NCT03673462

A Randomized Study to Describe the Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers

Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the United States and Puerto Rico

Clinical Study Protocol

Health Authority File Number:	BB-IND #: 14171
WHO Universal Trial Number (UTN):	U1111-1183-6261
Study Code:	MET41
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular
Indication For This Study:	MenACYW conjugate vaccine administered to healthy infants and toddlers at 2, 4, 6, and 12 months of age
Manufacturer:	Same as Sponsor
Coordinating Investigator	To be determined
Sponsor's Responsible Medical Officer:	[redacted]
Pharmacovigilance Global Safety Expert:	
Regional Clinical Trial Manager:	
Version and Date of the Protocol:	Version 4.0 dated 29 May 2019

History of Protocol Versions

Previous versions of the protocol

Version	Date	Comments
1.0	19 October 2017	Internal version not submitted
2.0	4 May 2018	Internal version not submitted
3.0	9 May 2018	First version of the Protocol

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Synopsis

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

Title of the Trial:	A Randomized Study to Describe the Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers
Development Phase:	Phase III
Coordinating Investigator:	To be determined
Trial Centers:	This will be a multi-center study conducted at approximately 65 sites in the United States and Puerto Rico. Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Trial Period:	3Q 2018 to 2 Q 2021
Trial Design and Methodology:	A Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the United States and Puerto Rico. Approximately 3080 healthy infants aged ≥ 42 to ≤ 89 days will be randomized in 3:1 ratio to the following 2 groups: **Group 1:** MenACYW conjugate vaccine + routine pediatric vaccines **Group 2:** MENVEO® + routine pediatric vaccines All subjects will receive a dose of either MenACYW conjugate vaccine or MENVEO® with the following routine pediatric vaccines: Pentacel® (DTaP-IPV//Hib) at 2, 4, and 6 months of age*; PREVNAR 13® (pneumococcal 13-valent conjugate vaccine; PCV13) at 2, 4, 6, and 12 months of age; RotaTeq® (rotavirus vaccine) at 2, 4, and 6 months of age; ENGERIX-B® (hepatitis B vaccine) at 2 and 6 months of age†; and M-M-R® II (measles, mumps, and rubella vaccine) and VARIVAX® (varicella vaccine) at 12 months of age. *All subjects will complete the last study visit at 13 to 14 months of age. For all subjects, the 4th dose of Pentacel® should be administered by site personnel at 15 to 18 months of age as per standard practice. The 4th dose of Pentacel® will be provided by the Sponsor for completion of the DTaP series with vaccine from the same manufacturer, to ensure compliance with the Advisory Committee on Immunization Practices (ACIP) recommendation. † First dose of hepatitis B vaccine must be given at least 28 days prior to study enrollment. Study vaccines will be administered as part of the study on the following schedules: **Group 1**: MenACYW conjugate vaccine and routine pediatric vaccines at 2, 4, 6, and 12 months of age **Group 2**: MENVEO® and routine pediatric vaccines at 2, 4, 6, and 12 months of age

	Safety data will be collected as follows: Immediate unsolicited systemic adverse events (AEs) will be collected within 30 minutes after each vaccination. Solicited AE information will be collected from D0 to D07 after each vaccination; unsolicited AE information will be collected from D0 after each vaccination to the next study visit; serious adverse event (SAE) information (including adverse events of special interest [AESIs]) and medically-attended adverse events (MAAEs) will be collected throughout the study from Visit 1 (day of first vaccination) until the end of the 6-month follow up period after the last vaccination.
Early Safety Data Review:	No Early Safety Data Review (i.e., no early safety review[s] of preliminary safety data occurring at pre-determined milestones defined in the protocol, with pause in enrollment) is planned for this trial as MenACYW conjugate vaccine has been previously administered to infants, toddlers, and adults with an acceptable safety profile and no safety concerns have been identified in the clinical trials completed so far. There will be an internal team at the level of the Sponsor (Safety Management Team, [SMT]), which will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The SMT is empowered to recommend a pause in both recruitment and/or further vaccination while it investigates any potential signal or concern. This trial may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), or the governing regulatory authorities in the US where the trial is taking place. If the trial is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the subjects' parents / guardians and should assure appropriate therapy (if needed) and follow-up.
Objective:	To describe the safety profile of MenACYW conjugate vaccine and MENVEO® when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers.
Endpoints:	The following endpoints will be used for all subjects for the evaluation of safety: • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination. • Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and electronic case report book [CRB]) injection site reactions occurring up to D07 after each vaccination. • Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to D07 after each vaccination.

	• Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination. • Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination. • Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study for MAAEs throughout the trial, from Visit 1 to the 6-month follow-up contact after the last vaccination.
Planned Sample Size:	Approximately 3080 subjects are planned to be enrolled: **Group 1 (MenACYW conjugate vaccine):** n = 2310 **Group 2 (MENVEO®):** n = 770
Schedule of Study Procedures:	Vaccination All subjects will receive a dose of either MenACYW conjugate vaccine or MENVEO® with routine pediatric vaccines at 2, 4, 6, and 12 months of age. All subjects will receive the routine pediatric vaccines as per the approved ACIP recommended schedules: Pentacel® at 2, 4, and 6 months of age*; PREVNAR 13® at 2, 4, 6, and 12 months of age; RotaTeq® at 2, 4, and 6 months of age; ENGERIX-B® at 2 and 6 months of age†; and M-M-R® II and VARIVAX® at 12 months of age. Study vaccines will be administered according to the following schedules: **Group 1**: MenACYW conjugate vaccine and routine pediatric vaccines will be administered at 2, 4, 6, and 12 months of age. **Group 2**: MENVEO® vaccine and routine pediatric vaccines will be administered at 2, 4, 6, and 12 months of age. * All subjects will complete the last study visit at 13 to 14 months of age. For all subjects, the 4th dose of Pentacel® should be administered by site personnel at 15 to 18 months of age as per standard practice. The 4th dose of Pentacel® will be provided by the Sponsor for completion of the DTaP series with vaccine from the same manufacturer, to ensure compliance with the ACIP recommendation. † First dose of hepatitis B vaccine must be given at least 28 days prior to study enrollment. Blood sampling No blood samples will be collected as this is a safety study. Collection of safety data • All subjects will be followed for safety from Visit 1 to 6 months after the last vaccinations at 12 months of age.

	• 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 CRB. • The subject's parent / guardian will record information in a diary card about solicited reactions from D0 to D07 after each vaccination and unsolicited AEs from D0 after each vaccination to the next study visit.
	• SAEs (including AESIs) and MAAEs will be recorded throughout the study. The subject's parent / guardian will record information in a diary card about SAEs and MAAEs from Visit 1 to Visit 2, from Visit 2 to Visit 3, from Visit 3 to Visit 4, and from Visit 4 to Visit 5. SAEs and MAAEs will also be recorded in a memory aid from D31 after the last vaccination visit until the 6-month follow up phone call. • The subject's parent/ guardian will be asked to notify the site immediately about any potential SAEs at any time during the trial. • Staff will contact the subjects' parent/ guardian by telephone 8 days (+2 days) after each vaccination visit to identify the occurrence of any SAEs (including AESIs) not yet reported and to remind them to complete the diary card after each vaccination visit and to bring it back at the subsequent visit. • The completed diary cards will each be collected and reviewed with the subject's parent/ guardian at the subsequent visit. • Staff will contact the subjects' parent/ guardian by telephone within 14 days before Visit 4 to remind them about the forthcoming study visit. If the subject's participation in the study is discontinued, the information recorded on the diary card will be reviewed at this time and the subject's parent / guardian will be asked to mail the diary card to the site. • Staff will contact the subjects' parent/ guardian by telephone at 6 months (+30 days) after the last vaccination visit to review the memory aid and identify the occurrence of any MAAEs, as well as SAEs (including AESIs) that have not been reported.
Duration of Participation in the Trial:	The duration of each subject's participation in the trial will be approximately 16 months, which will include a safety follow-up contact at 6 months after the final vaccination.
Investigational Product:	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)
Form:	Liquid solution
Composition:	Each 0.5 milliliter (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:	MENVEO®: Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine (GSK Vaccines, Srl, Bellaria-Rosia 53018, Sovicille [SI], Italy)
Form:	Lyophilized powder and liquid components are combined to produce a Solution for Intramuscular Injection
Composition:	Each 0.5 mL dose of vaccine contains the following active ingredients: MenA oligosaccharide ..... 10 mcg MenC oligosaccharide ..... 5 mcg MenY oligosaccharide ..... 5 mcg MenW-135 oligosaccharide ..... 5 mcg CRM_{197} protein ..... 32.7 to 64.1 mcg Other ingredients per 0.5 mL dose: residual formaldehyde ≤ 0.30 mcg.
Route:	IM
Batch Number:	To be determined
Other Product 1:	**Pentacel®:** (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Sanofi Pasteur Ltd, Toronto, Ontario, Canada)
Form:	Liquid DTaP-IPV used to reconstitute lyophilized ActHIB®
Composition:	Each 0.5 mL dose contains: Diphtheria toxoid ..... 15 Limit of Flocculation (Lf) Tetanus toxoid ..... 5 Lf Acellular pertussis antigens: Pertussis toxin (PT) ..... 20 µg Filamentous hemagglutinin (FHA) ..... 20 µg Pertactin (PRN) ..... 3 µg Fimbriae Types 2 and 3 (FIM) ..... 5 µg Inactivated polioviruses: Type 1 (Mahoney) ..... 40 D-antigen units (DU) Type 2 (MEF-1) ..... 8 DU Type 3 (Saukett) ..... 32 DU *H. influenzae* type b (PRP) ..... 10 µg Tetanus toxoid (PRP-T) ..... 24 µg Excipients: Aluminum phosphate (0.33 mg aluminum) (adjuvant) ..... 1.5 mg Polysorbate 80 ..... approximately 10 parts per million (ppm) by calculation Sucrose ..... 42.5 mg Residual formaldehyde ..... ≤ 5 µg Residual glutaraldehyde ..... < 50 ng Residual bovine serum albumin ..... ≤ 50ng 2-phenoxyethanol ..... 3.3 mg (0.6% v/v) Neomycin ..... < 4 picogram (pg) Polymyxin B sulfate ..... < 4 pg
Route:	IM
Batch Number:	To be determined

