACYW conjugate vaccine and will allow for the EU and global data to be placed in context of each other through the data generated for subjects in all Groups (including those receiving the 3+1 schedule in Group 4). The descriptive set of clinical data using the 3+1 schedule of MenACYW conjugate vaccine will be put in perspective with data generated in the non-EU studies where the 3+1 schedule and the 2+1 schedule of MenACYW conjugate vaccine will be assessed with different concomitant pediatric vaccines. Those clinical data generated would cover any possible use in EU and internationally (if needed due to evolution of epidemiology in the future or to adapt to the increasing complexity of immunization schedules in infants and toddlers worldwide).

In the Phase II MET39 study conducted in the US, MenACYW conjugate vaccine was co-administered in a population of infants with recommended pediatric vaccines at several schedules (1+1, 2+1 and 3+1) and demonstrated good safety profile regardless of the immunization schedule and the number of doses administered. All analyses will evaluate the immune responses to serogroups A, C, W, and Y. The immune response to all routine vaccines administered concomitantly with MenACYW conjugate vaccine or Nimenrix® will also be assessed. To avoid any potential immune interference the Meningococcal Group B vaccine cannot be administered before inclusion in the study and during the study period.

The rotavirus program varies across MET58 countries (36). Among countries in which subjects will contribute to the primary objective assessment, Finland is the only country with a largely implemented and publicly-funded rotavirus vaccine (37). The vaccination coverage rate is quite high (VCR >90%) (37). Subjects in Finland, Sweden or Poland may receive their rotavirus vaccine concomitantly with study vaccines at study vaccination visits Visit 1 and Visit 2. If not,

the rotavirus vaccine can be administered with a time interval of at least 2 weeks before or 2 weeks after Visit 1 and/or Visit 2. The rotavirus vaccines will be sourced by the study sites and administered as per local standard practices. According to the respective product information, no immune interference has been reported between licensed rotavirus vaccines and standard of care vaccines administered in this study. In the ongoing phase III MET42 study conducted in infants in the US, the immunogenicity of the rotavirus vaccine will be evaluated when administered concomitantly with MenACYW conjugate vaccine and other pediatric routine vaccines (38).

The country selection for MET58 took into consideration the current status of the Meningococcal B vaccination program in the EU countries and select countries/regions where the implementation is not yet done or where the vaccination coverage is still low (ie, below the national vaccination coverage). The status of the Meningococcal B vaccination program in the MET58 countries/regions will be monitored on ongoing basis throughout the study conduct. Depending on the evolution of the local requirement for the Meningococcal B vaccination, the participation of the country/sites would be reassessed accordingly to ensure that the benefit for subjects to participate to MET58 outweigh any lack of chance for not receiving standard-of-care vaccines.

After the end of their study participation, the subjects will continue with the vaccination schedule recommended in their respective countries according to their age. Amongst the countries which are part of the MET58 study, Italy is the only country where the MenB vaccination has been implemented in the national immunization schedule and is free of charge. In this country, the investigators will advise parents to contact the local health care centers after the end of the study for their child to receive the Meningococcal B vaccination as per Bexsero® Product Information (39).

In other countries where vaccination advisory boards or national pediatric associations have recommended the Meningococcal B vaccine but it is not public funded (ie Czech Republic, Spain, and Poland) (40) (41), subjects will be offered 2 doses of the Meningococcal B vaccine (Bexsero®) when parents are willing to vaccinate their child within the second year of life. This vaccine is a non-study vaccine to be administered as per local standard practices at additional optional visits after the end of the trial (ie, after the subject will have completed the last study procedure at the last study visit). This vaccine will be outside the scope of the study evaluations. No immunogenicity and safety data will be collected after its administration. The Meningococcal B vaccine (Bexsero®) will be reimbursed by the Sponsor.

To perform an appropriate safety description, the study will be partially modified double-blind. The MenACYW conjugate vaccine and Nimenrix® will be administered in a modified double-blind manner in the vaccine groups directly compared, ie, when administered in the 2+1 schedule concomitantly with PCV10 (Synflorix®) and the Sanofi Pasteur hexavalent vaccine. The MenACYW conjugate vaccine in other vaccine groups and all other concomitant vaccines in all vaccine groups will be administered in an open-label manner.

5.1.3 Study Plan

Approximately 1652 healthy infants aged 6 to 12 weeks at enrollment will be randomized. Approximately 20% of subjects 6 to 8 weeks of age (≥ 42 to ≤ 59 days) should be enrolled Groups

1 and 2 to provide safety and immunogenicity data for this population, as described below (refer to Section 6.5 for more details):

- Group 1 and Group 2: approximately 144 subjects in each group;
- Group 3 and Group 4: approximately 22 subjects in each group.

The vaccination and blood sampling schedules are detailed in Table 5.1 and Table 5.2.

Table 5.1: Vaccination and blood sampling schedule in Groups 1, 2, and 3

Visit #	Visit 1		Visit 2	Visit 3	Visit 4		Visit 5*
Group	**BL0001†**	**3 vaccinations**	**3 vaccinations**	**BL0002**	**BL0003†**	**4 vaccinations**	**BL0004**
1	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV10‡	MenACYW conjugate vaccine Hexavalent vaccine PCV10	X	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV10‡ MMR vaccine	X
2	X	Nimenrix® Hexavalent vaccine‡ PCV10‡	Nimenrix® Hexavalent vaccine‡ PCV10‡	X	X	Nimenrix® Hexavalent vaccine‡ PCV10‡ MMR vaccine	X
3	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV13‡	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV13‡	X	X	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV13‡ MMR vaccine	X

PCV10: Synflorix®

PCV13: Prevenar 13®

MMR vaccine (M-M-RVAXPRO®) may be received concomitantly with other vaccines at Visit 4.

*Last study visit for Groups 1, 2, and 3. Other routine vaccines can be administered as per standard of care after study procedures are completed

†Blood will be drawn prior to vaccinations

‡The hexavalent vaccine and PCV10 (or PCV13 in Group 3) be administered in a 2+1 regimen, concomitantly with the 1st and 2nd doses in infancy and the toddler dose of MenACYW conjugate vaccine. Subjects in Finland, Sweden or Poland may receive the licensed rotavirus vaccine concomitantly with study vaccines at Visit 1 and Visit 2. No serological testing will be done for rotavirus immunogenicity

Table 5.2: Vaccination and blood sampling schedule in Group 4

Visit #	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5		Visit 6*
Group	**BL0001†**	**3 vaccinations**	**3 vaccinations**	**1 vaccination**	**BL0002**	**BL0003†**	**4 vaccinations**	**BL0004**
4	x	MenACYW conjugate vaccine Hexavalent vaccine‡ PCV13‡	MenACYW conjugate vaccine Hexavalent vaccine PCV13	MenACYW conjugate vaccine§	x	X	MenACYW conjugate vaccine Hexavalent vaccine PCV13 MMR vaccine	x

PCV13: Prevenar 13®

MMR vaccine (M-M-RVAXPRO®) may be received concomitantly with other vaccines at Visit 5.

*Last study visit for group 4. Other routine vaccines can be administered as per standard of care after study procedures are completed

†Blood will be drawn prior to vaccinations

‡The hexavalent vaccine and Prevenar 13 will be administered in a 2+1 regimen, concomitantly with the 1st and 2nd doses in infancy and the toddler dose of MenACYW conjugate vaccine

§The 3rd dose of MenACYW conjugate vaccine is administered alone, without any other routine pediatric vaccines

Vaccinations

Healthy infants will be randomized as follows depending on the pneumococcal vaccines that will be administered in the respective countries.

Countries where the pneumococcal vaccination administered will be PCV10 (Czech Republic, Romania, Sweden, Finland, and Poland): 1432 subjects will be randomized in a 1:1 ratio to one of the following 2 groups:

- Group 1: MenACYW conjugate vaccine (3 doses) (2+1 regimen) + PCV10 + Hexavalent vaccine + MMR vaccine (n=716)
- Group 2: Nimenrix® (3 doses) (2+1 regimen) + PCV10 + Hexavalent vaccine + MMR vaccine (n=716)

Countries where the pneumococcal vaccination administered will be PCV13 (Italy and Spain): 220 subjects will be randomized in a 1:1 ratio to one of the following 2 groups:

- Group 3: MenACYW conjugate vaccine (3 doses) (2+1 regimen) + PCV13 + Hexavalent vaccine + MMR vaccine (n=110)
- Group 4: MenACYW conjugate vaccine (4 doses) (3+1 regimen) + PCV13 + Hexavalent vaccine + MMR vaccine (n=110)

For all 4 vaccine groups, the MMR vaccine may be preferably administered concomitantly with the other vaccines at 12 to 18 months of age. If not, the subject will receive a licensed Measles, Mumps and Rubella vaccine with a gap of at least 4 weeks before any study vaccines or after the end of the study (ie, after the subject will have completed the last study procedure at the last study visit). When administered outside the study visits, the licensed Measles, Mumps and Rubella vaccine will be sourced by the health care system, according to the national immunization program.

Subjects in Finland, Sweden or Poland may receive the licensed rotavirus vaccine concomitantly with study vaccines at study vaccination visits Visit 1 and Visit 2. If not, the rotavirus vaccine can be administered with a time interval of at least 2 weeks before or 2 weeks after Visit 1 and/or Visit 2. The rotavirus vaccines will be administered, as per local standard practices.

Subjects in Spain, Czech Republic, and Poland will be offered 2 doses of the Meningococcal B vaccine (Bexsero®) when parents are willing to vaccinate their child within the second year of life. This vaccine is a non-study vaccine to be administered as per local standard practices at additional optional visits after the end of the trial (ie, after the subject has completed the last study procedure at the last study visit). This vaccine will be outside the scope of the study evaluations. No immunogenicity and safety data will be collected after its administration. The Meningococcal B vaccine (Bexsero®) will be reimbursed by the Sponsor.

Note: To perform an appropriate description of the safety of MenACYW conjugate vaccine and Nimenrix® in Groups 1 and 2 (ie, when each of these vaccines are administered as a 3-dose series concomitantly with PCV10 and hexavalent vaccine), MenACYW conjugate vaccine and Nimenrix® will be administered in a modified double-blind manner in these 2 groups. The MenACYW conjugate vaccine in Groups 3 and 4 and all other concomitant vaccines in all vaccine groups will be administered in an open-label manner.

Refer to Section 6.4 for more details.

Blood sampling

All subjects will provide 4 blood samples.

Subjects in Groups 1, 2, and 3 will provide blood samples for immunogenicity assessment as follows:

- at baseline (pre-primary vaccination 1, Day 0)
- 30 days (+21 days) after the 2nd dose of MenACYW conjugate vaccine / Nimenrix®
- prior to the 3rd dose (toddler dose) of MenACYW conjugate vaccine / Nimenrix®
- 30 days (+21 days) after the 3rd dose (toddler dose) of MenACYW conjugate vaccine / Nimenrix®

Subjects in Group 4 will provide blood samples for immunogenicity assessment as follows:

- at baseline (pre-primary vaccination 1, Day 0)
- 30 days (+21 days) after the 3rd dose of MenACYW conjugate vaccine
- prior to the 4th dose (toddler dose) of MenACYW conjugate vaccine
- 30 days (+21 days) after the 4th dose (toddler dose) of MenACYW conjugate vaccine

Collection of safety data

- All subjects will be followed for safety from Day 0 to the last study visit
- All subjects will be observed for 30 minutes after each vaccination and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the electronic case report book (CRB).
- The subject's parent / legally acceptable representative will record information in a diary card about solicited reactions from Day 0 to Day 7 after each vaccination and unsolicited AEs will be recorded from Day 0 to Day 30 after each vaccination.
- SAEs, including adverse events of special interest (AESIs) will be recorded in a diary card throughout the study. The subject's parent / legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the study.
- Study site staff will contact subjects' parent / legally acceptable representative by telephone on 8 days (+2 days) after each vaccination visit to identify the occurrence of any SAEs not yet reported and to remind them to complete the diary card after each vaccination visit and bring it back to the subsequent visit so that it can be reviewed at the study site.
- Staff will also contact subjects' parent / legally acceptable representative by telephone 5 months after the last visit in infancy and at least 14 days before Visit 4 (Groups 1, 2, and 3) or Visit 5 (Group 4). This contact is to identify the occurrence of any SAEs not yet reported, but also to remind them that routine vaccinations will be provided in the context of this study and that they should bring back the diary card to the subsequent visit so that it can be reviewed at the study site. If the subject does not continue in the study, the information

recorded on the diary card will be reviewed during this call, and the diary card will be retrieved by the site.

