NCT03632720

Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Infants and Toddlers when Administered Using a 1+1 Schedule in a National Immunization Schedule Having a Meningococcal Group B Vaccine as Standard of Care

Phase III, open-label, randomized, parallel-group, active-controlled, multi-center study to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine when administered concomitantly with a Meningococcal Group B vaccine and other routine pediatric vaccines as part of the National Immunization Schedule in healthy infants and toddlers in the United Kingdom

Clinical Study Protocol, Amendment 3

Health Authority File Numbers:	EudraCT #: 2017-004520-30
WHO Universal Trial Number (UTN):	U1111-1183-6530
Study Code:	MET52
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid Solution / Intramuscular
Indication For This Study:	MenACYW conjugate vaccine administered to healthy infants at 3 and 12 months of age
Manufacturer:	Same as Sponsor
Coordinating Investigator:	[redacted]
Sponsor's Responsible Medical Officer:	[redacted]

Global Safety Officer: [redacted]

Clinical Trial Manager: [redacted]

Version and Date of the Protocol: Version 6.0 dated 03 May 2021

History of Protocol Versions

Previous versions to the protocol

Version	Date	Comments
1.0	28 November 2017	Version not approved by the IEC/IRB
2.0	02 February 2018	Version not approved by the IEC/IRB
3.0	23 February 2018	Version approved by the IEC/IRB/ First version used in the study
4.0	06 December 2018	Version approved by the IEC/IRB/ Amendment 1
5.0	27 June 2019	Version approved by the IEC/IRB/ Amendment 2

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	MenACYW conjugate vaccine
Active Substances:	Capsular polysaccharide from meningococcal serogroups A, C, W, and Y conjugated to tetanus toxoid
Title of the Study:	Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Infants and Toddlers when Administered Using a 1+1 Schedule in a National Immunization Schedule Having Meningococcal Group B Vaccine as Standard of Care
Development Phase:	Phase III
Coordinating Investigator:	[redacted]
Study Sites:	This will be a multi-center study in the United Kingdom (UK). Investigators and sites are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Q4 2018 to Q4 2022
Study Design, Schedule of Study Procedures and Methodology:	Phase III, open-label, randomized, parallel-group, active-controlled, multi-center study to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine when administered concomitantly with a meningococcal group B vaccine (Bexsero®) and other routine pediatric vaccines as part of the National Immunization Schedule in healthy infants and toddlers in the UK. Approximately 800 healthy infants aged ≥ 56 to ≤ 89 days (approximately 2 months of age) will be randomized 2:2:1 to the following 3 groups: **Group 1**: MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero® at 2, 4, and 12 to 13 months of age **Group 2**: MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero® at 2 and 4 months of age **Group 3**: Bexsero® at 2, 4, and 12 to 13 months of age Routine pediatric vaccines will be given to subjects in all groups according to the UK immunization schedule: • Infanrix hexa® (Combined Diphtheria-Tetanus-acellular Pertussis [DTPa], Hepatitis B, Inactivated Poliovirus and *Haemophilus influenzae* type b Vaccine; DTPa-HBV-IPV+Hib) at 2, 3, and 4 months of age • Rotarix® (rotavirus vaccine; RV) at 2 and 3 months of age • Prevenar 13® (pneumococcal 13-valent conjugate vaccine; PCV13) at 2 and 4 months of age