Other Product 2:	**PREVNAR 13®:** Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc, Philadelphia, PA, USA)
Form:	Suspension for injection
Composition:	Each 0.5 mL dose of the vaccine is formulated to contain *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides .....approximately 2.2 µg of each 6B saccharides ..... 4.4 µg Excipients: CRM_{197} carrier protein.....34 µg Polysorbate 80 .....100 µg Succinate buffer.....295 µg Aluminum as aluminum phosphate adjuvant.....125 µg
Route:	IM
Batch Number:	To be determined
Other Product 3:	**RotaTeq®:** (Rotavirus Vaccine, Live, Oral, Pentavalent) (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)
Form:	Oral solution
Composition:	Each 2 mL dose contains the following 5 live reassortant rotaviruses: G1 serotype.....2.2×10^6 infectious units (IU) G2 serotype.....2.8×10^6 IU G3 serotype.....2.2×10^6 IU G4 serotype.....2.0×10^6IU P1A(8) .....2.3×10^6IU The reassortants are suspended in a buffered stabilizer solution. Each 2 mL vaccine dose also contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum.
Route:	Oral (PO)
Batch Number:	To be determined
Other Product 4:	**ENGERIX-B®:** (Hepatitis B Vaccine [Recombinant]) (GlaxoSmithKline Biologicals 441 Rixensart, Belgium)
Form:	Suspension for injection
Composition:	Each 0.5 mL pediatric/adolescent dose contains 10 µg of hepatitis B virus surface antigen (HBsAg) adsorbed on 0.25 mg aluminum as aluminum hydroxide. Excipients: Sodium chloride.....9 mg/mL Disodium phosphate dihydrate .....0.98 mg/mL Sodium dihydrogen phosphate dihydrate.....0.71 mg/mL
Route:	IM
Batch Number:	To be determined

Other Product 5:	**M-M-R® II** (Measles, Mumps, and Rubella Virus Vaccine Live) (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)
Form:	Lyophilized live virus vaccine
Composition:	Each 0.5 mL dose contains live, attenuated virus: Measles virus (derived from Ender's Edmonston strain) propagated in chick embryo cell culture .....not less than 1000 $TCID_{50}$* Mumps virus (Jeryl Lynn™ [B level] strain) propagated in chick embryo cell culture ..... not less than 12,500 $TCID_{50}$* Rubella virus (Wistar RA 27/3 strain) propagated in WI-38 human diploid lung fibroblasts ..... not less than 1000 $TCID_{50}$* *$TCID_{50}$ = tissue culture infectious doses 50% Each 0.5 mL dose is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤ 0.3 mg), fetal bovine serum (< 1 ppm), other buffer and media ingredients and approximately 25 µg of neomycin.
Route:	Subcutaneous (SC)
Batch Number:	To be determined
Other Product 6:	**VARIVAX®:** Varicella Virus Vaccine Live (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)
Form:	Suspension for injection supplied as lyophilized vaccine to be reconstituted using the accompanying sterile diluent
Composition:	Each approximately 0.5 mL dose contains: Oka/Merck varicella virus .....at least 1350 plaque-forming units (PFU) Excipients: Sucrose ..... 25 mg Hydrolyzed gelatin..... 12.5 mg Sodium chloride..... 3.2 mg Monosodium L-glutamate..... 0.5 mg Sodium phosphate dibasic ..... 0.45 mg Potassium phosphate monobasic ..... 0.08 mg Potassium chloride..... 0.08 mg The vaccine contains residual components of MRC-5 cells including DNA and protein and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum. The vaccine contains no preservative.
Route:	SC
Batch Number:	To be determined

Inclusion Criteria:	An individual must fulfill *all* of the following criteria in order 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 guardian and by an independent witness if required by local regulations. 4) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures. 5) Infants who received the first dose of hepatitis B vaccine at least 28 days before the first study visit.
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1) Participation at the time of study enrollment or in the 4 weeks preceding the first trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure. 2) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks before and / or following any trial vaccination except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines. 3) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B serogroup-containing vaccine). 4) Previous vaccination against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis A, measles, mumps, rubella, varicella; and *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and /or rotavirus infection or disease 5) Receipt of more than 1 previous dose of hepatitis B vaccine. 6) Receipt of immune globulins, blood or blood-derived products since birth. 7) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth. 8) Family history of congenital or hereditary immunodeficiency until the immune competence of the potential vaccine recipient is demonstrated. 9) Individuals with blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems. 10) Individuals with active tuberculosis 11) History of any *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically.

	12) History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, varicella, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and /or rotavirus infection/disease. 13) At high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease). 14) History of intussusception. 15) History of any neurologic disorders, including seizures and progressive neurologic disorders. 16) History of Guillain-Barré syndrome. 17) Known systemic hypersensitivity to any of the vaccine components or to latex, or history of a life-threatening reaction to the vaccine(s) used in the trial or to a vaccine containing any of the same substances, including neomycin, gelatin, and yeast. 18) Verbal report of thrombocytopenia contraindicating intramuscular vaccination in the Investigator's opinion. 19) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion 20) 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 trial conduct or completion 21) Any condition which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives 22) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38°C [≥ 100.4°F]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided. 23) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.
Statistical Methods:	***Safety / Reactogenicity*** The Safety Analysis Set (SafAS) is defined as those subjects who have received at least 1 dose of the study vaccine and have any safety data available. All subjects will have their safety analyzed for each dose according to the vaccine they actually received at that dose. Safety analysis after all of the 4-dose vaccinations will be conducted as well. If the vaccine received by a subject does not correspond to any study group, the subject will be excluded from the SafAS. The corresponding safety data will be presented in separate listings. *Safety analysis will include but not be limited to the following:* The number and percentage of subjects reporting any solicited injection site reactions and solicited systemic reactions occurring from D0 to D07 after each vaccination will be summarized by study group for intensity, time of onset period, days of occurrence, and action taken.

	Immediate unsolicited systemic AEs and unsolicited AEs occurring up to D30 after each vaccination will be summarized. The number and percentage of subjects reporting any unsolicited non-serious AEs will be summarized by study group, 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 of any MAAEs will be summarized throughout the study. The number and percentage of subjects reporting at least one of any SAEs will be summarized by study group, seriousness criterion, outcome, and by MedDRA preferred term and SOC, as well as by relationship to the study vaccine. The number and percentage of subjects reporting at least one of any AESIs will be summarized throughout the study. Exact (Clopper-Pearson) 2-sided 95% confidence intervals (CIs) will be calculated for the percentages. ***Sample Size Calculation*** The sample size of this study was chosen to provide safety data; it is not intended for the purposes of hypothesis testing. No formal sample size calculation is performed. Though there are no statistically powered hypotheses, the overall study cohort of 3080 subjects will provide a probability of approximately 95% of observing any AE with a true incidence of 0.15%. In the treatment arm with 2310 subjects, there is a probability of approximately 95% of observing any AE with a true incidence of 0.2%.

Table of Study Procedures

Phase III Study, 5 Visits, 4 Vaccination visits, 6 Telephone calls, 18 Vaccinations, 16-Months' Duration Per Subject

Visit/Contact	**Visit 1**	**Telephone Call (TC) 1**	**Visit 2**	**TC2**	**Visit 3***	**TC3**	**TC4**	**Visit 4†**	**TC5**	**Visit 5**	**TC6 Follow-up contact**
Approximate age of subject	2 months (42 to 89 days)	-	4 months	-	6 months (164 to 224 days)	-		12 months	-	13 months	18 months
Trial timelines (days)	D0	Visit 1 + 8 days	Visit 1 + 60 days	Visit 2 + 8 days	Visit 2 + 60 days	Visit 3 + 8 days	Visit 4 -14 days		Visit 4 + 8 days	Visit 4 + 30 days	Visit 4 + 180 days
Time windows (days)		+2 days	+14 days	+2 days	+14 days	+2 days			+2 days	+21 days	+30 days
Informed consent form signed and dated	X										
Inclusion/exclusion criteria	X										
Collection of demographic data	X										
Medical history	X										
Physical examination	X							X			
Temperature measurement	X		X		X			X			
Contact IRT system for randomization / allocation of subject number / vaccine group assignment	X										
Review of warnings and precautions to vaccinations	X		X		X			X			
Review of contraindications to subsequent vaccinations and conditions for withdrawal‡			X		X			X			

Visit/Contact	Visit 1	Telephone Call (TC) 1	Visit 2	TC2	Visit 3*	TC3	TC4	Visit 4†	TC5	Visit 5	TC6 Follow-up contact
Contact IRT system for dose allocation for all vaccines			X		X			X			
Vaccination with MenACYW conjugate vaccine or MENVEO®	**X**		**X**		**X**			**X**			
Vaccination with routine pediatric vaccines§	**X**		**X**		**X**			**X**			
Immediate surveillance (30 minutes)	X		X		X			X			
Diary card (DC) provided	DC1		DC2		DC3			DC4			
Telephone call		X**		X**		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 AEs		Recorded from D0 to D30 after each vaccination visit									
Reporting of SAEs (including AESIs) and MAAEs ***		To be reported throughout the study period									
Collection of reportable concomitant medications	X		X		X			X		X	
Memory aid (MA) provided										MA†††	
Trial termination record (termination of active portion of the trial)										X	

* At Visit 3, subjects must be at least 24 weeks of age (the minimum age for the last dose of hepatitis B vaccine) and no more than 32 weeks of age (the maximum age for the last dose of rotavirus vaccine).