5.1.4 Visit Procedures

Visit 1 (D0; 2 months [6 to 12 weeks] of age): Inclusion, Randomization, Blood Sample, and Vaccination

1) Give the subject's parent / legally acceptable representative information about the study, obtain written informed consent, and give him / her a signed copy.

2) Check inclusion and exclusion criteria for eligibility. Review vaccination history from the child's immunization record.

3) Collect demographic data (including birth weight and gestational age).

4) Obtain verbal medical history about the subject, including ongoing medication.

5) Conduct a physical examination as per standard of care. Perform a physical examination, including, but not limited to, examination of the head (ear, nose, and throat), neck, heart, lungs, abdomen, and extremities. If a routine examination had been performed within the last week by the Investigator, a sub-investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area.

6) Take the subject's temperature (Refer to Section 9.3.2.3.2 for accurate temperature assessment). If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.

7) Take the subject's weight to determine if 2 or 3 ml are to be collected for BL0001 (refer to the Operating Guidelines for further instructions).

8) Contact the interactive response technology (IRT) system for vaccine group randomization (at least allocation of subject number, dose number of all vaccines).

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

10) Collect 2 or 3 mL of blood (BL0001) depending on the weight of the subject at inclusion from all subjects including those subjects in the rSBA subset (see Section 7.1 for detailed instructions regarding the handling of blood samples and Section 6.5 for more details on the rSBA subset). If attempts to obtain the first blood draw are unsuccessful (after reasonable attempts as per local regulations) either the Visit 1 can be rescheduled to a later date at which point inclusion/exclusion criteria must be re-validated or the subject will be withdrawn from the study without being vaccinated. If during the rescheduled visit the first blood draw cannot be obtained, the subject will be withdrawn from the study without being vaccinated.

11) Review warnings and precautions to vaccinations.

12) Administer the investigation product, the control product and other products in the assigned location (see Operating Guidelines) and documented appropriately:

Table 5.3: Vaccinations and route of administration

Vaccine		Group 1 or Group 2	Group 3 or Group 4	Route of administration
MenACYW Conjugate or Nimenrix®	Modified double-blind	X		Inject IM into the anterolateral area of the thigh, preferably the right thigh
MenACYW Conjugate	Open-label		X	Inject IM into the anterolateral area of the thigh, preferably the right thigh
Hexavalent vaccine	Open-label	X	X	Inject IM into the anterolateral area of the thigh, preferably the left thigh (ie, the opposite leg from that used for meningococcal vaccine administration)
PCV10	Open-label	X		Inject IM into the anterolateral area of the thigh, preferably the left thigh (ie, the opposite leg from that used for meningococcal vaccine administration)
PCV13	Open-label		X	Inject IM into the anterolateral area of the thigh, preferably the left thigh (ie, the opposite leg from that used for meningococcal vaccine administration)

If multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are administered in the same limb, the injection sites should be separated by 2.5 cm or more, so that any local reactions can be differentiated.

Do not administer the hexavalent vaccine or pneumococcal vaccine (PCV10 or PCV 13) in the same thigh as the meningococcal vaccine. For details see Operating Guidelines.

Efforts should be made to administer the vaccines at the recommended sites. Any failure to administer vaccines in the designated limb should be recorded as a comment in the electronic case report form (CRF). If the initial vaccines are administered in the wrong limbs, this should be corrected for subsequent injections.

1) Keep the subject under observation for 30 minutes, and record any AEs in the source document. In the event of a local reaction, indicate the associated vaccine.

2) Give the parent / legally acceptable representative a diary card (DC1), a thermometer, and a ruler, and go over the instructions for their use. At each subsequent visit, confirm that the parent / legally acceptable representative has retained the thermometer and ruler, replace only as necessary.

3) Remind the parent / legally acceptable representative 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.

4) Remind the parent / legally acceptable representative to notify the site in case of an SAE.

5) 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 (including AESI) occurred, follow the instructions in Section 10 for reporting it.

2) Remind the parent / legally acceptable representative to do the following:
   - Complete the D0 to D07 pages of the diary card.
   - Complete the remaining pages of the diary card and bring them to Visit 2.
   - Notify the site in case of an SAE.

Routine pediatric vaccines and the meningococcal vaccine will be administered at Visit 2, as described in Table 5.1 and Table 5.2.

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

1) Collect and review the diary card (DC1) with the parent / legally acceptable representative, 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 vaccination history from the child's immunization record if routine pediatric vaccinations have already been performed since the last study visit.
3) Review contraindications to subsequent vaccinations and conditions for withdrawal.
4) Review warnings and precautions to vaccinations.
5) Take the subject's temperature (Refer to Section 9.3.2.3.2 for accurate temperature assessment). If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.
6) Contact the IRT system for dose number of all vaccines
7) Administer the investigation product, the control product and other products to subjects. Each vaccine should be administered in the assigned location (see Operating Guidelines) and documented appropriately. Refer to Table 5.3 for details on vaccinations and route of administration.

   If multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are administered in the same limb, the injection sites should be separated by 2.5 cm or more, so that any local reactions can be differentiated.

   Do not administer the hexavalent vaccine or pneumococcal vaccine (PCV10 or PCV 13) in the same thigh as the meningococcal vaccine. For details see Operating Guidelines.

Efforts should be made to administer the vaccines at the recommended sites. Any failure to administer vaccines in the designated limb 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.

8) Observe the subject for 30 minutes and record any AEs in the source document. In the event of a local reaction, indicate the associated vaccine.

9) Give the parent / legally acceptable representative a diary card (DC2).

10) Remind the parent / legally acceptable representative 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.

11) Remind the parent / legally acceptable representative to notify the site in case of an SAE.

12) Complete the relevant CRFs for this visit.

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

Refer to steps in Telephone Call 1.

Remind the parent / legally acceptable representative that routine pediatric vaccines will not be administered at Visit 3, as described in Table 5.1 and Table 5.2.

Visit 3 for all Groups:

Visit Procedures applicable to subjects in Groups 1, 2, and 3: Collection of Safety Information and Blood Sample

Visit 3 will be conducted 30 [+21] days after Visit 2 in Groups 1, 2, and 3

1) Collect and review the diary card (DC2) with the parent / legally acceptable representative, 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) Take the subject's weight to determine if 3 or 4 ml should be collected for BL0002 (refer to Operating Guidelines for further instructions).

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

4) Collect 3 or 4 mL of blood depending on the weight of the subject at Visit 3 (BL0002) from all subjects including those subjects in the rSBA subset (see Section 7.1 for detailed instructions regarding the handling of blood samples and Section 6.5 for more details on the rSBA subset).

5) Give the parent / legally acceptable representative a diary card (DC3).

6) Remind the parent / legally acceptable representative to expect a telephone call 5 months after Visit 3 and to bring back the diary card when they return for Visit 4 at a specified date and time.

7) Remind the parent / legally acceptable representative to notify the site in case of an SAE.

8) Complete the relevant CRFs for this visit.

Telephone Call 3 (5 months after Visit 3 and at least 14 days before Visit 4) for Groups 1, 2, and 3:

- Staff will contact subjects' parent / legally acceptable representative by telephone 5 months after the last visit in infancy and at least 14 days before Visit 4. This contact is to identify the occurrence of any SAEs (including any AESI) not yet reported.
- Remind the parent / legally acceptable representative that they should bring back the diary card to the subsequent visit so that it can be reviewed at the study site, and to confirm the date and time of the next visit. If the subject does not continue in the study, the information recorded on the diary card will be reviewed during this call, and the diary card will be retrieved by the site.
- Remind the parent / legally acceptable representative that routine pediatric vaccines will be administered at Visit 4.

Visit Procedures applicable to subjects in Group 4: Collection of Safety Information and Vaccination

Visit 3 will be conducted 60 [+14] days after Visit 2 in Group 4

1) Collect and review the diary card (DC2) with the parent / legally acceptable representative, 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) Take the subject's temperature (Refer to Section 9.3.2.3.2 for accurate temperature assessment). If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.

3) Review vaccination history from the child's immunization record if routine pediatric vaccinations have already been performed since the last study visit.

4) Review warnings and precautions to vaccinations.

5) Review contraindications to subsequent vaccinations and conditions for withdrawal.

6) Contact the IRT system for dose number of all vaccines.

7) Administer MenACYW conjugate vaccine: inject IM into the anterolateral area of the thigh, preferably the right thigh.

8) Observe the subject for 30 minutes and record any AEs in the source document.

9) Give the parent / legally acceptable representative a diary card (DC3).

10) Remind the parent / legally acceptable representative 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.

11) Remind the parent / legally acceptable representative to notify the site in case of an SAE.

12) Complete the relevant CRFs for this visit.

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

- Refer to steps in Telephone Call 1.
- None of the routine pediatric vaccines will be administered at Visit 4.

Visit 4 for all Groups:

Visit Procedures applicable to subjects in Groups 1, 2, and 3: Collection of Safety Information, Vaccination, and Blood Sample

Visit 4 will be conducted at 12 to 18 months of age and at least 180 days after Visit 2 in Groups 1, 2, and 3

1) Collect and review the diary card (DC3) with the parent / legally acceptable representative, 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) Conduct a physical examination as per standard of care. Perform a physical examination, including, but not limited to, examination of the head (ear, nose, and throat), neck, heart, lungs, abdomen, and extremities. If a routine examination had been performed within the last week by the Investigator, a sub-investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area.

3) Take the subject's temperature (Refer to Section 9.3.2.3.2 for accurate temperature assessment). If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.

4) Review vaccination history from the child's immunization record if routine pediatric vaccinations have already been performed since the last study visit.

5) Review warnings and precautions to vaccinations.

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

7) Collect 5 mL of blood (BL0003) from all subjects except for subjects included in the rSBA subset. Collect 6 mL of blood (BL0003) from subjects included in the rSBA subset (see Section 7.1 for detailed instructions regarding the handling of blood samples and Section 6.5 for more details on the rSBA subset).

8) Review contraindications to subsequent vaccinations and conditions for withdrawal.

9) Contact the IRT system for dose number of all vaccines.

10) Administer the investigation product, the control product and other products to subjects. Each vaccine should be administered in the assigned location (see Operating Guidelines) and

documented appropriately. Refer to Table 5.3 for details on vaccinations and route of administration.

If multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are administered in the same limb, the injection sites should be separated by 2.5 cm or more, so that any local reactions can be differentiated.

Do not administer the hexavalent vaccine or pneumococcal vaccine (PCV10 or PCV 13) in the same thigh as the meningococcal vaccine. In addition, when administered at the same visit, inject M-M-RVAXPRO® either IM or subcutaneously (SC) in the deltoid area of upper arm according to the local standard of care. For details see Operating Guidelines.

Efforts should be made to administer the vaccines at the recommended sites. Any failure to administer vaccines in the designated limb 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.

11) Observe the subject for 30 minutes and record any AEs in the source document. In the event of a local reaction, indicate the associated vaccine.

12) Give the parent / legally acceptable representative a diary card (DC4).

13) Remind the parent / legally acceptable representative to expect a telephone call 8 days after Visit 4 and to bring back the diary card when they return for Visit 5 at a specified date and time.

14) Remind the parent / legally acceptable representative to notify the site in case of an SAE.