	The routine pediatric vaccines administered in the second year of life (Menitorix®, Priorix®/M-M-RVAXPRO®, and PCV13 [for all groups], and Bexsero® [for Group 2]) may be given as per standard of care at the last study visit after completion of study procedures (Visit 5 at 13 to 14 months). For Group 2, Bexsero® will be provided by the Sponsor to complete the vaccination series for subjects enrolled in this group. Subjects in Group 3 will be offered a single dose of the licensed ACWY conjugate meningococcal vaccine (Nimenrix®). This is a non-study vaccine to be administered at least 30 days after the last study visit (Visit 5) at an additional optional visit and will be outside the scope of the study evaluations. No immunogenicity and safety data will be collected after the administration of these vaccines. Blood Sampling Subjects will provide the following blood samples: Groups 1 and 2: 160 subjects in each group will be randomized to have 3 blood draws at the intervals mentioned below. The remaining subjects will only have 1 blood draw at Visit 5. Group 3: all 160 subjects will have 3 blood draws. For the subjects randomized to have 3 blood draws in Group 1 and Group 2, the first 2 blood draws will be performed in a staggered way – approximately half of the subjects (~70 subjects in each group) will have blood draws at Visit 2 and Visit 3 (subset A), and the remaining half (~90 subjects in each group) will have blood draws at Visit 3 and Visit 4 (subset B). The third blood draw will be performed at Visit 5 for all subjects. **Subset A** (~70 subjects in each group): • a pre-vaccination blood sample at Visit 2 • a blood sample at Visit 3 (30 days after vaccination at Visit 2) • a blood sample at Visit 5 (30 days after vaccination at Visit 4) **Subset B** (~90 subjects in each group): • a blood sample at Visit 3 (30 days after vaccination at Visit 2) • a pre-vaccination blood sample at Visit 4 • a blood sample at Visit 5 (30 days after vaccination at Visit 4) For the subjects randomized to Group 3, the first 2 blood draws will be performed in a staggered way – approximately half of the subjects (~70 subjects) will have blood draws at Visit 2 and Visit 3 (subset A), and the remaining half (~90 subjects) will have blood draws at Visit 3 and Visit 4 (subset B). The third blood draw will be performed at Visit 5 for all subjects. **Subset A** (~70 subjects): • a pre-vaccination blood sample at Visit 2 • a blood sample at Visit 3 (30 days after vaccination at Visit 2) • a blood sample at Visit 5 (30 days after vaccination at Visit 4) **Subset B** (~90 subjects): • a blood sample at Visit 3 (30 days after vaccination at Visit 2) • a pre-vaccination blood sample at Visit 4 • a blood sample at Visit 5 (30 days after vaccination at Visit 4)

Antibodies to meningococcal serogroups A, C, W, and Y antigens will be measured by serum bactericidal assay using human complement (hSBA) for all subjects providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4, and Visit 5), and by serum bactericidal assay using baby rabbit complement (rSBA) for a subset of subjects (the first 100 subjects randomized to have 3 blood draws in each of the 3 groups).

Table S1: Schedule of vaccinations and blood draws

Group	Procedure	Visit (age in months)				
		Visit 1 (2 mo)	**Visit 2 (3 mo)**	**Visit 3 (4 mo)**	**Visit 4 (12-13 mo)**	**Visit 5* (13-14 mo)**
1	Vaccine(s):	**BX / R**	**IP / R**	**BX / R**	**IP / BX**	R
	Blood draw:		X†	X†	X†	X
2	Vaccine(s):	**BX / R**	**IP /R**	**BX / R**	**IP**	R / BX
	Blood draw:		**X†**	**X†**	X†	**X**
3‡	Vaccine(s):	**BX / R**	**R**	**BX / R**	**BX**	R
	Blood draw:		X†	**X**	X†	**X**

*Vaccines administered outside of the study will be given after the study procedures have been completed
†From a subset of subjects
‡Licensed ACWY conjugate meningococcal vaccine (Nimenrix®) will be offered at least 30 days after the last study visit (Visit 5) at an additional optional visit.
IP: MenACYW conjugate vaccine; BX: Bexsero®
R: Routine vaccines

Note: Each visit may be conducted at the site (site visit) or at the subject's home (home visit).

Collection of safety data

Safety data will be collected as follows: Immediate unsolicited systemic adverse events (AEs) will be collected within 30 minutes after each vaccination. Solicited AEs will be collected from Day (D) 0 to D07 after each vaccination; unsolicited AEs will be collected from D0 to D30 after each vaccination; serious adverse events (SAEs) (including adverse events of special interest [AESIs]) will be collected throughout the study from D0 to Visit 5. All AESIs collected in this study will be considered as SAEs.