† At Visit 4, subjects must be 12 months of age, (from the day subjects turn 12 months of age until the day before turning 13 months of age).

‡ Physical examination should be performed on the basis of relevant medical history at the time of the visit according to the Investigator's clinical judgment. Temperature needs to be measured before each vaccination and recorded in the source documents.

§ Routine pediatric vaccines at Visit 1: Pentacel®, PREVNAR 13®, RotaTeq®, ENGERIX-B®; at Visit 2: Pentacel®, PREVNAR 13®, and RotaTeq®; at Visit 3: Pentacel®, PREVNAR 13®, RotaTeq®, and ENGERIX-B®; at Visit 4: PREVNAR 13®, M-M-R® II, and VARIVAX®.

** This call is made 8 days after the respective vaccinations. If D08 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 AESIs) and / or MAAE not yet reported, and will remind the subject's parent / guardian to continue using the diary card, to bring the diary card to the study center at the next visit, and confirm the date and time of the next visit.

†† Staff will contact the subjects' parent/ guardian by telephone within 14 days before Visit 4 (any time between 14 days and 1 day before Visit 4) to remind them about the forthcoming study visit. If the subject's participation in the study is discontinued, the information recorded on the diary card will be reviewed at this time and the subject's parent / guardian will be asked to mail the diary card to the site.

‡‡ Staff will contact the subject's parent/ guardian by telephone at 6 months (+ 30 days) after the last vaccination visit to identify the occurrence of any SAEs (including any AESIs) and MAAEs not yet reported. The final telephone call will continue until contact is made or 28 days have passed at which time the subject will be considered lost to follow-up.

§§ Solicited injection site and systemic reactions will be recorded from D0 through D07 after each vaccination visit.

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

††† The memory aid is used only for the recording of SAEs (including AESIs) and MAAEs from Visit 5 to the 6-month follow-up phone call (TC6).

List of Abbreviations

µg	micrograms
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
AR	adverse reaction
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
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	Day
DC	diary card
DTAP	diphtheria tetanus acellular pertussis
EDC	electronic data capture
FAS	full analysis set
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
HBsAg	hepatitis B virus surface antigen
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
hSBA	serum bactericidal assay using human complement
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IM	intramuscular
IMD	invasive meningococcal disease
IME	important medical event
IND	investigational new drug (application)
IOM	Institute of Medicine
IPV	inactivated poliovirus vaccine
IRB	Institutional Review Board
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IU	infectious units
LCLS	last contact, last subject
LLT	lowest level term
MA	memory aid
MAAE	medically-attended adverse event
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MMR	measles, mumps, rubella
NSAID	non-steroidal anti-inflammatory drug
PCV	pneumococcal conjugate vaccine
PFU	plaque-forming units
pg	picogram
ppm	parts per million
PRN	Pertactin
PRP	polyribosylribitol phosphate
PPAS	per-protocol analysis set
PS	polysaccharide
PT	pertussis toxin
PV	pharmacovigilance
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set

SC	Subcutaneous
SCID	severe combined immunodeficiency
SMT	safety management team
SOC	system organ class
$TCID_{50}$	tissue culture infectious doses 50%
TMF	trial master file
UTN	Universal Trial Number
v/v	Volume per volume
WHO	World Health Organization

1 Introduction

1.1 Background

This study (MET41) will evaluate the safety of a 4-dose series of the quadrivalent Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in children starting immunization at 6 weeks of age. The purpose of the MET41 study is to demonstrate that the safety profile of the MenACYW conjugate vaccine is similar to that of MENVEO® when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the United States (US) and Puerto Rico.

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *N. meningitidis*, a Gram-negative diplococcus found exclusively in humans. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). At least 12 different meningococcal serogroups have been classified based on the immunochemistry of the capsular 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 US during the last five-year period: a prolonged outbreak of serogroup B on a university campus in Ohio from 2008 – 2010 and 2 universities in New Jersey and California in 2013 (21) (22).

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

Surveillance data from England and Wales showed an increase in endemic meningococcal serogroup W disease across all age groups, accounting for 15% of all IMD cases in 2013 - 2014 compared with an average of 1% to 2% of all IMD cases in earlier years (24). A gradual increase

in serogroup Y IMD has also been recently reported in England and Wales between 2007-2009 (25) and in Sweden during 2005 – 2012 (26) (27). Nearly 50% of all IMD in Sweden was caused by serogroup Y in 2012 (26). Similarly, an increase in the proportion of IMD caused by serogroup Y has been observed in other Nordic countries, accounting for 31% in Norway in 2009 - 2010 (28) and 38% in Finland in 2010 (29).

In the US, the incidence rate of IMD was 0.14 per 100,000 in all ages; 0.83 per 100,000 in infants less than 1 year; 0.62 per 100,000 in toddlers 1 year of age; 0.27 per 100,000 in children 2 to 4 years of age; and 0.02 per 100,000 in children 5 to 17 years of age in 2013. The age specific incidence rate per 100,000 was 0.08 in adults 50 to 64 years of age, 0.03 in adults 65 to 74 years of age, 0.14 in adults 75 to 84 years of age, and 0.43 in adults 85 years of age and older in 2013 (30). Serogroups B, C, and Y are the major causes of meningococcal disease in the US, each being responsible for approximately one-third of the overall cases. The proportion of cases caused by each serogroup varies by age group. Serogroups C, W, or Y, which are included in vaccines available in the US, cause 73% of all cases of meningococcal disease among persons 11 years of age or older (31). Approximately 60% of disease among children aged 0 through 59 months is caused by serogroup B, for which no conjugate vaccine is licensed or available in the US. More than 50% of meningococcal disease in children 0 to 6 months of age is caused by serogroup B; serogroup Y is also more prevalent in this age group (20).

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

1.2 Background of the Investigational Product

1.2.1 Clinical

The MenACYW conjugate vaccine formulation was finalized based on data provided by 2 studies: MET28, a Phase I study in infants, toddlers, and adults 18 to < 40 years of age; and MET32, a Phase I/II study in toddlers.

The formulation has been evaluated in over 2000 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in completed studies MET39, MET44, MET50, MET54 and MET56. MenACYW conjugate vaccine is also being evaluated in ongoing global Phase III studies: MET51 and MET57 in toddlers (12 to 23 months of age); MET35 in children (2 to 9 years of age); MET43 (15 to 55 years of age); and MET49 in older adults (≥ 56 years of age).

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

1.2.1.1 Study MET39 (Phase II)

MET39 was a Phase II, randomized, open-label, multi-center study conducted in the US for which 580 healthy subjects from 2 to 15 months of age were enrolled. This study evaluated the optimal vaccination schedule in the infant/toddler population. Subjects in Group 1 through Group 4 received 1, 2, or 3 primary doses plus an additional dose of the MenACYW conjugate

vaccine in the second year of life, concomitantly with routine pediatric vaccines at several different vaccination schedules. Subjects in Group 5 received 1 dose of the MenACYW conjugate vaccine concomitantly with routine pediatric vaccines. The routine pediatric vaccines given concomitantly with MenACYW conjugate vaccine at various schedules included PREVNAR® (pneumococcal conjugate vaccine) or PREVNAR 13® (pneumococcal 13-valent conjugate vaccine [PCV13]), Pentacel® (diphtheria, tetanus, pertussis [acellular, component]-poliovirus [inactivated]//*Haemophilus influenzae* type b [dTaP-IPV//Hib]), ROTARIX® (monovalent rotavirus vaccine [RV1]) or RotaTeq® (pentavalent rotavirus vaccine[RV5]), hepatitis B vaccine, 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 of age), between 91% and 100% of the subjects achieved the protective threshold regardless of the number of doses they received in the first year of life.

Safety

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

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

1.2.1.2 Study MET54 (Phase II)

MET54 was a Phase II, randomized, open-label, active-controlled, multi-center study conducted in Europe (Finland). This study evaluated the immunogenicity and safety profile of a single dose

of MenACYW conjugate vaccine when given alone in healthy, meningococcal-vaccine naïve toddlers compared to that of the licensed vaccine Nimenrix®. A total of 188 meningococcal vaccine naïve subjects aged 12 to 23 months on the day of enrollment were randomized to 1 of 2 groups. Group 1 received a single dose of MenACYW conjugate vaccine and Group 2 received a single dose of Nimenrix®.

Immunogenicity

Antibody responses to the antigens (serogroups A, C, Y, and W) were evaluated by serum bactericidal assay using baby rabbit complement (rSBA) and human complement (hSBA). MenACYW conjugate vaccine immune responses evaluated by rSBA and hSBA were generally comparable to Nimenrix® immune responses with some variation by serogroup.

rSBA

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

hSBA

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

Safety

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

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

No new clinically important safety findings were identified with administration of the MenACYW conjugate vaccine. The MenACYW conjugate vaccine was well tolerated and immunogenic. Single dose of the MenACYW conjugate vaccine demonstrated excellent potential to be an alternative vaccine option for toddlers, receiving meningococcal vaccination for the first time.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

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

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

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

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine or MENVEO® may cause injection site reactions such as pain, swelling, and erythema, or certain systemic events such as fever, irritability, drowsiness, loss of appetite, abnormal crying, and vomiting when administered to infants / toddlers. There may be a rare possibility of an allergic reaction, which could be severe. There may also be a risk of febrile convulsion in some children who experience high fever. There may be other risks for MenACYW conjugate vaccine or MENVEO® that are not yet known.

In a previous study with MenACYW conjugate vaccine (MET32), 1 SAE of reactive arthritis reported in a toddler was considered by the Investigator to be related to the investigational vaccine. The subject developed right knee inflammation the day after receiving MenACYW conjugate vaccine, given by 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 studies.

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 (32). 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 (33).

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 (34). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (35). Arthus reactions are rarely reported after vaccination and can occur after tetanus toxoid-containing vaccines (36).