15) Complete the relevant CRFs for this visit.

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

Refer to steps in Telephone Call 1.

Visit Procedures applicable to subjects in Group 4: Collection of Safety Information and Blood Sample

Visit 4 will be conducted 30 [+21] days after Visit 3 in Group 4

1) Collect and review the diary card (DC3) with the parent / legally acceptable representative, 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) Take the subject's weight to determine if 3 or 4 ml should be collected for BL0002 (refer to Operating Guidelines for further instructions).

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

4) Collect 3 or 4 mL of blood depending on the weight of the subject at Visit 3 (BL0002) from all subjects including those subjects in the rSBA subset (see Section 7.1 for detailed

instructions regarding the handling of blood samples and Section 6.5 for more details on the rSBA subset).

5) Give the parent / legally acceptable representative a diary card (DC4).
6) Remind the parent / legally acceptable representative to expect a telephone call 5 months after Visit 4 and to bring back the diary card when they return for Visit 5 at a specified date and time.
7) Remind the parent / legally acceptable representative to notify the site in case of an SAE.
8) Complete the relevant CRFs for this visit.

Telephone Call 4 (5 months after Visit 4 and at least 14 days before Visit 5) in Group 4

- Staff will contact the subject's parent / legally acceptable representative by telephone 5 months after the last visit in infancy and at least 14 days before Visit 5. This contact is to identify the occurrence of any SAEs (including AESI) not yet reported.
- Remind the subject's parent / legally acceptable representative that they should bring back the diary card to the subsequent visit so that it can be reviewed at the study site, and to confirm the date and time of the next visit. If the subject does not continue in the study, the information recorded on the diary card will be reviewed during this call, and the diary card will be retrieved by the site.
- Remind the parent / legally acceptable representative that routine pediatric vaccines will be administered at Visit 5.

Visit 5 for all Groups:

Visit Procedures applicable to subjects in Groups 1, 2, and 3: Collection of Safety Information and Blood Sample

Visit 5 will be conducted 30 [+21] days after Visit 4 in Groups 1, 2, and 3

1) Collect and review the diary card (DC4) with the parent / legally acceptable representative, 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 5 mL of blood (BL0004) from all subjects except for subjects included in the rSBA subset. Collect 6 mL of blood (BL0004) from subjects included in the rSBA subset (see Section 7.1 for detailed instructions regarding the handling of blood samples and Section 6.5 for more details on the rSBA subset).
4) Remind the parent / legally acceptable representative to notify the site in case of an SAE.
5) Complete the relevant CRFs for this visit.
6) Complete the trial termination record.

Visit Procedures applicable to subjects in Group 4: Collection of Safety Information, Blood Sample, and Vaccination

Visit 5 will be conducted at 12 to 18 months of age and at least 180 days after Visit 3 in Group 4

1) Collect and review the diary card (DC4) with the parent / legally acceptable representative, 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) Conduct a physical examination as per standard of care. Perform a physical examination, including, but not limited to, examination of the head (ear, nose, and throat), neck, heart, lungs, abdomen, and extremities. If a routine examination had been performed within the last week by the Investigator, a sub-investigator, or a licensed nurse practitioner, it does not need to be repeated unless there were some changes in health status, in which case it may be limited to the affected area
3) Take the subject's temperature (rectal, oral, or axillary according to local practices, with the rectal route preferred for infants and the axillary route preferred for toddlers). If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.
4) Review vaccination history from the child's immunization record if routine pediatric vaccinations have already been performed since the last study visit.
5) Review warnings and precautions to vaccinations.
6) Review temporary contraindications for blood sampling. Ensure the subject has not had any antibiotics within the previous 72 hours (3 days).
7) Collect 5 mL of blood (BL0003) from all subjects except for subjects included in the rSBA subset. Collect 6 mL of blood (BL0003) from subjects included in the rSBA subset (see Section 7.1 for detailed instructions regarding the handling of blood samples and Section 6.5 for more details on the rSBA subset).
8) Review contraindications to subsequent vaccinations and conditions for withdrawal.
9) Contact the IRT system for dose number of all vaccines.
10) Administer the investigation product, the control product and other products to subjects. Each vaccine should be administered in the assigned location (see Operating Guidelines) and documented appropriately. Refer to Table 5.3 for details on vaccinations and route of administration.

    If multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are administered in the same limb, the injection sites should be separated by 2.5 cm or more, so that any local reactions can be differentiated.

    Do not administer the hexavalent vaccine or pneumococcal vaccine (PCV10 or PCV 13) in the same thigh as the meningococcal vaccine. In addition, when administered at the same visit, inject M-M-RVAXPRO® either IM or subcutaneously (SC) in the deltoid area of upper arm according to the local standard of care. For details see Operating Guidelines.

    Efforts should be made to administer the vaccines at the recommended sites. Any failure to administer vaccines in the designated limb 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.

7) Observe the subject for 30 minutes and record any AEs in the source document. In the event of a local reaction, indicate the associated vaccine.
8) Give the parent / legally acceptable representative a diary card (DC5).
9) Remind the parent / legally acceptable representative 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.
10) Remind the parent / legally acceptable representative to notify the site in case of an SAE.
11) Complete the relevant CRFs for this visit.

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

Refer to steps in Telephone Call 1.

Visit 6 (30 [+21] days after Visit 5) for Group 4: Collection of Safety Information and Blood Sample

1) Collect and review the diary card (DC5) with the parent / legally acceptable representative, 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 5 mL of blood (BL0004) from all subjects except for subjects included in the rSBA subset. Collect 6 mL of blood (BL0004) from subjects included in the rSBA subset (see Section 7.1 for detailed instructions regarding the handling of blood samples and Section 6.5 for more details on the rSBA subset).
4) Remind the parent / legally acceptable representative to notify the site in case of an SAE.
5) Complete the relevant CRFs for this visit.
6) Complete the trial termination record.

Follow-up of subjects with Related AEs or with AEs That Led to Study/Vaccination Discontinuation:

Unless a subject's parent/legally acceptable representative refuses further contact, each subject who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the subject's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the product administered.
- The AE caused the discontinuation of the subject from the study or from vaccination.

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 subject period - FVFS (first visit, first subject) to LVLS (last visit, last subject): Q4 2018 to Q4 2023

Planned inclusion period - FVFS to FVLS (first visit, last subject): Q4 2018 to Q2 2022

Planned end of study - LVLS (last visit, last subject): Q4 2023

Planned date of final clinical study report: Q4 2024

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Each site will be responsible for devising a recruitment plan for enrolling eligible subjects. Advertisements and other recruitment aids will be approved by the Sponsor and the site's IRB/IEC prior to use by the clinical site.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject's parent / legally acceptable representative voluntarily confirms his or her willingness to let his/her child 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 subject's parent / legally acceptable representative 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 subject's parent / legally acceptable representative'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.

ICFs 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 / legally acceptable representative.

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

Rationale for Including Subjects Unable to Give Consent:

MET58 is a study to be conducted in children approximately 6 weeks to 18 months of age to obtain safety and immunogenicity data (see Section 1.4).

Since these subjects are unable to give their consent, written informed consent must be obtained from the parent or legally acceptable representative in accordance with local practices before participation in the study and before any study related procedure is done (eg, collection of blood sample). The signature on the ICF must be dated by the parent / legally acceptable representative in accordance with local practices. The parent / legally acceptable representative should be able to consent for their child. The child of minor parents must not be included in the study.

5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

5.2.4 Inclusion Criteria

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

1) Aged ≥ 42 to ≤ 89 days on the day of the first study visit
2) Healthy infants as determined by medical history, physical examination and judgment of the Investigator
3) Informed consent form has been signed and dated by the parent(s) or other legally acceptable representative
4) Subject and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures
5) Covered by health insurance according to local regulations

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 study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure.
2) Receipt of any vaccine in the 4 weeks preceding the first study vaccination or planned receipt of any vaccine in the 4 weeks before and/or following any study vaccination except for influenza vaccination and rotavirus vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. This exclusion criterion does not apply to subjects in Finland, Sweden or Poland who plan to receive the licensed rotavirus vaccine concomitantly with study vaccines at study vaccination visits V1 and V2.
3) Receipt or planned receipt during the study period vaccination against meningococcal disease with either the study vaccine or another vaccine (ie., mono- or polyvalent, polysaccharide, or

conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B serogroup-containing vaccine

4) Previous vaccination against diphtheria, tetanus, pertussis, Haemophilus influenzae type b (Hib), poliovirus, Streptococcus pneumoniae, measles, mumps, or rubella. Previous vaccination against hepatitis B specific to risk groups, as per local recommendation
5) Receipt of immune globulins, blood or blood-derived products since birth
6) 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
7) Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated
8) Individuals with blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems
9) Individuals with active tuberculosis
10) History of *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically
11) History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, measles, mumps, rubella, and of *Haemophilus influenzae* type b, and / or *Streptococcus pneumoniae* infection or disease
12) At high risk for meningococcal infection during the study (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)
13) Individuals with underlying conditions predisposing them to invasive pneumococcal disease (specifically, but not limited to, subjects with sickle cell disease or human immunodeficiency virus [HIV] infection)
14) History of any neurologic disorders, including seizures and progressive neurologic disorders
15) History of Guillain-Barré syndrome
16) Known systemic hypersensitivity to any of the vaccine components, or history of a severe allergic reaction (eg., anaphylaxis) to the vaccine(s) used in the study or to a vaccine containing any of the same substances including neomycin, streptomycin, polymyxin B, glutaraldehyde, formaldehyde, and gelatin[a]
17) Verbal report of thrombocytopenia, contraindicating intramuscular vaccination in the investigator's opinion
18) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the investigator's opinion

[a] The components of all study vaccines are listed in Section 6 of the Investigator's Brochure

19) Chronic illness (including, but not limited to, cardiac disorders, congenital heart disease, chronic lung disease, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases) that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion
20) Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives
21) 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.
22) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
23) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study
24) Infants born preterm (by less than 37 weeks of gestation) requiring specific immunization schedule for routine childhood vaccines and/or specific care at the time of vaccination, as per national recommendations

If the subject has a primary physician who is not the Investigator, the site must contact this physician with the parent's / legally acceptable representative'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 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.

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.

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.

1) Febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment
2) Receipt of any vaccine (other than the study vaccine[s]) in the 4 weeks preceding any vaccination or planned receipt of any vaccine in the 4 weeks following any study vaccination except for influenza vaccination and rotavirus vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. This temporary contraindication does not apply to subjects in Finland, Sweden or Poland who plan to receive the licensed rotavirus vaccine concomitantly with study vaccines at study vaccination visits V1 and V2. If, for any reason a subject receives any routine pediatric vaccine considered as study vaccine (eg, PCV10, PCV13, Hexyon®/Hexacima®) or non-study vaccine similar to the routine pediatric study vaccines (eg Infanrix hexa®, Priorix®) out of the study, the interval of at least 4 weeks following the study vaccination(s) should be respected. The investigator should make efforts to ensure that the subject receives these study vaccines within the timelines concomitantly with the investigation or control meningococcal vaccines, as per protocol corresponding visits.
3) Immune globulins, blood, or blood-derived products: used in the 3 months preceding any study vaccination
4) 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) used in the 6 months preceding any study vaccination.

5.2.7.2 Definitive Contraindications

Should a subject experience at least 1 of the conditions listed below, the Investigator will discontinue vaccination:

1) Having received Meningococcal Group B vaccination since the last visit
2) An anaphylactic or other significant allergic reaction to the previous dose of vaccine
3) Any related SAE after a previous study vaccination

Subjects with a definitive contraindication will continue to be followed up for the study-defined safety and immunogenicity assessments, as applicable.

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

The following AEs constitute absolute contraindications to subsequent vaccinations, according to their respective Summary of Product Characteristics (SmPC). If a subject should experience any of these events during the study, irrespective of causality, 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. Only the vaccine which has a related SAE or a definite contraindication will be stopped wherever it is possible to identify the vaccine that caused the event.