- All subjects will be observed for 30 minutes after each vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the electronic case report book (CRB).
- The subject's parent / legally acceptable representative will record information in a diary card about solicited reactions from D0 to D07 after all vaccinations and unsolicited AEs from D0 until the next study visit. SAEs (including AESIs) will be recorded throughout the study.
- The subject's parent / legally acceptable representative will record information in a diary card about SAEs (including AESIs) 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.

	• The subject's parent/ legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the trial. • Staff will contact the subject's parent/ legally acceptable representative by telephone 8 days after vaccination(s) at Visit 1, Visit 2, Visit 3 and Visit 4 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. • The completed diary cards will each be collected and reviewed with the subject's parent/ legally acceptable representative at the subsequent visit.
Interruption of the Study:	The study may be discontinued at any time if new data about the investigational product resulting from this study or any other studies become available, or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in the UK where the study 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 study is prematurely terminated for any reason, the Investigator will promptly inform the subjects' parents/legally acceptable representatives and should assure appropriate therapy and follow-up. There will be an internal team at the level of the Sponsor (Safety Management Team, [SMT]), which will review the data being generated from all the ongoing studies with MenACYW conjugate vaccine at regular intervals for any new safety signals or safety concerns. The SMT is empowered to recommend a pause in both recruitment and / or further vaccination while it investigates any potential signal or concern.
Primary Objective:	To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, W, and Y in terms of hSBA vaccine seroprotection (antibody titer ≥ 1:8) when MenACYW conjugate vaccine is administered concomitantly with Bexsero® in the second year of life compared to when MenACYW conjugate vaccine is given alone.
Primary Endpoint:	Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y measured by hSBA assessed 30 days after vaccination(s) at 12 to 13 months of age (Group 1 versus Group 2)

Secondary Objectives:	1) To compare the hSBA antibody response in terms of geometric mean titers (GMTs) against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine is administered concomitantly with Bexsero® or when MenACYW conjugate vaccine is given alone in the second year of life 2) To describe the hSBA and rSBA antibody responses against meningococcal serogroups A, C, W, and Y before and after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age, before and after the 2nd dose of MenACYW conjugate vaccine administered at 12 to 13 months of age for Group 1 and Group 2 3) To describe the hSBA and rSBA antibody persistence against meningococcal serogroups A, C, W, and Y after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age for Group 1 and Group 2
Secondary Endpoints:	1) Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA 30 days after vaccinations with MenACYW conjugate vaccine concomitantly with Bexsero® or alone at 12 to 13 months of age (Group 1 vs Group 2) 2) Before and 30 days after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age, before and 30 days after the 2nd dose of MenACYW conjugate vaccine administered at 12 to 13 months of age, the following endpoints against meningococcal serogroups A, C, W, and Y will be assessed using hSBA and rSBA (subset) for Group 1 and Group 2: - hSBA and rSBA antibody titer (GMT) - titer distribution and RCDC - hSBA antibody titer ≥ 1:4 and titers ≥ 1:8 - rSBA antibody titer ≥ 1:8 and titers ≥ 1:128 - antibody titer ≥ 4-fold rise from pre-vaccination to post-vaccination - hSBA and rSBA vaccine seroresponse* *hSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as: - For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16. - For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer. *rSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as: - For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:32. - For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer. 3) 30 days after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age, and before the 2nd dose of MenACYW conjugate vaccine administered at 12 to 13 months of age, the following endpoints against meningococcal serogroups A, C, W, and Y will be assessed using hSBA and rSBA (subset) for Group 1 and Group 2 antibody persistence evaluation: - hSBA and rSBA antibody titer (GMT) - hSBA antibody titer ≥ 1:4 and titers ≥ 1:8 - rSBA antibody titer ≥ 1:8 and titers ≥ 1:128