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

The potential risks listed here are not exhaustive. Refer to the Investigator's Brochure of the investigational vaccine and to the package insert for MENVEO® (37) as well as the 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, Y, and W. Compared to a previous Sanofi Pasteur meningococcal conjugate vaccine, Menactra®, the MenACYW conjugate vaccine is prepared using tetanus toxoid as the carrier protein. Conjugation of PS antigens to a protein carrier can induce T cell-dependent immune responses, which are anticipated to give rise to higher antibody titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response. The program targets licensure of the MenACYW conjugate vaccine in many countries in North America, Europe, Latin America, Africa, the Middle East, and Asia Pacific.

The MenACYW conjugate vaccine is designed to cover broader age groups than those covered by Menomune® -A/C/Y/W-135 and Menactra®. Menactra® has been very successful since its licensure in 2005; however, it is not licensed in Europe and is not indicated in persons 8 months of age or younger or 56 years of age and older. While Menomune® -A/C/Y/W-135 and Menactra® are currently licensed in different parts of the world, the MenACYW conjugate vaccine is being developed by Sanofi Pasteur to ultimately replace Menomune® -A/C/Y/W-135 and Menactra® in the global market as a quadrivalent meningococcal conjugate vaccine indicated in infants/toddlers, children, adolescents, adults, and older adults > 56 years of age.

Meningococcal PS vaccines have two important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) PSs alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of PS vaccines in infants and children has been shown to be improved by conjugating the PSs to protein carriers. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of PS-specific total immunoglobulin 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 or subsequent trials using the final formulation or in the earlier trials.

MenACYW conjugate vaccine is being developed for the US infant/toddler population as a 4-dose (2, 4, 6, 12 to 18 months of age) and 2-dose series. Three Phase III studies (including MET41) will generate data to primarily support the licensing of the MenACYW conjugate vaccine in the US with an infant/toddler indication from 6 weeks of age. The purpose of the MET41 study is to describe the safety profile of the MenACYW conjugate vaccine and the comparator MENVEO® when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the US. MET41 study will generate data which will significantly contribute towards the overall safety database of the MenACYW conjugate vaccine in the US and in general.

2 Study Objective

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

The endpoints for the study objective are presented in Section 9.1.1.

3 Investigators and Study Organization

This study will be conducted in approximately 65 centers in the US. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator. Details of the study centers, the Investigators at each center, and the Coordinating Investigator are provided in the "List of Investigators and Centers Involved in the Trial" document.

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

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

4 Independent Ethics Committee / Institutional Review Board

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

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and / or the Sponsor are responsible for obtaining this approval and / or favorable opinion before the start

of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator to the Sponsor together with the composition of the IEC / IRB (the names and qualifications of the members attending and voting at the meetings).

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

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

This study is a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the US.

Approximately 3080 healthy infants aged ≥ 42 to ≤ 89 days will be randomized in a 3:1 ratio to the following 2 groups:

- **Group 1:** MenACYW conjugate vaccine + routine pediatric vaccines (N=2310)
- **Group 2:** MENVEO®+ routine pediatric vaccines (N=770)

All subjects will receive a dose of either MenACYW conjugate vaccine or MENVEO® with the following routine pediatric vaccines: Pentacel® (DTaP-IPV//Hib) at 2, 4, and 6 months of age; PREVNAR 13® (pneumococcal 13-valent conjugate vaccine; PCV13) at 2, 4, 6, and 12 months of age; RotaTeq® (rotavirus vaccine) at 2, 4, and 6 months of age; ENGERIX-B® (hepatitis B vaccine) at 2 and 6 months of age[a]; and M-M-R® II (measles, mumps, and rubella vaccine) and VARIVAX® (varicella vaccine) at 12 months of age. All subjects will complete the last study visit at 13 to 14 months of age. For all subjects, the 4th dose of Pentacel® should be administered by site personnel at 15 to 18 months of age as per standard practice. The 4th dose of Pentacel® will be provided by the Sponsor for completion of the DTaP series with vaccine from the same manufacturer, to ensure compliance with the Advisory Committee on Immunization Practices (ACIP) recommendation.

[a] First dose of hepatitis B vaccine must be given at least 28 days prior to study enrollment.

Study vaccines will be administered as part of the study on the following schedules:

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

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

Safety data will be collected as follows: Immediate unsolicited systemic AEs will be collected within 30 minutes after each vaccination. Solicited AE information will be collected from D0 to D07 after each vaccination; unsolicited AE information will be collected from D0 after each vaccination to the next study visit; SAE (including adverse events of special interest [AESIs]) and medically-attended adverse event (MAAE) information will be collected throughout the study from Visit 1 until the end of the 6-month follow-up period after the last vaccination.

5.1.2 Justification of the Study Design

The MET41 study is part of an ongoing development program that focuses on demonstrating that the safety profile of the MenACYW conjugate vaccine is acceptable and not different from that of licensed quadrivalent meningococcal conjugate vaccines, and that the immunogenicity of the MenACYW conjugate vaccine is non-inferior to licensed comparators in direct comparison trials. MET41 is a pivotal Phase III safety study in which the vaccine candidate will be evaluated in infants/toddlers receiving concomitantly licensed routine pediatric vaccines in the US. This study is designed to describe the safety profile following a 4-dose series of the MenACYW conjugate vaccine or the licensed comparator MENVEO® in this population. Enrollment in the study will start at 6 to 8 weeks of age.

The concomitant administration of standard of care pediatric vaccines together with 5 different administration schedules of the MenACYW conjugate vaccine has been assessed in infants/toddlers 2 to 15 months of age in the US in the MET39 study. The subjects received during, or prior to the study, a number of licensed recommended vaccines at 2, 4, and 6 months of age: Pentacel®, either Prevnar® or Prevnar 13®, RotaTeq® or ROTARIX®, and ENGERIX-B® or RECOMBIVAX HB®. All subjects received M-M-R® II and VARIVAX® at 12 months of age. A total of 457 subjects completed the study. The immunogenicity and safety profiles of selected licensed pediatric vaccines (Pentacel®, Prevnar® or Prevnar 13®, M-M-R® II, and VARIVAX®) were assessed when administered either concomitantly with or without MenACYW conjugate vaccine. There was no evidence of interference with the pediatric routine vaccines administered concomitantly with MenACYW conjugate vaccine and the vaccine was safe and well tolerated regardless of the number of doses administered during the first year of life.

In the US, meningococcal vaccination is not routinely recommended for children ≤ 10 years of age, however the vaccination is recommended for individuals at increased risk of disease. ACIP recommends routine administration of quadrivalent meningococcal conjugate vaccines (MCV4) for all persons aged 11 through 18 years. A single dose of vaccine should be administered at age 11 or 12 years, and a booster dose should be administered at age 16 years. In infants at increased risk of disease , the ACIP recommends starting vaccination at 8 weeks of age using a 4-dose series that includes doses at 2 ,4, 6 and 12 months of age. Since MENVEO® is the only quadrivalent meningococcal conjugate vaccine licensed for use in infants as young as 2 months of age in the US, the selection of MENVEO® as a comparator was considered most appropriate and aligned with the MET41 study design.

Given that the meningococcal vaccines used in this study have different appearances and preparation methods, the study has a modified double blind design, and thus, with the exception of the personnel administering the vaccine, everyone involved in study (participants, care provider, investigator, safety outcomes assessor, Sponsor) is blinded to avoid any bias.

5.1.3 Study Plan

Vaccination

All subjects will receive a dose of either MenACYW conjugate vaccine or MENVEO® with routine pediatric vaccines at 2, 4, 6, and 12 months of age. All subjects will receive the routine pediatric vaccines at the approved ACIP recommended schedules: Pentacel® at 2, 4, and 6 months of age[a]; PREVNAR 13® at 2, 4, 6, and 12 months of age; RotaTeq® at 2, 4, and 6 months of age; ENGERIX-B® at 2 and 6 months of age[b]; and M-M-R® II and VARIVAX® at 12 months of age.

Study vaccines will be administered according to the following schedules:

Group 1: MenACYW conjugate vaccine and routine pediatric vaccines will be administered at 2, 4, 6, and 12 months of age.

Group 2: MENVEO® vaccine and routine pediatric vaccines will be administered at 2, 4, 6, and 12 months of age.

Blood sampling

No blood samples will be collected as this is a safety study.

Collection of safety data

- All subjects will be followed for safety from Visit 1 to 6 months after the last vaccinations at 12 months of age.
- 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 case report book (CRB). (See Section 9.1.1.3.1)
- The subject's parent / guardian will record information in a diary card about solicited reactions from D0 to D07 after each vaccination and unsolicited AEs from D0 after each vaccination to the next study visit.
- SAEs (including AESIs) and MAAEs will be recorded throughout the study. The subject's parent / guardian will record information in a diary card about SAEs and MAAEs from Visit 1 to Visit 2, from Visit 2 to Visit 3, from Visit 3 to Visit 4, and from Visit 4 to Visit 5. SAEs

[a] All subjects will complete the last study visit at 13 to 14 months of age. For all subjects, the 4th dose of Pentacel® should be administered by site personnel at 15 to 18 months of age as per standard practice. The 4th dose of Pentacel® will be provided by the Sponsor for completion of the DTaP series with vaccine from the same manufacturer, as per ACIP recommendation.

[b] First dose of hepatitis B vaccine must be given at least 28 days prior to study enrollment.

and MAAEs will also be recorded in a memory aid from D31 after the last vaccination visit until the 6-month follow up phone call.