Meningococcal vaccines: (MenACYW conjugate vaccine or Nimenrix®):

1) History of Guillain-Barré syndrome within 6 weeks after vaccination with a tetanus toxoid-containing vaccine
2) History of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine
3) Severe allergic reaction (eg, anaphylaxis) after a previous dose of meningococcal capsular polysaccharide-, tetanus toxoid carrier protein – containing vaccines or to any component of meningococcal vaccines
4) Persons with familial complement deficiencies (for example, C5 or C3 deficiencies) and persons receiving treatments that inhibit terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by Neisseria meningitidis groups A, C, W-135 and Y, even if they develop antibodies following vaccination with Nimenrix®.

Hexyon® or Hexacima®:

1) History of anaphylactic reaction after a previous administration of Hexyon® or Hexacima®
2) Hypersensitivity to the active substances, to any of the excipients, to trace residuals (glutaraldehyde, formaldehyde, neomycin, streptomycin, and polymyxin B), to any pertussis vaccine, or after previous administration of Hexyon® or Hexacima® or a vaccine containing the same components or constituents
3) Encephalopathy of unknown etiology occurring within 7 days of vaccination with a previous pertussis-containing vaccine (whole cell or acellular pertussis vaccines)
4) Uncontrolled neurologic disorder or uncontrolled epilepsy until a treatment regimen has been established and the condition has stabilized and the benefit clearly outweighs the risk

Prevenar 13®: (pneumococcal 13-valent conjugate vaccine; PCV13) :

1) Hypersensitivity to the active substances, to any of the excipients, to diphtheria toxoid, or to a previous dose of Prevenar 13®

Synflorix®: (pneumococcal polysaccharide conjugate vaccine; PCV10):

1) Hypersensitivity to the active substances, to any of the excipients, to any of the carrier proteins, or to a previous dose of Synflorix®

M-M-RVAXPRO® (measles, mumps, and rubella vaccine):

1) Hypersensitivity to any measles, mumps, or rubella vaccine, or to any of the excipients, including neomycin
2) Active untreated tuberculosis

3) Blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
4) Severe humoral or cellular (primary or acquired) immunodeficiency (eg, severe combined immunodeficiency, agammaglobulinemia and acquired immune deficiency syndrome [AIDS] or symptomatic HIV infection)
5) Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

5.2.7.3 Warnings and Precautions to Vaccination

Prior to vaccination, check the warnings and precautions for individual vaccines administered. For the licensed vaccines, refer to the individual package inserts. For MenACYW conjugate vaccine, refer to the Investigator's Brochure.

5.2.8 Contraindications for Subsequent Blood Draw

Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the blood draws, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination or 30 to 51 days after vaccination, depending on the visit). If postponement would result in the sample collection falling outside of this 30 to 44 day or 30 to 51 day timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

5.2.9 Conditions for Withdrawal

Parents / legally acceptable representatives 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:

- 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)
- At the request of the parent / legally acceptable representative (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.

5.2.10 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (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.

5.2.11 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 CRF 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 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 5.2.10. The certified letter was sent by the investigator and returned unsigned, and the subject's parent/ legally acceptable representative 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 noncompliance 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 subject's parent/ legally acceptable representative 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 Parent / Legally Acceptable Representative	To be used: When the subject's parent/ legally acceptable representative indicated unwillingness to allow his / her child continue in the study When the subject or parent/ legally acceptable representative made the decision to discontinue his / her child's participation in the study for any personal reason other than an SAE/AE (eg, subject is relocating, inform consent withdrawal, etc.)

5.2.12 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the 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.

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 notified of administrative changes and will provide approval according to 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) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the study subjects' parents / legally acceptable representative 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

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product

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

Form: Liquid solution

Dose: 0.5 milliliter (mL)

Route: IM

Batch number: To be determined (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 components:

Meningococcal capsular polysaccharides:

Serogroup A.....10 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).

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 (for vaccination and route of administration, see Table 5.3).

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

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.

6.1.1.3 Dose Selection and Timing

- Subjects in Groups 1 and 3 will receive 3 doses of MenACYW conjugate vaccine administered concomitantly with routine vaccines at 2 months of age (Visit 1), 4 months of age (Visit 2), and 12 to 18 months of age (Visit 4)
- Subjects in Group 4 will receive 4 doses of MenACYW conjugate vaccine with routine vaccines at 2 months of age (Visit 1), 4 months of age (Visit 2), 6 months of age (Visit 3; MenACYW conjugate vaccine only), and 12 to 18 months of age (Visit 5; MenACYW conjugate vaccine and routine vaccines)

6.1.2 Identity of Control Product

Nimenrix®: Meningococcal group A, C, W-135, and Y conjugate vaccine (Pfizer Limited, Sandwich, United Kingdom)

Form: Powder and solvent for solution for injection in a pre-filled syringe

Dose: 0.5 mL

Route: IM

Batch number: TBD

6.1.2.1 Composition

After reconstitution, each 0.5 mL dose contains:

Neisseria meningitidis group A polysaccharide* ..... 5 µg
Neisseria meningitidis group C polysaccharide* ..... 5 µg
Neisseria meningitidis group W-135 polysaccharide* ..... 5 µg
Neisseria meningitidis group Y polysaccharide* ..... 5 µg

*conjugated to tetanus toxoid protein carrier ..... 44 µg

The vaccine also contains the excipients: sucrose, trometamol, sodium chloride, water for injections

6.1.2.2 Preparation and Administration

Nimenrix® is supplied as a white powder or cake in a single dose glass vial and a clear and colorless solvent in a pre-filled syringe.

A single dose of Nimenrix® should be administered by IM injection, usually in the upper arm or thigh. See the Nimenrix® EU SmPC (42) (for vaccination and route of administration, see Table 5.3).

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.1.2.3 Dose Selection and Timing

- Subjects in Group 2 will receive 3 doses of Nimenrix® administered concomitantly with routine vaccines at 2 months of age (Visit 1), 4 months of age (Visit 2), and 12 to 18 months of age (Visit 4).

6.2 Identity of Other Products

6.2.1 Identity of Other Product 1

DTaP-IPV-HB-Hib: Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed) (Sanofi Pasteur SA, Marcy L'Etoile, France) (licensed products: Hexyon®, Hexacima®), referred to as **hexavalent vaccine** in the protocol

Form: Suspension for injection

Dose: 0.5 mL

Route: IM

Batch number: TBD

6.2.1.1 Composition

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

Diphtheria Toxoid ..... not less than 20 IU[b]
Tetanus Toxoid ..... not less than 40 IU[b]

Bordetella pertussis antigens

Pertussis Toxoid ..... 25 µg
Filamentous Haemagglutinin ..... 25 µg

Poliovirus (Inactivated)[c]

[a] Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al^{3+})
[b] As lower confidence limit (p=0.95)
[c] Produced on Vero cells

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

Hepatitis B surface antigen[b] ..... 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.

6.2.1.2 Preparation and Administration

Hexavalent vaccines are supplied as a suspension in a pre-filled syringe.

Hexavalent vaccines should be administered as an IM injection, preferably in the antero-lateral area of the thigh. See the Hexyon ® (43) EU SmPC and Hexacima ® (44) EU SmPC.

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2 (for vaccination and route of administration, see Table 5.3).

6.2.1.3 Dose Selection and Timing

- All subjects will receive 3 doses of a hexavalent vaccine administered concomitantly with either MenACYW conjugate vaccine or Nimenrix® at 2 months of age (Visit 1), 4 months of age (Visit 2), and 12 to 18 months of age (Visit 4/Visit 5).

6.2.2 Identity of Other Product 2

Synflorix®: Pneumococcal polysaccharide conjugate vaccine (adsorbed) (GlaxoSmithKline Biologicals SA, Rixensart, Belgium), referred to as **PCV10**

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

[a] Or equivalent antigenic quantity determined by a suitable immunochemical method
[b] Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

6.2.2.1 Composition

Each 0.5 mL dose is formulated to contain the following:

Pneumococcal polysaccharide serotype 1[ab] ..... 1 µg
Pneumococcal polysaccharide serotype 4[ab] ..... 3 µg
Pneumococcal polysaccharide serotype 5[ab] ..... 1 µg
Pneumococcal polysaccharide serotype 6B[ab] ..... 1 µg
Pneumococcal polysaccharide serotype 7F[ab] ..... 1 µg
Pneumococcal polysaccharide serotype 9V[ab] ..... 1 µg
Pneumococcal polysaccharide serotype 14[ab] ..... 1 µg
Pneumococcal polysaccharide serotype 18C[ac] ..... 3 µg
Pneumococcal polysaccharide serotype 19F[ad] ..... 3 µg
Pneumococcal polysaccharide serotype 23F[ab] ..... 1 µg

The vaccine also contains the excipients: sodium chloride, water for injections.

6.2.2.2 Preparation and Administration

Synflorix® is supplied as a suspension in a pre-filled syringe.

Synflorix® should be administered as an IM injection, preferably in the anterolateral area of the thigh. See the Synflorix® EU SmPC (45).

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2 (for vaccination and route of administration, see Table 5.3).

6.2.2.3 Dose Selection and Timing

- Subjects in Group 1 and Group 2 will receive 3 doses of PCV10 vaccine administered concomitantly with either MenACYW conjugate vaccine or Nimenrix® at 2 months of age (Visit 1), 4 months of age (Visit 2), and 12 to 18 months of age (Visit 4).

6.2.3 Identity of Other Product 3

Prevenar 13®: Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Pfizer Limited, Sandwich, United Kingdom), referred to as **PCV13**

Form: Suspension for injection

Dose: 0.5 mL

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[a] adsorbed on aluminum phosphate 0.5 mg Al^{3+}

[b] conjugated to protein D (derived from non-typable *Haemophilus influenzae*) carrier protein 9-16 µg

[c] conjugated to tetanus toxoid carrier protein 5-10 µg

[d] conjugated to diphtheria toxoid carrier protein 3-6 µg

Route: IM

Batch number: TBD

6.2.3.1 Composition

Each 0.5 mL dose is formulated to contain the following:

Pneumococcal polysaccharide serotype 1 ..... 2.2 µg
Pneumococcal polysaccharide serotype 3 ..... 2.2 µg
Pneumococcal polysaccharide serotype 4 ..... 2.2 µg
Pneumococcal polysaccharide serotype 5 ..... 2.2 µg
Pneumococcal polysaccharide serotype 6A ..... 2.2 µg
Pneumococcal polysaccharide serotype 6B..... 4.4 µg
Pneumococcal polysaccharide serotype 7F ..... 2.2 µg
Pneumococcal polysaccharide serotype 9V ..... 2.2 µg
Pneumococcal polysaccharide serotype 14 ..... 2.2 µg
Pneumococcal polysaccharide serotype 18C..... 2.2 µg
Pneumococcal polysaccharide serotype 19A ..... 2.2 µg
Pneumococcal polysaccharide serotype 19F ..... 2.2 µg
Pneumococcal polysaccharide serotype 23F ..... 2.2 µg

The pneumococcal polysaccharides are conjugated to CRM_{197} carrier protein and adsorbed on aluminum phosphate (0.125 mg aluminum).

The vaccine also contains the excipients: sodium chloride, succinic acid, Polysorbate 80, water for injections.

6.2.3.2 Preparation and Administration

Prevenar 13® is supplied as a suspension in a pre-filled syringe.

Prevenar 13® should be administered as an IM injection, preferably in the anterolateral area of the thigh. See the Prevenar 13® EU SmPC (46).

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2 (for vaccination and route of administration, see Table 5.3).

6.2.3.3 Dose Selection and Timing

- Subjects in Group 3 and Group 4 will receive 3 doses of PCV13 vaccine administered concomitantly with MenACYW conjugate vaccine at 2 months of age (Visit 1), 4 months of age (Visit 2), and 12 to 18 months of age (Visit 4/Visit 5).

6.2.4 Identity of Other Product 4

M-M-RVAXPRO®: Measles, mumps, and rubella vaccine (live) (Merck Sharp & Dohme B.V., Haarlem, The Netherlands), referred to as **MMR vaccine**

Form: Powder and solvent for suspension for injection

Dose: 0.5 mL
Route: IM
Batch number: TBD

6.2.4.1 Composition

Each 0.5 mL dose is formulated to contain the following:

Measles virus[a] Enders' Edmonston strain (live, attenuated) ..... not less than $1x10^3$ cell culture infection dose 50% ($CCID_{50}$)[b]
Mumps virus[a] Jeryl Lynn™ [Level B] strain (live, attenuated) ..... not less than $12.5x10^3$ $CCID_{50}$[b]
Rubella virus[c] Wistar RA 27/3 strain (live attenuated) ..... not less than $1x10^3$ $CCID_{50}$[b]

The vaccine contains the following excipients: sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolyzed gelatin, Medium 199 with Hanks' salts, Minimum Essential Medium Eagle, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH), water for injections. The vaccine may also contain traces of recombinant human albumin.

6.2.4.2 Preparation and Administration

M-M-RVAXPRO® is supplied as a powder and solvent for suspension for injection.

M-M-RVAXPRO® should be administered as an IM injection or subcutaneously, preferably in the deltoid muscle of upper arm. See the M-M-RVAXPRO® EU SmPC (47).

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.2.4.3 Dose Selection and Timing

All subjects may receive 1 dose of MMR vaccine administered concomitantly with MenACYW conjugate vaccine or Nimenrix® at 12 to 18 months of age (Visit 4/Visit 5). If not, the subject will receive a licensed Measles, Mumps and Rubella vaccine with a gap of at least 4 weeks before any study vaccines or after the end of the study (ie, after the subject will have completed the last study procedure at the last study visit). When administered outside the study visits, the licensed Measles, Mumps and Rubella vaccine will be sourced by the health care system, according to the national immunization program.

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[a] produced in chick embryo cells

[b] 50% cell culture infectious dose

[c] produced in WI-38 human diploid lung fibroblasts

6.3 Product Logistics

6.3.1 Labeling and Packaging

The investigational product, MenACYW conjugate vaccine (single-dose vials), control product, and other products will be supplied with investigational labeling and packaging according to national regulations. Each single dose of investigational, control product or other products will be identified by a unique number on the detachable label and on the outer carton label. The detachable label is for the sites to attach to the source documents. See the Operating Guidelines for additional label detail.

The investigational and control products are blinded for Group 1 and Group 2. The investigational product will be open label for Group 3 and Group 4.

The concomitant products (licensed routine vaccines) are not blinded.

The rotavirus vaccines will be sourced by the study sites in Finland, Sweden, and Poland.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Clinical Logistics Coordinator 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. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C and should be protected from light. The vaccines must not be frozen. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the 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 (if applicable).

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 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

To perform an appropriate description of the safety of MenACYW conjugate vaccine and Nimenrix® in Groups 1 and 2 (ie, when each of these vaccines is administered as a 3-dose series concomitantly with PCV10 and hexavalent vaccine), MenACYW conjugate vaccine and Nimenrix® will be administered in a modified double-blind manner in these 2 groups. The MenACYW conjugate vaccine in Groups 3 and 4 and all other concomitant vaccines in all vaccine groups will be administered in an open-label manner.

A modified double-blind trial means that the subject's parent / legally acceptable representative, the Investigator, and other study personnel remain unaware of the treatment assignments throughout the trial. An unblinded vaccine administrator will administer the appropriate vaccine but will not be involved in safety data collection.

The Sponsor and laboratory personnel performing the serology testing for all groups will also remain blinded to treatment assignments throughout the trial until database lock.

Given that the meningococcal vaccines in Groups 3 and 4 have different vaccination schedules in the number of vaccines administered and timing of their administration, these vaccines will be administered in an open-label manner.

Other concomitant vaccines in all groups will be administered in an open-label manner to ensure the subjects received appropriate vaccines as per local standard of care.

The code may be broken in the event of an AE only when the identification of the vaccine received could influence the treatment of the subject. Code-breaking should be limited to the subject(s) experiencing the AE.

The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur RMO if a subject's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code breaking CRF is to be completed.

A request for the code to be broken may also be made:

- by the GPV Department through an internal system for reporting to Health authorities in the case of an SAE as described in International Council for Harmonisation (ICH) E2A.[a] In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (ie, the subject's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

The IEC / IRB must be notified of the code-breaking. All documentation pertaining to the event must be retained in the site's study records and in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

6.5 Randomization and Allocation Procedures

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and whose parent / legally acceptable representative sign the ICF will be randomly assigned to Groups 1 through 4. Countries where PCV10 will be administered for pneumococcal vaccination, 1432 subjects will be randomized in a 1:1 ratio to 2 groups such that Groups 1 and 2 will have approximately 716 subjects each; and countries where PCV13 will be administered for pneumococcal vaccination, 220 subjects will be randomized in a 1:1 ratio to 2 groups such Groups 3 and 4 will have approximately 110 subjects each.

Randomization will be performed with permuted block method with stratification by center and age categories as follows: approximately 6 to 8 weeks (≥ 42 to ≤ 59 days), and 9 to 12 weeks (≥ 60 to ≤ 89 days).

[a] All unexpected and related SAEs submitted to EU competent authorities must be unblinded.

The IRT system will also be used to allocate subjects in the rSBA subset in the countries included in the subsets as follows:

- 100 subjects randomized to Group 1; 100 subjects randomized to Group 2
- 50 subjects randomized to Group 3; 50 subjects randomized to Group 4

The rSBA subset will include subjects from all countries except Poland.

The vaccination / 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 at least the vaccine dose number (except for the rotavirus vaccine) and subject number. The full detailed procedures for group allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the study, then the 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 724000100005 is the fifth subject enrolled in Center Number 1 in Spain (724 being the Spain 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 for pediatric population.
- 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 medications (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: 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 study vaccine, including the day of the study vaccination visit
  - Rotavirus vaccines administered within 14 days pre or post each study vaccination visit[b]. Any vaccine other than study vaccines (vaccines non-described in the Protocol[c]) 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 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.

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[a] 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.

[b] Subjects from Finland, Sweden and Poland can receive rotavirus vaccine concomitantly with study vaccinations at V1 and V2

[c] if for any reason a study vaccine (PCV10, or PCV13 and/or Hexyon®/Hexacima®) is not administered concomitantly with investigation/control meningococcal vaccine, an interval of 4 weeks between this vaccination prior or following the investigational/control vaccine must be respected, otherwise, this vaccine administration out of the study will be considered as Category 2)

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

In addition, the following vaccines should be recorded in the concomitant medication CRB as Category 2:

- Licensed Measles, Mumps and Rubella vaccines administered during the study participation (if MMR vaccination [including M-M-RVAXPRO®] occurred within the 28 days (4 weeks) preceding or after the trial vaccination visit, it will be used to define the PPAS definition)
- Licensed rotavirus vaccines received during the first year of life (if rotavirus vaccination occurred within the 14 days (2 weeks) preceding or after the trial vaccination visit, it will be used to define the PPAS definition)
- Hepatitis B Vaccine received before the inclusion in the study (if Hepatitis B vaccination occurred within the 28 days (4 weeks) preceding or after the trial vaccination visit, it will be used to define the PPAS definition)

- 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.

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

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected and subjects in Groups 1, 2, and 3 will provide blood samples for immunogenicity assessment as follows:

- at baseline (pre-primary vaccination 1, Day 0)
- 30 days (+21 days) after the 2nd dose of MenACYW conjugate vaccine / Nimenrix®
- prior to the 3rd dose (toddler dose) of MenACYW conjugate vaccine / Nimenrix®
- 30 days (+21 days) after the 3rd dose (toddler dose) of MenACYW conjugate vaccine / Nimenrix®

Subjects in Group 4 will provide blood samples for immunogenicity assessment as follows:

- at baseline (pre-primary vaccination 1, Day 0)
- 30 days (+21 days) after the 3rd dose of MenACYW conjugate vaccine
- prior to the 4th dose (toddler dose) of MenACYW conjugate vaccine
- 30 days (+21 days) after the 4th dose (toddler dose) of MenACYW conjugate vaccine

See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

A total of 4 blood samples will be collected from all subjects during their study participation by staff experienced in blood collection in a pediatric population.

The Investigators should comply with European Regulation on the maximum amount of blood drawn that could be collected at any one time from children. According to European Regulation, the amount of blood drawn at any one time from the children in the study must not exceed 1% of their total blood volume (refer to Operating Guidelines for more detailed instructions) (48).

At Visit 1, 2 or 3 mL of blood will be collected depending on the subject's weight at the time of study visit; at Visit 3, 3 or 4 mL of blood will be collected depending on the subject's weight at the time of study visit; and at Visits 4 and 5, 5 mL (or 6 mL) of blood will be collected from subjects in Groups 1, 2, and 3. For subjects in Group 4, 2 or 3 mL of blood will be collected at Visit 1 depending on the subject's weight at the time of study visit, 3 or 4 mL of blood will be collected at Visit 4 depending on the subject's weight at the time of study visit, and 5 mL (or 6 mL) of blood will be collected at Visits 5 and 6 in tubes provided by or recommended by the Sponsor.

For Groups 1, 2, and 3, the blood sample volume indicated will be taken from all subjects and those subjects included in a subset to assess the antibody response to meningococcal serogroups (A, C, W, and Y) measured by rSBA assay in addition to hSBA assay at Visits 1 and 3. At Visits 4 and 5, blood sample volume of 5 mL will be taken from all subjects except subjects included in the rSBA subset. Blood sample volume of 6 mL will be taken from subjects included in the rSBA subset.

For Group 4, the blood sample volume indicated will be taken from all subjects and those subjects included in a subset to assess the antibody response to meningococcal serogroups (A, C, W, and

Y) measured by rSBA assay in addition to hSBA assay at Visits 1 and 4. At Visits 5 and 6, blood sample volume of 5 mL will be taken from all subjects except subjects included in the rSBA subset. Blood sample volume of 6 mL will be taken from subjects included in the rSBA subset.

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.

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.

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours 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 after the period of clotting at room temperature and must be centrifuged within a maximum of 24 hours.

The samples are then centrifuged, and the serum is transferred to the appropriate number of aliquoting tubes. 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.

7.3 Sample Storage and Shipment

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 laboratory 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 (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to R&D Global Operations at Sanofi Pasteur. The address is provided in the Operating Guidelines.

7.4 Future Use of Stored Serum Samples for Research

Subjects will be asked to indicate in the ICF whether they will permit the future use of any leftover stored serum samples for additional research not related to this study. If they consent, leftover serum samples will be securely stored at R&D Global Operations for up to 25 years after the end of the study. 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.

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.

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines.

They must allow approximately 1 week for an order to be filled and to have the supplies sent to their site.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Safety

There are no primary objectives for safety.

9.1.2 Immunogenicity

9.1.2.1 Immunogenicity Endpoint

The primary endpoint for the evaluation of immunogenicity is:

Antibody titers (geometric mean titers [GMTs]) against meningococcal serogroups A, C, W, and Y measured by hSBA in Groups 1 and 2, 30 days after the booster dose (third dose/toddler dose) of MenACYW conjugate vaccine or Nimenrix® when administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) to infants and toddlers from 6 weeks to 18 months of age (Group 1 versus Group 2)

9.1.2.2 Immunogenicity Assessment Methods

All assays will be performed at GCI, Swiftwater, PA or at qualified contract laboratories for GCI.

For all samples, hSBA analysis will be done for all 4 serogroups.