- The subject's parent/ guardian will be asked to notify the site immediately about any potential SAEs at any time during the trial.
- Site staff will contact the subjects' parent/ guardian by telephone 8 days (+2 days) after each vaccination visit to identify the occurrence of any SAEs (including AESIs) and/or MAAEs not yet reported and to remind them to complete the diary card after each vaccination visit and to bring it back at the subsequent visit.
- The completed diary cards will each be collected and reviewed with the subject's parent/ guardian at the subsequent visit.
- Site staff will contact the subjects' parent/ guardian by telephone within 14 days before Visit 4 to remind them about the forthcoming study visit. If the subject's participation in the study is discontinued, the information recorded on the diary card will be reviewed at this time and the subject's parent / guardian will be asked to mail the diary card to the site.
- Site staff will contact the subjects' parent/ guardian by telephone at 6 months (+30 days) after the last vaccination visit to review the memory aid and identify the occurrence of any MAAEs, as well as SAEs (including AESIs) that have not been reported.

Table 5.1: Vaccination schedule

Visit/Contact	Visit 1	Visit 2	Visit 3	Visit 4
Age of Subject	2 months	4 months	6 months	12 months
Group 1	MenACYW DTaP-IPV//Hib PCV13 Rotavirus Hep B	MenACYW DTaP-IPV//Hib PCV13 Rotavirus	MenACYW DTaP-IPV//Hib PCV13 Rotavirus Hep B	MenACYW PCV13 MMR Varicella
Group 2	MENVEO DTaP-IPV//Hib PCV13 Rotavirus Hep B	MENVEO DTaP-IPV//Hib PCV13 Rotavirus	MENVEO DTaP-IPV//Hib PCV13 Rotavirus Hep B	MENVEO PCV13 MMR Varicella

DTaP-IPV//Hib: Pentacel®; PCV13: PREVNAR 13®; Rotavirus: RotaTeq®; Hep B: ENGERIX-B®; MMR: M-M-R® II; Varicella: VARIVAX®

5.1.4 Visit Procedures

Visit 1 (D0; 2 months of age): Inclusion, Randomization, and Vaccination

1) Give the parent / guardian information about the study, obtain written informed consent, and give him/her a signed copy.
2) Check inclusion and exclusion criteria for eligibility.
3) Collect demographic data.

4) Obtain verbal medical history about the subject, including ongoing medications.
5) 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 past week by a qualified health care provider, it does not need to be repeated unless there were changes in health status, in which case it may be limited to the affected area.
6) Measure temperature. If the temperature is ≥38°C (≥ 100.4°F), postpone vaccination until the condition is resolved.
7) Contact the interactive response technology (IRT) system for randomization, subject number, and vaccine allocation.
8) Review warnings and precautions to vaccinations.
9) Administer the following study vaccines. Each vaccine should be administered in the assigned location (see Operating Guidelines) and documented appropriately.
    a) Meningococcal vaccine (MenACYW conjugate vaccine and MENVEO®): inject IM into the anterolateral area of the thigh, preferably the right thigh.
    b) ENGERIX-B®: inject IM into the anterolateral area of the thigh, preferably the right thigh.
    c) Pentacel®: inject IM into the anterolateral area of the thigh, preferably the left thigh (i.e., the opposite leg from that used for meningococcal vaccine administration).
    d) PREVNAR 13®: inject IM into the anterolateral area of the thigh preferably the left thigh (i.e., the opposite leg from that used for meningococcal vaccine administration).
    e) RotaTeq®: administer orally per instructions in the package insert.

    When multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. The injection sites should be separated by 1 inch or more so that any local reactions can be differentiated (38). Meningococcal vaccine and Engerix-B® should be given in the same thigh. Do not administer Pentacel® or PREVNAR 13® in the same thigh as the meningococcal vaccine. For details see Operating Guidelines.

    Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the CRF. If the initial vaccines are administered in the wrong limbs, this should be corrected for subsequent injections.
10) 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.
11) Give the parent / guardian a diary card (DC1), a thermometer, and a ruler, and go over the instructions for their use. Instruct the parent / guardian to retain the thermometer and ruler throughout the duration of the study. At each subsequent visit, confirm that the parent / guardian has retained the thermometer and ruler, replace only as necessary

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

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

14) Complete the relevant case report forms (CRFs) for this visit.

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

Note: If day 8 after vaccination 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 an AESI, has occurred, follow the instructions in Section 10 for reporting it.

2) Remind the parent / guardian to do the following:
   - Complete the D0 to D07 pages of the diary card.
   - Complete the remaining pages of the diary card, and bring them to the next visit.
   - Notify the site in case of an SAE.

Visit 2 (60 [+14] days after Visit 1; 4 months of age): Collection of Safety Information and Vaccination

1) Collect and review the diary card (DC1) with the parent / guardian, including any AEs, medications, or therapy that occurred since the last visit. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.

2) Review warnings and precautions to vaccinations.

3) Review contraindications to subsequent vaccinations and condition for withdrawal.

4) Measure temperature prior to vaccination. If the temperature is ≥ 38°C (≥ 100.4°F), postpone vaccination until the condition is resolved.

5) Contact IRT system to receive vaccine assignments.

6) Administer the following study vaccines. Each vaccine should be administered in an assigned location and documented appropriately.

   a) Meningococcal vaccine (MenACYW conjugate vaccine or MENVEO®): inject IM into the anterolateral area of the thigh, preferably the right thigh.

   b) Pentacel®: inject IM into the anterolateral area of the thigh, preferably the left thigh (i.e., the opposite leg from that used for meningococcal vaccine administration).

   c) PREVNAR 13®: inject IM into the anterolateral area of the thigh, preferably the left thigh (i.e., the opposite leg from that used for meningococcal vaccine administration).

   d) RotaTeq®: administer orally per instructions in the package insert.

   When multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. The injection sites should be separated by 1 inch or more so that any local reactions can be differentiated (38). Do not administer

Pentacel® or PREVNAR 13® in the same thigh as the meningococcal vaccine. For details see Operating Guidelines.

Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the CRF.

7) Observe the subject for 30 minutes and record any AE in the source document. In the event of a local reaction, indicate the associated vaccine.
8) Give the parent / guardian a diary card (DC2).
9) Remind the parent / guardian to expect a telephone call 8 days after Visit 2 and to bring back the diary card when they return for Visit 3 at a specified date and time.
10) Remind the parent / guardian to notify the site in case of an SAE.
11) Complete the relevant CRFs for this visit.

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

Refer to steps in Telephone Call 1.

Visit 3 (60 [+14] days after Visit 2; 6 months of age): Collection of Safety Information and Vaccination

1) Collect and review the diary card (DC2) with the parent / guardian, including any AEs, medications, or therapy that occurred since the last visit. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) Review warnings and precautions to vaccinations.
3) Review contraindications to subsequent vaccinations and conditions for withdrawal.
4) Measure temperature prior to vaccination. If the temperature is ≥ 38°C (≥ 100.4°F), postpone vaccination until the condition is resolved.
5) Contact IRT system to receive vaccine assignments.
6) Administer the appropriate study vaccines as described for Visit 1.
7) Observe the subject for 30 minutes and record any AE in the source document. In the event of a local reaction, indicate the associated vaccine.
8) Give the parent / guardian a diary card (DC3).
9) Remind the parent / guardian to expect a telephone call 8 days after Visit 3.
10) Remind the parent / guardian to expect a telephone call within 14 days before the next visit, Visit 4, and to bring back the diary card when they return for that visit.
11) Remind the parent / guardian 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)

Refer to steps in Telephone Call 1.

Telephone Call 4 (within 14 days before Visit 4)

1) Contact the subjects' parent/ guardian by telephone within 14 days before Visit 4 to remind them about the forthcoming study visit.
2) If the subject will not continue in the study:
    a) Review the diary card including any AEs, medications, or therapy that occurred since the last visit.
    b) Ask the subject's parent / guardian if the subject has experienced any SAE and / or MAAE in the time since vaccination that has not been reported to the study personnel. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
    c) Ask the subject's parent / guardian to mail the diary card to the site.

Visit 4 (6 months after Visit 3 [Subject must be 12 months of age]): Collection of Safety Information and Vaccination

1) Collect and review the diary card (DC3) with the parent / guardian, including any AEs, medications, or therapy that occurred since the last visit. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.
2) 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 past week by a qualified health care provider, it does not need to be repeated unless there were changes in health status, in which case it may be limited to the affected area.
3) Measure temperature. If the temperature is ≥ 38°C (≥ 100.4°F), postpone vaccination until the condition is resolved.
4) Review warnings and precautions to vaccinations.
5) Review contraindications to subsequent vaccinations and conditions for withdrawal.
6) Contact IRT system to receive vaccine assignments.
7) Administer the following study vaccines. Each vaccine should be administered in an assigned location (see Operating Guidelines) and documented appropriately.
    a) Meningococcal vaccine (MenACYW conjugate vaccine or MENVEO®): inject IM into the anterolateral area of the thigh, preferably the right thigh. Do not administer any other vaccine with the meningococcal vaccine in the same thigh.
    b) PREVNAR 13®: inject IM into the anterolateral area of the thigh, preferably the left thigh (i.e., the opposite leg from that used for meningococcal vaccine administration).
    c) M-M-R® II: inject SC into the outer aspect of the upper arm.
    d) VARIVAX®: inject SC into the outer aspect of the upper arm.

e) When multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. The injection sites should be separated by 1 inch or more so that any local reactions can be differentiated (38).

f) Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the CRF.

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

9) Give the parent / guardian a diary card (DC4)

10) Remind the parent / guardian 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 4)

Refer to steps in Telephone Call 1.

Visit 5 (30 [+21] days after Visit 4): Collection of Safety Information

1) Collect and review the diary card (DC4) with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination. If an SAE, including AESI, has occurred, follow the instruction in Section 10 for reporting it.

2) Give the parent / guardian a MA to record SAE and MAAEs from Visit 5 until the 6-month follow-up phone call.

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

4) Complete the trial termination record.

Safety Follow-up Telephone Call (180 [+30] days after Visit 4): Collection of SAEs (including AESIs) and MAAEs

1) Ask the parent / guardian if the subject has experienced any SAE and / or MAAE since the last study visit. If an SAE, including an AESI, has occurred, follow the instructions in Section 10 for reporting it.

2) Complete the relevant CRFs for this visit.