Antibodies to meningococcal antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, W, and Y 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 blood samples (refer to Table 9.1 and Table 9.2) for all study groups. In the event of insufficient serum sample volume, the conduct of the hSBA assay is of higher priority than the rSBA assay and the assays for antigens of concomitant vaccines.

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Safety

There are no secondary objectives for safety.

9.2.2 Immunogenicity

9.2.2.1 Immunogenicity Endpoints

Secondary immunogenicity endpoints will include at least the following:

1) Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y assessed at 30 days after Dose 2 of MenACYW conjugate vaccine or Nimenrix® measured by hSBA, when administered concomitantly with routine pediatric vaccines (Group 1 versus Group 2)
2) Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA in Group 3 at the following time points:
   - Day 0 (before Dose 1 of MenACYW conjugate vaccine)

     In addition, the following endpoints will be assessed:

     - Antibody titers ≥ 1:4 and titers ≥ 1:8
   - 30 days after Dose 2 of MenACYW conjugate vaccine in infancy, and before and 30 days after the booster dose (Dose 3)

     In addition, the following endpoints will be assessed:

     - Antibody titers ≥ 1:4 and titers ≥ 1:8
     - Post-vaccination titers ≥ 4 times the latest pre vaccination titers
     - 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 at least 4-fold greater than the pre vaccination titer.
3) Antibody titers or concentrations against the antigens of hexavalent vaccine (DTaP-IPV-HB-Hib) in Groups 1, 2, and 3 at the following time points:
   - Day 0 (before Dose 1)
     - Anti-pertussis antibody concentrations (pertussis toxin [PT], filamentous hemagglutinin [FHA])
   - 30 days after Dose 2 in infancy
     - Antibody concentrations/titers for all antigens
     - Anti-tetanus antibody concentrations ≥ 0.01 international units (IU)/ milliliter (mL) and ≥ 0.1 IU/mL
     - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL
     - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
     - Anti-polyribosyl-ribitol phosphate (PRP) antibody concentrations ≥ 0.15 µg/mL
     - Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as:
       - If the pre-primary vaccination concentration is < 4 × LLOQ, post-primary vaccination concentration ≥ 4 × LLOQ
       - If the pre-primary vaccination concentration is ≥ 4 × LLOQ, post-primary vaccination concentration ≥ pre-primary vaccination concentration

- Anti-hepatitis B surface antigen (HBsAg) antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

- Before and 30 days after the booster dose (Dose 3):
  - 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-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
  - Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as:
    - If the pre-booster vaccination concentration is < 4 × LLOQ, post-booster vaccination concentration ≥ 4 × pre-booster concentration
    - If the pre-booster vaccination concentration is ≥ 4 × LLOQ, post-booster vaccination concentration ≥ 2 × pre-booster concentration
  - Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

Antibody concentrations against the antigens of PCV10 in Groups 1 and 2, 30 days after Dose 2 in infancy and 30 days after the booster dose (Dose 3):

- Anti-pneumococcal antibody concentrations for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F
- Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F

Antibody concentrations against the antigens of PCV13 in Group 3, 30 days after Dose 2 in infancy and 30 days after the booster dose (Dose 3):

- Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Antibody concentrations against the antigens of MMR vaccine 30 days after the MMR vaccine injection[a]

- Antibody concentrations for all antigens
- Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL)
- Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
- Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)

[a] when the MMR vaccine has been administered concomitantly with the study vaccines

4) Antibody titers against meningococcal serogroups A, C, W, and Y measured by hSBA in Groups 1 and 2, as detailed for the Secondary Endpoints 2 (similar time points and endpoints)

5) Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA in Group 4 on Day 0 (before Dose 1 of MenACYW conjugate vaccine), 30 days after Dose 3 in infancy, and before and 30 days after the booster dose (Dose 4) at the following timepoints:

- Day 0 (before Dose 1 of MenACYW conjugate vaccine

In addition, the following endpoints will be assessed:

- Antibody titers ≥ 1:4 and titers ≥ 1:8

- 30 days after Dose 3 of MenACYW conjugate vaccine in infancy, and before and 30 days after the booster dose (Dose 4)

In addition, the following endpoints will be assessed:

- Antibody titers ≥ 1:4 and titers ≥ 1:8
- Post-vaccination titers ≥ 4 times the latest pre vaccination titers
- 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 at least 4-fold greater than the pre vaccination titer.

6) For Group 4, antibody titers or concentrations against the antigens of DTaP-IPV-HB-Hib vaccine before and 30 days after the booster dose (Dose 4), antibody concentrations against the antigens of PCV13 vaccine 30 days after the booster dose (Dose 4), and antibody concentrations against the antigens of MMR vaccine 30 days after vaccination[a].

The timepoints are:

Antibody titers or concentrations against the antigens of hexavalent vaccine (DTaP-IPV-HB-Hib):

- Pre-booster dose
  - Anti-pertussis antibody concentrations anti-PT, anti-FHA
- 30 days after the booster dose (Dose 4):
  - 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-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
  - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL

[a] when the MMR vaccine has been administered concomitantly with the study vaccines

- Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined as:
  - If the pre-booster vaccination concentration is < 4 × LLOQ, post-booster vaccination concentration ≥ 4 × pre-booster concentration
  - If the pre-booster vaccination concentration is ≥ 4 × LLOQ, post-booster vaccination concentration ≥ 2 × pre-booster concentration

Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

Antibody concentrations against the antigens of PCV13 in Group 4, 30 days after the booster dose (Dose 4):

- Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A,6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Antibody concentrations against the antigens of MMR vaccine 30 days after the MMR vaccine injection[a]

- Antibody concentrations for all antigens
- Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL)
- Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Abunits/mL)
- Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)

9.2.2.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the meningococcal serogroups A, C, W, and Y antibody titers for the secondary endpoints are the same as that presented in Section 9.1.2.2.

Antibody responses against the antigens of routine vaccines will also be measured in blood samples (see Table 9.1, Table 9.2, Table 9.3).

Considering the number of antigens to test, and to mitigate any risk to fail testing in MET58, different profile testing will be performed according to odd- or even-numbered subject ID (ie, different ranking for testing antigens), in case of lower blood volume collected. In the event of insufficient serum sample volume, the immunogenicity assessment method (hSBA assay) for meningococcal serogroups A, C, W, and Y antibody titers will be the prioritized assay. (Refer to Section 9.1.2.2)

[a] when the MMR vaccine has been administered concomitantly with the study vaccines

Table 9.1: Blood sampling schedule and testing plan in Groups 1 and 2

Age in months	**2 months**	**5 months**	**12-18 months**	**13-19 months**
Visit and BL numbers	**Visit 1** **(pre-vaccination)** **BL0001**	**Visit 3** **BL0002**	**Visit 4** **(pre-vaccination)** **BL0003**	**Visit 5** **BL0004**
Antigens (Group 1 N= 716 Group 2 N= 716)	Meningococcal serogroups A, C, W, Y Pertussis (PT, FHA)	Meningococcal serogroups A, C, W, Y · Hib (PRP) · Hep B (HBsAg) · Pertussis (PT, FHA) · PCV10 · Poliovirus (types 1, 2, 3) · Diphtheria · Tetanus	Meningococcal serogroups A, C, W, Y · Hib (PRP) · Hep B (HBsAg) · Pertussis (PT, FHA) · Poliovirus (types 1, 2, 3) · Diphtheria · Tetanus	Meningococcal serogroups A, C, W, Y · Measles† · Mumps† · Rubella† · Hib (PRP) · Hep B (HBsAg) · Pertussis (PT, FHA) · PCV10 · Poliovirus (types 1, 2, 3) · Diphtheria · Tetanus
Blood sample volume*	2mL or 3 mL (depending on weight)	3mL or 4 mL (depending on weight)	5mL or 6 mL (for rSBA subset)	5mL or 6 mL (for rSBA subset)

PT: pertussis toxin; FHA: filamentous hemagluttinin; PRP: polyribosyl-ribitol phosphate; Hib: *Haemophilus influenzae* type b; Hep B: Hepatitis B; HBsAg: Hepatitis B surface antigen; PCV10: pneumococcal conjugate vaccine 10-valent.
*Blood sample volume indicated for BL0001 and BL0002 will be taken from all subjects including those subjects in the rSBA subset, with 2 or 3 mL for BL0001 and 3 or 4 mL collected depending on weight at study visit. The blood sample volume for BL0003 and BL0004 is 5 mL, except for subjects included in the rSBA subset for which blood sample volume is 6 mL. In the rSBA subset, the antibody response to meningococcal serogroups (A, C, W, and Y) will be measured by rSBA assay in addition to hSBA assay (refer to Section 6.5 for more details on the rSBA subset).
†when the MMR vaccine has been administered concomitantly with the study vaccines
For each visit, antigens are listed in descending order of assay priority (highest to lowest priority).
For PCV10: Highest to lowest priority anti-pneumococcal serotypes: 1, 5, 7F, 4, 6B, 9V, 14, 18C,19F, and 23F

Table 9.2: Blood sampling schedule and testing plan in Group 3

Age in months	**2 months**	**5 months**	**12-18 months**	**13-19 months**
Visit and BL numbers	**Visit 1** **(pre-vaccination)** **BL0001**	**Visit 3** **BL0002**	**Visit 4** **(pre-vaccination)** **BL0003**	**Visit 5** **BL0004**
Antigens **(Group 3 N= 110)**	• Meningococcal serogroups A, C, W, Y • Pertussis (PT, FHA)	• Meningococcal serogroups A, C, W, Y • Hib (PRP) • Hep B (HBsAg) • Pertussis (PT, FHA) • PCV13 • Poliovirus (types 1, 2, 3) • Diphtheria • Tetanus	• Meningococcal serogroups A, C, W, Y • Hib (PRP) • Hep B (HBsAg) • Pertussis (PT, FHA) • Poliovirus (types 1, 2, 3) • Diphtheria • Tetanus	• Meningococcal serogroups A, C, W, Y • Measles† • Mumps† • Rubella† • Hib (PRP) • Hep B (HBsAg) • Pertussis (PT, FHA) • PCV13 • Poliovirus (types 1, 2, 3) • Diphtheria • Tetanus
Blood sample volume*	2mL or 3 mL (depending on weight)	3mL or 4 mL (depending on weight)	5mL or 6 mL (for rSBA subset)	5mL or 6 mL (for rSBA subset)

PT: pertussis toxin; FHA: filamentous hemagluttinin; PRP: polyribosyl-ribitol phosphate; Hib: *Haemophilus influenzae* type b; Hep B: Hepatitis B; HBsAg: Hepatitis B surface antigen; PCV13:pneumococcal conjugate vaccine 13-valent.

*Blood sample volume indicated for BL0001 and BL0002 will be taken from all subjects including those subjects in the rSBA subset, with 2 or 3 mL for BL0001 and 3 or 4 mL collected depending on weight at study visit. The blood sample volume for BL0003 and BL0004 is 5 mL, except for subjects included in the rSBA subset for which blood sample volume is 6 mL. In the rSBA subset, the antibody response to meningococcal serogroups (A, C, W, and Y) will be measured by rSBA assay in addition tohSBA assay (refer to Section 6.5 for more details on the rSBA subset).

†when the MMR vaccine has been administered concomitantly with the study vaccines

For each visit, antigens are listed in descending order of assay priority (highest to lowest priority).

For PCV13: Highest to lowest priority anti-pneumococcal serotypes: 1, 3, 5, 6A, 7F, 19A, 4, 6B, 9V, 14, 18C,19F, and 23F

Table 9.3: Blood sampling schedule and testing plan in Group 4

Age in months	**2 months**	**7 months**	**12-18 months**	**13-19 months**
Visit and BL numbers	**Visit 1** **(pre-vaccination)** **BL0001**	**Visit 4** **BL0002**	**Visit 5** **(pre-vaccination)** **BL0003**	**Visit 5** **BL0004**
Antigens **(Group 4 N= 110)**	• Meningococcal serogroups A, C, W, Y	• Meningococcal serogroups A, C, W, Y	• Meningococcal serogroups A, C, W, Y • Hib (PRP) • Hep B (HBsAg) • Pertussis (PT, FHA) • Poliovirus (types 1, 2, 3) • Diphtheria • Tetanus	• Meningococcal serogroups A, C, W, Y • Measles† • Mumps† • Rubella† • Hib (PRP) • Hep B (HBsAg) • Pertussis (PT, FHA) • PCV13 • Poliovirus (types 1, 2, 3) • Diphtheria • Tetanus
Blood sample volume*	2mL or 3 mL (depending on weight)	3mL or 4 mL (depending on weight)	5mL or 6 mL (for rSBA subset)	5mL or 6 mL (for rSBA subset)

PT: pertussis toxin; FHA: filamentous hemagluttinin; PRP: polyribosyl-ribitol phosphate; Hib: *Haemophilus influenzae* type b; Hep B: Hepatitis B; HBsAg: Hepatitis B surface antigen; PCV13: pneumococcal conjugate vaccine 13-valent.

*Blood sample volume indicated for BL0001 and BL0002 will be taken from all subjects including those subjects in the rSBA subset with 2 or 3 mL for BL0001 and 3 or 4 mL collected depending on weight at study visit. The blood sample volume for BL0003 and BL0004 is 5 mL, except for subjects included in the rSBA subset for which blood sample volume is 6 mL. In the rSBA subset, the antibody response to meningococcal serogroups (A, C, W, and Y) will be measured by rSBA assay in addition tohSBA assay (refer to Section 6.5 for more details on the rSBA subset).

†when the MMR vaccine has been administered concomitantly with the study vaccines

For each visit, antigens are listed in descending order of assay priority (highest to lowest priority).

For PCV13: Highest to lowest priority anti-pneumococcal serotypes: 1, 3, 5, 6A, 7F, 19A, 4, 6B, 9V, 14, 18C,19F, and 23F

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

Anti-PRP concentrations will be measured using a Farr-type radioimmunoassay (RIA). Serum levels of anti-*Haemophilus influenzae* type b (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 antibodies bind 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 (CBER), Lot No. 1983 reference standard. The LLOQ of the anti-PRP RIA is 0.06 µg/mL.

Anti-Diphtheria, Tetanus, and Pertussis Antibodies

The DTP (Diphtheria, Tetanus, and Pertussis) ECL (electrochemiluminescent) is a multiplexed serological assay which allows for the simultaneous quantification of human antibodies to 6 specific antigens including diphtheria toxoid, tetanus toxoid, 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 SULFO-TAG 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

Anti-Pneumococcal Antibodies

The pneumococcal capsular PS (PnPS) IgG ECL assay is used to quantitate the amount of anti-*Streptococcus pneumoniae* antibodies in human serum for 21 serotypes including all 10 serotypes in Synflorix® and 13 serotypes in Prevenar 13® (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14,15B, 18C, 19A, 19F, 22F, 23F and 33F). 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 using 3 types of plates to cover all 21 PnPS. Diluted serum samples (test samples, reference standard, and quality controls), pre-treated with pneumococcal cell wall absorbents (to reduce the interference of non-specific antibodies in the assay), are incubated in the wells. Specific antibodies in the serum samples bind to the immobilized antigen. Unbound antibodies are washed from the wells, and SULFO-TAG-conjugated anti-human immunoglobulin is added. The antibody conjugate binds to the antigen-antibody complex. Excess conjugate is washed away, and read buffer is added. The plate is read using electrochemiluminescence on an MSD imager. The intensity of the generated light is proportional to the amount of specific antibody bound to the antigen-coated spots. An international reference standard assayed on each plate is used to calculate the amount of anti-pneumococcal IgG antibodies (µg/mL) in human serum. The LLOQ for all PnPS serotypes is 0.15 µg/mL

Anti-Hepatitis B Antibodies

Anti-HB antibodies 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 total immunoglobulin in human serum. This involves the reaction of anti-

HBs in the sample with plasma-derived HBsAg (ad and ay subtypes) coated onto the wells. A horseradish peroxidase (HRP)-labeled HBsAg conjugate (ad and ay subtypes) then complexes with the bound anti-HBs 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 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 HBsAg (1977). The LLOQ is 5 mIU/mL.

Anti-Poliovirus (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 antibodies contained in the sera bind to and neutralize the challenge poliovirus. The neutralized poliovirus does not affect cellular viability and these cells continue to metabolize and release CO_2, reducing the pH of the culture medium. Cell survival correlates with the change in the pH indicator (phenol red to yellow at pH $\leq$ 7.0) contained in the medium. In the absence of neutralizing antibodies, 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 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 [dil]). The LLOQ of the anti-poliovirus types 1, 2, and 3 assays is 4 (1/dil).

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 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

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 the 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

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.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

9.3.1.1 Immunogenicity Endpoints

Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by rSBA in a subset of subjects in all groups[a] at Day 0 (before Dose 1) (all groups), 30 days after Dose 2 (Groups 1, 2, and 3) or 30 days after Dose 3 (Group 4) in infancy, and before and 30 days after the booster dose (in all groups)

In addition, the following endpoints will be assessed for all groups:

- Antibody titers, titers ≥ 1:8, and titers ≥ 1:128
- Post-vaccination titers ≥ 4 times the latest pre vaccination titers
- 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.

9.3.1.2 Immunogenicity Assessment Methods

The testing laboratories which will perform the assays described below will be reported in the final Clinical Study Report.

The rSBA testing is planned to take place at the Public Health England, Manchester, United Kingdom laboratory of [redacted].

Blood samples from a subset of subjects will be analyzed using rSBA for all 4 serogroups: 100 subjects each in Group 1 and Group 2 and 50 subjects each in Group 3 and Group 4.

Antibodies to meningococcal antigens (rSBA Method)

Functional meningococcal antibody activity against serogroups A, C, W, and Y will be measured in rSBA. 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, an agar overlay medium is added to the serum/complement/bacteria mixture, allowed to harden, and then incubated overnight

[a] The rSBA subset will comprise:

- Group 1 and Group 2: 100 subjects in each group
- Group 3 and Group 4: 50 subjects in each group

Whenever collection of 6 mL of blood sample in toddler population (ie from 12 to 19 months of age) does not comply with local regulations, the corresponding countries will not include subjects in the rSBA subset. The rSBA subset will include subjects from all countries except Poland.

at 37°C with 5% 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 LLOQ of the rSBA assay is a titer of 1:4. This method will be performed on blood samples (refer to Table 9.1 and Table 9.2) in a subset. If the event of insufficient serum sample volume, the conduct of the hSBA assay is of higher priority than the assays for antigens of concomitant vaccines and the conduct of the assays for antigens of concomitant vaccines is of higher priority than the rSBA assay.

9.3.2 Safety

9.3.2.1 Safety Definitions

The following definitions are taken from the 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.

Adverse Reaction:

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

(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" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (ieg, injection site tenderness or irritability occurring between D0 and D07 post-vaccination).

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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.

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.

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 headache between D0 and D07 is a solicited reaction (ie, prelisted in the protocol and CRB), then a headache starting on D07 is a solicited reaction, whereas headache starting on D08 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 headache, 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 following endpoints will be used for all subjects for the evaluation of safety:

- Unsolicited systemic AEs reported in the 30 minutes after each vaccination, including occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken, relationship to the product administered, and whether the event caused termination from the study.
- Solicited (prelisted in the subject's diary card and CRB) injection site and systemic reactions starting any time from Day 0 (day of vaccination) through Day 7 after each vaccination, including occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction caused termination from the study.
- Unsolicited non-serious AEs reported up to 30 days after each vaccination, including occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to the product administered, and whether the event caused termination from the study.
- SAEs (including AESIs) reported throughout the study, ie, from Visit 1 (first vaccination) to the last study visit (Visit 5 for Groups 1, 2, and 3 and Visit 6 for Group 4, occurring 30 days [+21 days] after the last vaccination), including occurrence, nature (MedDRA preferred term),

time of onset, duration, intensity, action taken, relationship to the product administered, whether the event caused termination from the study, outcome, elapsed time from last administration (if less than 24 hours), relationship to study procedures, and seriousness criterion.

9.3.2.3 Safety Assessment Methods

At each visit, the Investigator or a delegate will ask the parent / legally acceptable representative 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 Vaccination)

After each vaccination, subject's parents / legally acceptable representatives 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 D07) until resolution:

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

  The action(s) taken by the parent / legally acceptable representative 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

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

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

Table 9.4 and Table 9.5 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

Table 9.4: 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 / legally acceptable representatives 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 9.5: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA LLT)	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
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 all reactions but fever, parents / legally acceptable representatives 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 / legally acceptable representatives are to measure subject's 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 rectal, oral or axillary according to local practices, with the rectal route preferred for infants and the axillary route preferred for toddlers. 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 / legally acceptable representatives will be instructed to record any other medical events that may occur from Day 0 to Day 30 or until the subject returns for the next study visit, whichever comes first. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from Visit 1 until 30 days after the last vaccination. 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 9.4 and Table 9.5).

[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.

All other unsolicited AEs will be classified according to the following intensity scale:

- 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 / legally acceptable representative 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) (49) (50)
- Kawasaki disease (51) (52) (53)
- Guillain-Barré syndrome (54)
- Idiopathic thrombocytopenic purpura (ITP) (55) (56)

These events have been listed as AESIs based on the feedback received from the EU 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 Efficacy

No clinical efficacy data will be obtained in the study.

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, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

10.1 Initial Reporting by the Investigator

Serious adverse events 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 [M.D. or D.O.]) 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 as well as the appropriate Safety Complementary Information CRFs. 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 CRF and of the appropriate Safety Complementary Information CRFs and send them to the Sponsor by one of the following means:

- By fax, to the following number: (570)-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.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 [redacted] 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 Officer 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 Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

The following definition is used for the purpose of expedited reporting of suspected unexpected serious adverse reactions (SUSARs):

Suspected Unexpected Serious Adverse Reactions (SUSAR):

'Unexpected serious adverse reaction' means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information (at the time of occurrence of the SUSAR, "Reference Safety Information" within Section 6.2.2 of the Investigator Brochure). Serious adverse events considered reasonably associated with the investigational medical product administered and considered unexpected are subject to expedited safety reporting to regulatory agencies and to the Ethics Committee concerned.

The Sponsor's [redacted] will notify the Investigators in writing of the occurrence of any reportable SAEs.

The 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' parent / legally acceptable representative 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 9.4 and Table 9.5) as well as areas for free text to capture additional safety information or other relevant details. Parents / legally acceptable representatives 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 / legally acceptable representatives on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the parents / legally acceptable representatives 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 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 Officer 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, and laboratory data 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.

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

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 blinded (when applicable) safety data review will be performed by the Sponsor's Safety Management Team (SMT).

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

Clinical data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor.

12.1.1 Hypotheses and Statistical Methods for Primary Objective

12.1.1.1 Hypotheses

Non-inferiority of MenACYW conjugate vaccine (Group 1) compared to Nimenrix® (Group 2) in terms of hSBA antibody titers after a 3-dose series to infants and toddlers will be tested.

For each of the 4 serogroups (A, C, W, and Y), GMTs 30 days after a 3- dose series vaccination will be used to compare Group 1 and Group 2 with the following individual hypotheses:

H_0 *(Null hypothesis)*:

- $GMT_{MenACYW} / GMT_{Nimenrix} \leq 1/1.5$ (or $GMT_{Nimenrix} / GMT_{MenACYW} \geq 1.5$)

H_1 *(Alternative hypothesis)*:

- $GMT_{MenACYW} / GMT_{Nimenrix} > 1/1.5$ (or $GMT_{Nimenrix} / GMT_{MenACYW} < 1.5$)

12.1.1.2 Statistical Methods

Assuming that Log10 transformation of the data follows a normal distribution, the Log10(data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMT.