This call must be made by a qualified person.

A follow-up visit outside the scope of this study protocol can be arranged depending on the information recorded during the phone call.

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

A 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 study period -FVFS (first visit, first subject) to LCLS (last contact, last subject): 17 September 2018 to 05 April 2021

Planned inclusion period - FVFS to FVLS (first visit, last subject): 17 September 2018 to 17 September 2019

Planned end of study: 05 April 2021

Planned date of final clinical study report: 08 October 2021

Telephone call 6 (6-month follow up) of the last subject in either group is considered to be the end of the study.

5.1.6 Early Safety Data Review

No Early Safety Data Review (i.e., no early safety review[s] of preliminary safety data occurring at pre-determined milestones defined in the protocol, with pause in enrollment) is planned for this trial as MenACYW conjugate vaccine has been previously administered to infants, toddlers, and adults with an acceptable safety profile and no safety concerns have been identified in the clinical trials completed so far. There will be an internal team at the level of the Sponsor (Safety Management Team, [SMT]), which will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The SMT is empowered to recommend a pause in both recruitment and/or further vaccination while it investigates any potential signal or concern.

This study may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), or the governing regulatory authorities in the US where the trial is taking place.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial is prematurely terminated for any reason, the Investigator will promptly inform the subjects' parents / guardians and should assure appropriate therapy (if needed) and follow-up.

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 Sanofi Pasteur 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 and / or a parent / guardian voluntarily confirms his or her willingness to participate / allow the child to participate in a particular study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF.

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

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

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

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 / guardian.

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

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 guardian (and by an independent witness if required by local regulations).

4) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures.
5) Infants who received the first dose of hepatitis B vaccine at least 28 days before the first study visit.

5.2.5 Exclusion Criteria

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

1) Participation at the time of study enrollment or in the 4 weeks preceding the first trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure.
2) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks before and / or following any trial vaccination except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.
3) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, PS, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B serogroup-containing vaccine).
4) Previous vaccination against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis A, measles, mumps, rubella, varicella; and *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and /or rotavirus infection or disease.
5) Receipt of more than 1 previous dose of hepatitis B vaccine.
6) Receipt of immune globulins, blood or blood-derived products since birth.
7) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth.
8) Family history of congenital or hereditary immunodeficiency until the immune competence of the potential vaccine recipient is demonstrated.
9) Individuals with blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
10) Individuals with active tuberculosis
11) History of any *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically.
12) History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, varicella, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and /or rotavirus infection/disease.

13) At high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease).

14) History of intussusception.

15) History of any neurologic disorders, including seizures and progressive neurologic disorders.

16) History of Guillain-Barré syndrome.

17) Known systemic hypersensitivity to any of the vaccine components or to latex, or history of a life-threatening reaction to the vaccine(s) used in the trial or to a vaccine containing any of the same substances, including neomycin, gelatin, and yeast[a].

18) Verbal report of thrombocytopenia contraindicating intramuscular vaccination in the Investigator's opinion.

19) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion

20) 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 trial conduct or completion

21) Any condition which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives.

22) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38°C [≥ 100.4°F]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

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

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

5.2.6 Medical History

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

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

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.

- Febrile illness (temperature ≥ 38°C [≥ 100.4°F]) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment.
- Receipt of any vaccine (other than the study vaccines) in the 4 weeks preceding the first study vaccination or planned receipt of any vaccine in the 4 weeks before or following any study vaccination except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

5.2.7.2 Definitive Contraindications

Prior to vaccination, check the complete list of contraindications for each individual vaccine to be administered. For the licensed vaccines refer to the individual current package inserts. For MenACYW conjugate vaccine refer to the Investigator's Brochure.

Should a subject experience an anaphylactic or other significant allergic reaction to the previous dose of vaccine, the Investigator will discontinue vaccination.

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

The following AEs constitute absolute contraindications to subsequent vaccination with any of the study vaccines. If a subject should experience any of these events during the study, that subject is not to receive any additional study vaccines but will continue to be followed up during the study per the study defined safety as applicable.

Meningococcal vaccines (MenACYW conjugate vaccine and MENVEO®):

1) History of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine.
2) History of Guillain-Barré syndrome within 6 weeks after vaccination with a tetanus toxoid-containing vaccine
3) Severe allergic reaction (e.g., anaphylaxis) after a previous dose of vaccine, any component of the vaccines, or any other CRM_{197}, diphtheria toxoid or meningococcal-containing vaccine.

Pentacel®: DTaP-IPV//Hib vaccine

4) Severe allergic reaction (e.g., anaphylaxis) after a previous dose of Pentacel®, any ingredient of Pentacel®, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or *H. influenzae* type b vaccine.
5) Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause.
6) Progressive neurologic disorder including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized.

PREVNAR 13®: pneumococcal 13-valent conjugate vaccine; PCV13

7) Severe allergic reaction (e.g., anaphylaxis) to any component of PREVNAR 13® or any diphtheria toxoid-containing vaccine.

ENGERIX-B®: hepatitis B vaccine

8) Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B®, including yeast.

RotaTeq®: rotavirus vaccine

9) Demonstrated history of hypersensitivity to the rotavirus vaccine or any component of the vaccine.
10) Episode of intussusception.
11) History of severe combined immunodeficiency (SCID).

M-M-R® II: measles, mumps, and rubella vaccine

12) Hypersensitivity to any component of the vaccine, including gelatin.
13) Anaphylactic or anaphylactoid reactions to neomycin
14) Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.
15) Individuals with newly diagnosed (after inclusion in the study), blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
16) Newly diagnosed (after inclusion in the study) primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with acquired immune

deficiency syndrome (AIDS) or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

17) Individuals with family members newly diagnosed (after subject's inclusion in the study) with congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient has been demonstrated.

VARIVAX®: varicella vaccine

18) History of severe allergic reaction to any component of the vaccine (including neomycin and gelatin) or to a previous dose of varicella vaccine.

19) Newly diagnosed (after inclusion in the study) primary or acquired immunodeficiency states, leukemia, lymphoma or other malignant neoplasms affecting the bone marrow or lymphatic system, AIDS, or other clinical manifestations of infection with human immunodeficiency virus (HIV).

20) Individuals receiving immunosuppressive therapy, including individuals receiving immunosuppressive doses of corticosteroids.

    A substantially immunosuppressive steroid dose is considered to be ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent. For further information on contraindications to Varivax vaccination in persons receiving immunosuppressive therapies, consult the General Best Practices Guidelines for Immunization (39), the Recommendations of the Advisory Committee on Immunization Practices (ACIP) (40), and the Pinkbook (41).

21) Active, untreated tuberculosis.

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

5.2.7.3 Warnings and Precautions to Vaccination

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

5.2.8 Conditions for Withdrawal

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

A subject may be withdrawn from the study:

- 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 / guardian (dropout)

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

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

Withdrawn subjects will not be replaced.

5.2.9 Lost to Follow-up Procedures

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

5.2.10 Classification of Subjects Who Discontinue the Study

For any subject who discontinues the study prior to completion, the most significant reason for early termination will be checked in the CRB. Reasons are listed below from the most significant to the least significant (refer to the 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 9.1.1.1. 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 5.2.9. The certified letter was sent by the Investigator and returned unsigned, and the parent/guardian did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: In case of significant non-compliance with the protocol (e.g., deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). If the subject experiences a definitive contraindication that is a protocol deviation. The parent/guardian signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit.
Withdrawal by Parent / Guardian	To be used: When the parent/guardian indicated unwillingness to continue in the study When the parent/guardian made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (e.g., subject is relocating, inform consent withdrawal, etc.)

5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact the parent/guardian of 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's parent/guardian withdrew informed consent and specified that they do not want to be contacted again and it is documented in the source document, the site will not attempt to obtain further safety information.

If the subject's status at the end of the study is "Withdrawal by Parent / Guardian", the site will attempt to contact them for the 6-month follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

For subjects where the reason for early termination is voluntary withdrawal, the site will attempt to contact them for the 6-month follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

5.3 Safety Emergency Call

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

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

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

5.4 Modification of the Study and Protocol

Any amendments to this study plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments (e.g., 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 should be notified, but no formal approval will be required.

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 country 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 organizations used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subjects' parents / guardians and should assure appropriate subject therapy and/or follow-up.

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

6 Vaccines Administered

For proper management of the supply and accountability of the products, MenACYW conjugate vaccine and MENVEO® will be considered as Investigational Medicinal Product (IMP) and all other vaccines as Non-Investigational Medicinal Product (NIMP).

6.1 Identity of the Investigational Products

6.1.1 Identity of Study Product

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

Form: Liquid solution

Dose: 0.5 milliliter (mL)

Route: IM

Batch number: To be determined

6.1.1.1 Composition

Each 0.5 mL dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following ingredients:

Meningococcal capsular polysaccharides:

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

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

6.1.1.2 Preparation and Administration

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

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

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

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 Group 1 will receive MenACYW conjugate vaccine at 2, 4, 6, and 12 months of age.

6.1.2 Identity of Control Product

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

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

Dose: 0.5 mL

Route: IM

Batch number: To be determined

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

6.1.2.1 Composition

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

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

Other ingredients per 0.5 mL dose: residual formaldehyde .....≤ 0.30 mcg

6.1.2.2 Preparation and Administration

MENVEO® is supplied in 2 vials, a lyophilized MenA conjugate vaccine component to be reconstituted with the accompanying MenCYW-135 liquid conjugate component. A single dose after reconstitution is 0.5 mL. See the MENVEO® package insert (37).

The procedures for administering the control product are the same as those described for the trial product in Section 6.1.1.2. Each 0.5 mL dose is to be injected IM as indicated in the Operating Guidelines and Section 5.1.4.

6.1.2.3 Dose Selection and Timing

Subjects in Group 2 will receive MENVEO® at 2, 4, 6, and 12 months of age.