The statistical methodology will be based on the use of the 2-sided 95% confidence interval (CI) of the ratio of post-vaccination GMTs between Group 1 and Group 2. The CI will be calculated using a normal approximation of log-transformed titers.

Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected. For each serogroup, the 2-sided 95% CI of the GMT ratio Group 1 (MenACYW) / Group 2 (Nimenrix) should lie above 1/1.5

12.1.2 Hypotheses and Statistical Methods for Secondary Objectives

12.1.2.1 Hypotheses for Secondary Objective 1

If the primary objective is met, non-inferiority of MenACYW conjugate vaccine (Group 1) compared to Nimenrix® (Group 2) in terms of hSBA antibody titers ≥ 1:8 after a 2-dose series in infants will be tested (Secondary Objective 1).

For each of the 4 serogroups (A, C, W, and Y), the percentages of subjects who achieve an hSBA titer ≥ 1:8 30 days after the 2 dose administered in infancy will be used to compare responses between Group 1 and Group 2 with the following individual hypotheses:

- H_0 *(Null hypothesis)*: $p(_{MenACYW}) - p(_{Nimenrix}) \leq -10\%$
- H_1 *(Alternative hypothesis)*: $p(_{MenACYW}) - p(_{Nimenrix}) > -10\%$

where $p(_{MenACYW})$ and $p(_{Nimenrix})$ are the percentages of subjects who achieve an hSBA titer ≥ 1:8 in the MenACYW conjugate vaccine group and the Nimenrix® group, respectively.

12.1.2.2 Statistical Methods for Secondary Objective 1

Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages is > -10%, the non-inferiority will be demonstrated. The CI of the difference in percentages will be computed using the Wilson score method without continuity correction.

12.1.2.3 Hypotheses for Secondary Objectives 2, 3, 4, 5, 6 and 7

No hypotheses will be tested.

12.1.2.4 Statistical Methods for Secondary Objectives 2, 3, 4, 5, 6 and 7

The statistical analyses for the Secondary Objectives 2, 3, 4, 5, 6 and 7 will be descriptive.

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.

Reverse cumulative distribution curve (RCDC) figures may be also provided.

12.1.3 Statistical Methods for 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).

It will include but is not limited to the following:

- Number and percentages of subjects reporting any solicited injection sites reactions and solicited systemic reactions occurring from Day 0 to Day 7 after each vaccination will be summarized by intensity, time of onset period, days of occurrence, and action taken.
- Number and percentages of subjects reporting any immediate unsolicited systemic AEs occurring 30 minutes after each vaccination and unsolicited AEs occurring up to 30 minutes after each vaccination will be summarized
- The number and percentage of subjects reporting any unsolicited non-serious AEs occurring up to Day 30 will be summarized by intensity, time of onset period, duration, and by MedDRA preferred term and system organ class (SOC), as well as by relationship to the study vaccine
- The number and percentage of subjects reporting at least one SAEs occurring throughout the trial will be summarized by seriousness criterion, outcome and by MedDRA preferred term and SOC, as well by relationship to the study vaccine

- The number and percentage of subjects reporting at least one of any AESIs will be summarized throughout the trial

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

Main immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed on the Full Analysis Set (FAS) according to randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS).

12.2.1 Full Analysis Set

There will be 2 full analysis sets (FASs), one FAS for the primary series (FAS1) and one FAS for the booster vaccination (FAS2).

- FAS1 is defined as the subset of randomized subjects who received at least 1 dose of the study vaccine in the primary series and had a valid post-primary series vaccination blood sample result.
- FAS2 is defined as the subset of randomized subjects who received at least 1 dose of the study vaccine at booster vaccination and had a valid post-booster vaccination blood sample result.

12.2.2 Safety Analysis Set

The safety analysis set (SafAS is defined as those subjects who have received at least one dose of the study vaccine(s)[a] and have any safety data available. Specific safety analysis set will be defined and used after each vaccination. All subjects will have their safety analyzed after each dose according to the vaccine they actually received, and 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).

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

12.2.3 Overall Safety Analysis Set for Any Dose

The overall SafAS is defined as those subjects who have received at least one 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).

12.2.4 Safety Analysis Set for Vaccination at 2 Months of Age

The SafAS 1 for vaccination at around 2 months of age is defined as those subjects who have received the study vaccine at Visit 1 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 will be excluded from the analysis (and listed separately).

12.2.5 Safety Analysis Set for Vaccination at 4 Months of Age

The SafAS 2 for vaccination as those subjects who have received the study vaccine at Visit 2 and have any safety data available. All subjects will have their safety analyzed after the Visit 2 dose according to the vaccines they actually received at Visit 2.

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

12.2.6 Safety Analysis Set for Vaccination at 6 Months of Age (Group 4)

The SafAS 3 for vaccination as those subjects who have received the study vaccine at Visit 3 and have any safety data available. All subjects will have their safety analyzed after the Visit 3 dose according to the vaccines they actually received at Visit 3.

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

12.2.7 Safety Analysis Set for Vaccination at 12 to 18 Months of Age

The SafAS 4 for vaccination as those subjects who have received the study vaccine at Visit 4 / 5 (depending on the schedule) and have any safety data available. All subjects will have their safety analyzed after the Visit 4 / 5 dose according to the vaccines they actually received at Visit 4 / 5. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

12.2.8 Per-Protocol Analysis Set

The per-protocol analysis set (PPAS) is a subset of the FAS. There will be 2 PPAS; PPAS for the primary series (PPAS1), PPAS for the booster (PPAS2).

12.2.8.1 Per-Protocol Analysis Set for Primary Series (PPAS1)

The subjects presenting with at least one of the following relevant protocol deviations 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
    - Visit 2: Visit 1 + 60 days (+14 days)
    - Visit 3 (Group 4 only): Visit 2 + 60 days (+14 days)
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
    - Blood sampling 2 (BL0002):
        - Visit 3: Visit 2 + 30 days [+21 days] (Group 1, 2, 3)
        - Visit 4: Visit 3 + 30 days [+21 days] (Group 4)
- Subject received a protocol-prohibited therapy / medication / vaccine (identified among category 2 / category 3, not including the rotavirus vaccine administered at V1 and V2)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database

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

Vaccine correctness criteria apply to all the vaccines administered in the protocol, (ie, MenACYW conjugate vaccine / Nimenrix® and the concomitants vaccines.

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

12.2.8.2 Per-Protocol Analysis Set for Booster Series (PPAS2)

The subjects presenting with at least one of the following relevant protocol deviations 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
- 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 for the booster dose at 12 to 18 months of age (all groups) or at least 180 days after Visit 3 (Group 4)
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
    - Blood sampling 4 (BL0004):
        - Visit 5: Visit 4 + 30 days [+21 days] (Group 1, 2, 3)
        - Visit 6: Visit 5 + 30 days [+21 days] (Group 4)
- Subject received a protocol-prohibited therapy / medication / vaccine (identified among category 2 / category 3)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database

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

Vaccine correctness criteria apply to all the vaccines administered in the protocol, ie, MenACYW conjugate vaccine / Nimenrix® and the concomitants vaccines. A licensed Measles, Mumps and Rubella vaccine must be received either during the study visit (Visit 4/Visit 5) or with a gap of at least 4 weeks before any study vaccines or after the end of the study. In the event of a local or national immunization program with a pandemic influenza or coronavirus vaccine or any other vaccine as needed, subjects who receive the 1 or more doses of a pandemic influenza or coronavirus vaccine at any time during the study will not be withdrawn from the study.

12.2.9 Populations Used in Analyses

The main immunogenicity analyses will be performed on the PPAS analysis set including PPAS2 for the primary objective and PPAS1 for secondary objective 1, and will be confirmed on the FAS2 and FAS1. In the FAS1 and FAS2, subjects will be analyzed by the vaccine group to which they were randomized.

The safety analysis will be performed on the SafAS, SafAS1 to SafAS 4. Subjects will be analyzed according to the vaccine they actually received.

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:

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

If baseline or post baseline value is missing, then the vaccine seroresponse is missing.

12.4 Interim / Preliminary Analysis

No interim analyses are planned.

12.5 Determination of Sample Size and Power Calculation

Approximately a total of 1652 subjects will be enrolled.

For the Primary Objective

With 716 enrolled subjects in Group 1 and in Group 2, the study will have 96.2% power to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, Y hSBA antibody titers (ratio of GMTs in the 2 groups) after a 3-dose series to infants and toddlers 6 weeks to 18 months old, assuming:

- An estimated 26.2% dropout rate from the PPAS (528 subjects evaluable by group),
- a 1-sided alpha level of 2.5%,
- a non-inferiority margin of 1.5 (GMT ratio),
- a standard deviation (SD) of log10-transformed titers of 0.7 for serogroups A and C, 0.5 for serogroup Y, and 0.6 for serogroup W.

Table 12.1: Power of the study based on the primary objective

Antigen	MenACYW Standard Deviation*	Non-inferiority Margin	Power
A	0.7	1.5	98.3%
C	0.7	1.5	98.3%
Y	0.5	1.5	> 99.9%
W	0.6	1.5	99.7%
Overall			96.2%

Since the hypothesis needs to be met for all serogroups, no alpha adjustment for multiple comparisons is necessary in these calculations.

* SDs are based on the results of the MET39 (NCT01049035) MenACYW 2/4/12 months schedule (Group 3) after booster results. For the power computation, the same SD in the control group (Nimenrix®) is assumed.

For the Secondary Objective

With 716 enrolled subjects in Group 1 and in Group 2, the study will have a > 90% power (Farrington and Manning formula) to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, Y hSBA antibody titers ≥ 1:8 (difference in the percentage of seroprotected subjects in the 2 groups) after 2 doses in infancy at 2 months and 4 months of age, assuming:

- An estimated 26.2% dropout rate from the PPAS (528 subjects evaluable per group)
- A 1-sided alpha level of 2.5%,
- A non-inferiority margin of 10% (percentage difference)

Table 12.2: Power of the study for the secondary objective

Antigen	Estimated Percentage of hSBA Titer ≥ 1:8 Nimenrix®*	Non-inferiority margin†	Power
A	76%	10%	96.7%
C	94%	10%	> 99.9%
Y	71%	10%	94.7%
W	82%	10%	98.7%
Overall			90%

Since the hypothesis needs to be met for all serogroups, and the secondary objective is to be tested only if the primary objective succeeds, no alpha adjustment for multiple comparisons is necessary in these calculations.

* Percentages of subjects with an hSBA titer ≥ 1:8 are based on the MET39 (NCT01049035) MenACYW 2/4/12 months schedule (Group 3) post dose 2 results using estimates 2% lower than in the MenACYW group. The power is calculated with the assumption that the estimates from the investigational group equal that of the control group corresponding to the estimated percentages in the Nimenrix® group described above.

† A non-inferiority margin of 10% has been widely used in previous studies evaluating the same antigens and in a competitor's study of the same type. Also taking into account the level of the reference rate taken in the Nimenrix® group, it is reasonable to use 10%.

The sample size has been arbitrarily set to 110 subjects in Group 3 and Group 4 as these data are not intended to be used for any hypothesis testing. No formal sample size calculations were performed. In each group, there is more than 95% probability to observe an event with an incidence of 2.7%.

In case of unexpected situation 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, Data Protection and Access to Subject Records

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

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations, including the Global Data Protection Regulation (GDPR). Data

[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.

collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Subjects' race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, the FDA in the US).

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

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.

The following instruction manuals will be provided: the CRF 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. In exceptional situations (eg, lock down due to COVID-19) where the monitor cannot access site, and only after validation with Sponsor, the subject source data verification may be done remotely, under conditions defined in the Monitoring Plan.
- Determine the number of complete or ongoing issues identified at monitoring visits (ieg, 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 (CQA) 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

Subjects may be provided with a stipend according to local practice to compensate for the travel costs incurred 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-0541887 v7.0
Protocol Body_CLI_00002486_MET58

Approve & eSign	[redacted] Clinical [redacted]