6.2 Identity of Other Products

6.2.1 Identity of Other Product 1

Pentacel®: (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Sanofi Pasteur Ltd, Toronto, Ontario, Canada)

Form: Liquid DTaP-IPV used to reconstitute lyophilized ActHIB®
Dose: 0.5 mL
Route: IM
Batch number: To be determined

6.2.1.1 Composition

Each 0.5 mL dose contains:

Diphtheria toxoid..... 15 Limit of Flocculation (Lf)
Tetanus toxoid ..... 5 Lf

Acellular pertussis antigens:

Pertussis toxin (PT) .....20 µg
Filamentous hemagglutinin (FHA).....20 µg

Pertactin (PRN) ..... 3 µg
Fimbriae Types 2 and 3 (FIM) ..... 5 µg

Inactivated polioviruses:

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

H. influenzae type b (PRP) ..... 10 µg
Tetanus toxoid (PRP-T) ..... 24 µg

Excipients:

Aluminum phosphate (0.33 mg aluminum) (adjuvant) ..... 1.5 mg
Polysorbate 80 ..... approximately 10 parts per million (ppm) by calculation
Sucrose ..... 42.5 mg
Residual formaldehyde ..... ≤ 5 µg
Residual glutaraldehyde ..... < 50 ng
Residual bovine serum albumin ..... ≤ 50ng
2-phenoxyethanol ..... 3.3 mg (0.6% v/v)
Neomycin ..... < 4 picogram (pg)
Polymyxin B sulfate ..... < 4 pg

6.2.1.2 Preparation and Administration

Pentacel® is supplied as a liquid vaccine component (DTaP-IPV component) that is combined through reconstitution with a lyophilized vaccine component (ActHIB vaccine), both in single dose vials. A single dose after reconstitution is 0.5 mL. See the Pentacel® package insert (42).

The procedures for administering the product are the same as those described in Section 6.1.1.2.

Each 0.5 mL dose is to be injected IM as indicated in the Operating Guidelines and Section 5.1.4.

6.2.1.3 Dose Selection and Timing

All subjects will receive Pentacel® at 2, 4, and 6 months of age.

6.2.2 Identity of Other Product 2

PREVNAR 13®: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc, Philadelphia, PA, USA)

Form: Suspension for injection

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.2.2.1 Composition

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

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

Excipients:

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

6.2.2.2 Preparation and Administration

PREVNAR 13® is supplied in a single-dose prefilled syringe. See the PREVNAR 13® package insert (43).

The procedures for administering the product are the same as those described in Section 6.1.1.2.

Each 0.5 mL dose is to be injected IM as indicated in the Operating Guidelines and Section 5.1.4.

6.2.2.3 Dose Selection and Timing

All subjects will receive PREVNAR 13® at 2, 4, 6, and 12 months of age.

6.2.3 Identity of Other Product 3

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

Form: Oral solution
Dose: 2 mL
Route: Oral
Batch number: To be determined

6.2.3.1 Composition

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

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

The reassortants are suspended in a buffered stabilizer solution.

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

6.2.3.2 Preparation and Administration

RotaTeq® is supplied in a container consisting of a squeezable plastic dosing tube with a twist-off cap, allowing for direct oral administration. See the RotaTeq® package insert (44).

The procedures for administering the product are the same as those described in Section 6.1.1.2

Each 2 mL dose is to be administered orally, as indicated in the Operating Guidelines and Section 5.1.4.

6.2.3.3 Dose Selection and Timing

All subjects will receive RotaTeq® at 2, 4, and 6 months of age.

6.2.4 Identity of Other Product 4

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

Form: Suspension for injection

Dose: 0.5 mL

Route: IM

Batch number: To be determined

6.2.4.1 Composition

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

Excipients:

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

6.2.4.2 Preparation and Administration

ENGERIX-B® is supplied as 0.5 mL prefilled syringes. See the ENGERIX-B® package insert (45).

The procedures for administering the product are the same as those described in Section 6.1.1.2.

Each 0.5 mL dose is to be injected IM, as indicated in the Operating Guidelines and Section 5.1.4.

6.2.4.3 Dose Selection and Timing

All subjects will receive ENGERIX-B® at 2 and 6 months of age.

Note: The first dose of hepatitis B vaccine must be given at least 28 days prior to study enrollment.

6.2.5 Identity of Other Product 5

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

Form: Lyophilized live virus vaccine

Dose: 0.5 mL

Route: SC

Batch number: To be determined

6.2.5.1 Composition

Each 0.5 mL dose contains live attenuated virus:

Measles virus (derived from Ender's Edmonston strain) propagated in chick embryo cell culture.....not less than 1000 $TCID_{50}$[a]
Mumps virus (Jeryl Lynn™ [B level] strain) propagated in chick embryo cell culture .....not less than 12,500 $TCID_{50}$[a]
Rubella virus (Wistar RA 27/3 strain) propagated in WI-38 human diploid lung fibroblasts .....not less than 1000 $TCID_{50}$[a]

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

6.2.5.2 Preparation and Administration

M-M-R® II is supplied as a lyophilized vaccine to be reconstituted using the accompanying sterile diluent. See the M-M-R® II package insert (46).

The procedures for administering the product are the same as those described in Section 6.1.1.2.

Each 0.5 mL dose is to be injected SC in the outer aspect of the upper arm as indicated in the Operating Guidelines and Section 5.1.4.

[a] $TCID_{50}$ = tissue culture infectious doses 50%

6.2.5.3 Dose Selection and Timing

All subjects will receive M-M-R® II at 12 months of age.

6.2.6 Identity of Other Product 6

VARIVAX®: Varicella Virus Vaccine Live (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)

Form: Suspension for injection

Dose: 0.5 mL

Route: SC

Batch number: To be determined

6.2.6.1 Composition

Each approximately 0.5 mL dose contains:

Live, attenuated Oka/Merck varicella virus ..... at least 1350 plaque-forming units (PFU)

Excipients:

Sucrose ..... 25 mg
Hydrolyzed gelatin ..... 12.5 mg
Sodium chloride ..... 3.2 mg
Monosodium L-glutamate ..... 0.5 mg
Sodium phosphate dibasic ..... 0.45 mg
Potassium phosphate monobasic ..... 0.08 mg
Potassium chloride..... 0.08 mg

The vaccine contains residual components of MRC-5 cells including DNA and protein and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum. The vaccine contains no preservative.

6.2.6.2 Preparation and Administration

VARIVAX® is supplied as a lyophilized vaccine to be reconstituted using the accompanying sterile diluent. See the VARIVAX® package insert (47).

The procedures for administering the product are the same as those described in Section 6.1.1.2.

Each 0.5 mL dose is to be injected SC into the outer aspect of the upper arm, as indicated in the Operating Guidelines Section 5.1.4.

6.2.6.3 Dose Selection and Timing

All subjects will receive VARIVAX® at 12 months of age.

6.3 Product Logistics

6.3.1 Labeling and Packaging

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

The investigational and control products are blinded at the level of the carton.

All of the concomitant products will retain original commercial labeling and packaging with no additional labels to be applied.

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

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

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

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

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

At the site, products must be kept in a secure place with restricted access. The Study and Control Products (MenACYW conjugate vaccine or MENVEO®) will be stored in a refrigerator at a temperature ranging from +2°C to +8°C and never frozen. All commercially labeled products should be stored according to the manufacturer's instructions. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the study site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

6.3.2.3 Product Accountability

The person in charge of product management at the site will maintain records of product delivery to the study site, product inventory at the site, the dose 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 (e.g., because the syringe 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

This trial is a modified double-blind trial, which means that the subject's parent / guardian, 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 will also remain blinded to treatment assignments throughout the trial until database lock.

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 Conference on Harmonisation (ICH) E2A. In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (i.e., 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 / guardian signs the ICF will be randomly assigned to Group 1 or Group 2 in a 3:1 ratio such that Group 1 will have approximately 2310 subjects and Group 2 will have approximately 770 subjects.

Site staff will connect to the IRT system, enter the identification and security information, and confirm a minimal amount of data in response to IRT system prompts. The IRT system will then provide the vaccine assignment and subject number. The full detailed procedures for group allocation are described in the Operating Guidelines. If 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 840000100005 is the fifth subject enrolled in Center Number 1 in the US (840 being the US country code).

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

6.6 Treatment Compliance

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

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

6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications including but not limited to other therapies (e.g., blood products), should be recorded in the source documents. All new medications prescribed for new medical conditions / AEs during study participation should also be recorded in the source documents.

Documentation in the CRB of concomitant medication(s) will be limited to specific categories of medication(s) (Categories 1 and 2 as detailed below). Those will include Category 1 and 2 medications ongoing at the time of inclusion in the study, or started at any time during the subject's participation in the trial.

Collection Period in Source Documents

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

Categories of Reportable Medications and Reporting Period

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

Category 1: Reportable medications with potential impact on the evaluation of the safety of the study vaccines. For example, antipyretics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids (therapy duration less than 2 weeks), and other immune modulators.

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:
  - Influenza and other non-study vaccines: Influenza vaccine in the 2 weeks (14 days) preceding the trial vaccination up to the last study visit and any other vaccines (other than the study vaccine) in the 4 weeks preceding the trial vaccination up to the last study visit
  - Immune globulins, blood, or blood-derived products: used in the 3 months preceding the first trial vaccination and up to the last study visit
  - 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

[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 2 categories in the other source documents.

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 study visit.

- Category 2 medications will be reported in the CRB according to the collection period detailed above up to the last study visit.

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 or 2)
- 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 or 2, the detailed information will be collected in the source documents only.

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

7 Management of Samples

This is a safety study; no blood samples will be collected.

8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs, CRBs, SAE reporting forms, diary cards, memory aids, and other study documents, as well as with the following study materials: all study vaccines, 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, 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

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

Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products. Please see Operating Guidelines for further details.

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 Observational Endpoints and Assessment Methods

9.1.1 Safety

9.1.1.1 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 (e.g., asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious* which is based on 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)

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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.

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

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

Solicited Reaction:

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

Examples of solicited reactions include injection site tenderness or irritability occurring between D0 and D07 after vaccination.

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

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

The assessment of these reactions by the Investigator is mandatory.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if vomiting between D0 and D07 is a solicited reaction (i.e., pre-listed in the protocol and CRB), then vomiting starting on D07 is a solicited reaction, whereas vomiting 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 vomiting, fever, as well as localized or topical manifestations that are not associated with the vaccination or administration site (e.g., 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 (e.g., regulators) might also be warranted.

Medically-Attended Adverse Event (MAAE)

An MAAE is defined, for the purpose of this study, as a new onset of a condition that prompts the subject or subject's parent/guardian to seek unplanned medical advice at a health care provider's office or Emergency Department. This definition excludes pre-planned medical office visits for

routine pediatric check-ups or follow-up visits of chronic conditions with an onset prior to entry in the study. Health care provider contact made over the phone or by email will be considered a physician office visit for the purpose of MAAE collection. The outcome of the health care provider contact (whether it results in a prescription or not) will not be considered as a basis for reporting the event as an MAAE and all contacts should be reported. Sufficient data should be collected for the event to allow an assessment of the causality and diagnosis, if possible.

9.1.1.2 Safety Endpoints

The endpoints for the evaluation of safety are:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) injection site reactions occurring up to D07 after each vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to D07 after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (), and whether the event led to early termination from the study for MAAEs throughout the trial, from Visit 1 to the 6-month follow-up contact after the last vaccination.

9.1.1.3 Safety Assessment Methods

At each vaccination visit, the Investigator or a delegate will perform a physical examination on the basis of relevant medical history according to the Investigator's clinical judgment and will ask the parent / guardian about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

9.1.1.3.1 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.

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

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

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

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination

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

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

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

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

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

CRB term (MedDRA LLT)	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
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 / guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important Notes for the Accurate Assessment of Temperature:

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

9.1.1.3.3 Unsolicited Adverse Events

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

Information on SAEs will be collected and assessed throughout the study, from the time of vaccination until 6 months 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 (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE. See Section 10 for further details on SAE reporting.

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

- Start and stop dates[a]
- Intensity of the event:

  For measurable unsolicited AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 9.1 and Table 9.2).

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

  - Grade 1: A type of AE 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.

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

- Grade 2: A type of AE 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 AE 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 9.1.1.3.6.

  Action taken for each AE (e.g., medication)

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination
- Whether the AE was serious

  For each SAE, the Investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures).
- Whether the AE caused study discontinuation

9.1.1.3.4 Adverse Events of Special Interest

An AESI is defined as an 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) (48) (49)
- Kawasaki disease (50) (51) (52)
- Guillain-Barré syndrome (53)
- Idiopathic thrombocytopenic purpura (ITP) (54) (55)

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

No safety concerns relating to these AESIs have been identified with the use of MenACYW conjugate vaccine in the completed clinical trials. Because of their medical importance and to ensure expedited communication to the Sponsor, these AESIs are to be considered and collected as SAEs and reported to the Sponsor according to the procedure described in Section 10. Further

instructions on the data collection for these events and the relevant definitions will be provided in the Operating Guidelines.

9.1.1.3.5 Medically-Attended Adverse Events

MAAE information will be collected throughout the study. MAAEs will be recorded as unsolicited AEs for up to D30 after each vaccination and as MAAEs until the next study visit on the appropriate diary cards. MAAEs that occur from D31 after the last vaccination visit until the 6-month follow up phone call will be recorded in the appropriate memory aid. An MAAE that occurs within the study period but meets the definition of an SAE should be reported only on the SAE Reporting Form but not on the MAAE page of the CRB. The Investigator will assess the causal relationship between the MAAE and the investigational or study product as either "Not related" or "Related", as described in Section 9.1.1.3.6.

9.1.1.3.6 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.

AEs 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.

9.2 Immunogenicity

There are no objectives for immunogenicity in this study.

9.3 Efficacy

There are no objectives for efficacy in this 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 (e.g., medical records, discharge summary) 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

SAEs occurring during a subject's participation in the study or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The Investigator (licensed physician [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 RMO 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 RMO, [redacted], MD, PhD. 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 (e.g., 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 (e.g., medical records, discharge summary, autopsy) may be requested by the GPV Department.

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

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

Any SAE that occurs after a subject has completed the study but that is likely to be related to the investigational product(s), other products (e.g., 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 9.1.1.3.6.

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

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

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

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

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

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.1.1.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Parents / guardians will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct parents / guardians on how to correctly use these tools.

The 6-month follow-up will be done by interviewing subjects' parents / guardians over the telephone using a questionnaire to capture MAAEs, SAEs and AESIs, if applicable. A memory aid will be provided to the subjects' parents / guardians at the preceding study visit to help them record information on events occurring between this visit and the 6-month follow-up.

Relevant information will be transcribed into the AE CRF. Any SAEs captured during this 6-month follow-up period will be reported and followed-up as per the normal process for reporting SAEs.

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

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

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

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

11.2 Data Management

Management of SAE Data

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

The information from the GPV database cases will be reconciled with that in the clinical database.

Management of Clinical Data

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

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

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

11.3 Data Review

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

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

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

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

12.1.1 Hypotheses and Statistical Methods for the Objectives

12.1.1.1 Hypotheses

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

12.1.1.2 Statistical Methods

Safety analysis will include but not be limited to the following:

- The number and percentage of subjects reporting any solicited injection site reactions and solicited systemic reactions occurring from D0 to D07 after each vaccination will be summarized by study group for intensity, time of onset period, days of occurrence, and action taken.
- Immediate unsolicited systemic AEs and unsolicited AEs occurring up to D30 after each vaccination will be summarized.
- The number and percentage of subjects reporting any unsolicited non-serious AEs will be summarized by study group, 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 of any MAAEs will be summarized throughout the trial.
- The number and percentage of subjects reporting at least one of any SAEs will be summarized by study group, seriousness criterion, outcome, and by MedDRA preferred term and SOC, as well as 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.
- Exact (Clopper-Pearson) 2-sided 95% confidence intervals (CIs) will be calculated for the percentages. (56)

12.2 Analysis Sets

Six analysis sets will be used: the Overall Safety Analysis Set for any dose (SafAS), Safety Analysis Set for vaccination 1 (SafAS1), Safety Analysis Set for vaccination 2 (SafAS2), Safety Analysis Set for vaccination 3 (SafAS3), Safety Analysis Set for vaccination 4 (SafAS4), and Safety Analysis Set 5 for all 4-dose vaccinations (SafAS5).

12.2.1 Full Analysis Set

Not applicable to this study.

12.2.2 Safety Analysis Set

The SafAS is defined as those subjects who have received at least 1 dose of the study vaccine(s) [a] and have any safety data available. Specific safety analysis will be defined and used after each vaccination. Safety analysis after all 4-dose vaccinations will also be conducted as well.

All subjects will have their safety analyzed after each dose according to the vaccine they actually received, after any dose, and after all 4 doses according to the vaccine received at the first dose.

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

12.2.2.1 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).

12.2.2.2 Safety Analysis Set for Vaccination at 2 Months of Age

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

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

12.2.2.3 Safety Analysis Set for Vaccination at 4 Months of Age

The SafAS2 is defined as those subjects who have received the study vaccine at Visit 2 around 4 months of age and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccine they actually received at that visit.

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

12.2.2.4 Safety Analysis Set for Vaccination at 6 Months of Age

The SafAS3 is defined as those subjects who have received the study vaccine at Visit 3 at around 6 months of age and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccine they actually received at this visit.

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[a] A study vaccine is any vaccine that is administered as part of the study, including the investigational product (MenACYW conjugate vaccine), the control vaccine (Menveo), and the routine vaccines .

Safety data recorded for a vaccine received out of the protocol design at Visit 3 will be excluded from the analysis (and listed separately).

12.2.2.5 Safety Analysis Set for Vaccination at 12 Months of Age

The SafAS4 is defined as those subjects who have received the study vaccine at Visit 4 at around 12 months of age and have any safety data available. All subjects will have their safety analyzed after this dose according to the vaccine they actually received at that visit.

Safety data recorded for a vaccine received out of the protocol design at Visit 4 will be excluded from the analysis (and listed separately).

12.2.2.6 Safety Analysis Set for all 4-dose Vaccinations

The SafAS5 is defined as those subjects who have received all 4 doses of the study vaccine (3 doses in infancy and 1 dose in the second year of life at 12 months of age) and have any safety data available. All 4-dose vaccinations received in a series should be either all MenACYW conjugate vaccine or all MENVEO®.

Safety data recorded for subjects not receiving all 4 doses of MenACYW or MENVEO® will be excluded from the analysis (and listed separately).

12.2.3 Per-Protocol Analysis Set

Not applicable to this study.

12.2.4 Populations Used in Analyses

The safety analysis will be performed on the Safety Analysis Sets SafAS, and SafAS1 through SafAS5.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

No immunogenicity data will be collected.

12.3.3 Efficacy

No efficacy data will be collected.

12.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

12.5 Determination of Sample Size and Power Calculation

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

Though there are no statistically powered hypotheses, the overall study cohort of 3080 subjects will provide a probability of approximately 95% of observing any AE with a true incidence of 0.15%. In the treatment arm with 2310 subjects, there is a probability of approximately 95% of observing any AE with a true incidence of 0.2%.

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

[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.

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 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 the FDA in the US (57).

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 (i.e., before the inclusion of the first subject) in the first center the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the 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 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.

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, product management, cold-chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.

After all protocol procedures have been completed and the data have been entered into the 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 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

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

13.7 Publication Policy

Data derived from this study are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the study must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives recognition to the study group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

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

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

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15 Signature Page

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