Observational Objectives:	***Immunogenicity*** 1) To describe the prevalence of antibodies against meningococcal serogroups A, C, W, and Y in Group 3 after Bexsero® administration ***Safety*** 1) To describe the safety of MenACYW conjugate vaccine when given alone and when administered concomitantly with Bexsero® at 12 to 13 months of age 2) To describe the safety of Bexsero® when given alone and when administered concomitantly with MenACYW conjugate vaccine at 12 to 13 months of age 3) To describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine vaccines at 3 months of age 4) To describe the safety of routine vaccines when given alone or administered concomitantly with MenACYW conjugate vaccine at 3 months of age 5) To describe the safety profile of routine vaccines and Bexsero® administered concomitantly at 2 and 4 months of age
Observational Endpoints:	***Immunogenicity*** 1) At 3 months of age, 4 months of age, before and 30 days after vaccination with Bexsero® at 12 to 13 months of age, the following endpoints against meningococcal serogroups A, C, W, and Y will be assessed using hSBA and rSBA (subset) for Group 3: - hSBA and rSBA antibody titer (GMT) - hSBA antibody titer ≥ 1:4 and titers ≥ 1:8 - rSBA antibody titer ≥ 1:8 and titers ≥ 1:128
	Safety The following endpoints will be used for all subjects for the evaluation of the Safety Objectives: • 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(s) • 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 CRB) injection site reactions occurring up to D07 after each vaccination(s) • 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(s) • Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (for

	systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination(s) • 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) after vaccination(s) from D0 through the end of the trial
Planned Sample Size:	Approximately 800 subjects are planned to be enrolled (with an estimated non-adherence rate of 30%) Group 1: n=320 enrolled, 224 evaluable Group 2: n=320 enrolled, 224 evaluable Group 3: n=160 enrolled, 112 evaluable
Duration of Participation in the Study:	The duration of each subject's participation in the study will be approximately 11 to 12 months.
Investigational Product: ***Form:*** ***Composition:*** ***Route:*** **Batch Number:**	**MenACYW conjugate vaccine**: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA) Liquid solution 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. Intramuscular (IM) To be determined
Control Product: ***Form:***	**Bexsero®**: Meningococcal group B Vaccine (rDNA, component, adsorbed) Suspension for injection in pre-filled syringe

Composition:	Each 0.5 mL dose contains: Recombinant *Neisseria* (*N*) *meningitidis* group B NHBA fusion protein*†‡ ..... 50 µg Recombinant *N meningitidis* group B NadA protein*†‡ ..... 50 µg Recombinant *N meningitidis* group B fHbp fusion protein*†‡ ..... 50 µg Outer membrane vesicles from *N meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA Pl.4† ..... 25 µg *Produced in *E. coli* cells by recombinant DNA technology †Adsorbed on aluminium hydroxide (0.5 mg Al^{3+}) ‡ NHB (Neisseria Heparin Binding Antigen), NadA (Neisserial adhesin A), fHbp (factor H binding protein). The vaccine contains the following excipients: sodium chloride, histidine, sucrose, water for injections.
Route:	Deep IM
Batch Number:	To be determined
Other Product 1:	**Infanrix hexa®**: Diphtheria (D), tetanus (T), pertussis (acellular component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and *Haemophilus influenzae* type b (Hib) conjugate vaccine (adsorbed) (GlaxoSmithKline UK, Middlesex, UK)
Form:	Powder and suspension for suspension injection
Composition:	After reconstitution, each 0.5 mL dose contains: Diphtheria toxoid* ..... not less than 30 International Units (IU) Tetanus toxoid* ..... not less than 40 IU *Bordetella pertussis* antigens: Pertussis toxoid* ..... 25 µg Filamentous hemagglutinin (FHA)* ..... 25 µg Pertactin (PRN) ..... 8 µg Hepatitis B surface antigen (HBs)†‡ ..... 10 µg Poliovirus (inactivated) (IPV) type 1 (Mahoney strain)§ ..... 40 D-antigen unit type 2 (MEF-1 strain)§ ..... 8 D-antigen unit type 3 (Saukett strain)§ ..... 32 D-antigen unit *Haemophilus influenzae* type b polysaccharide ..... 10 µg (polyribosylribitol phosphate, PRP)‡ conjugated to tetanus toxoid as carrier protein..... approximately 25 µg * adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$).... 0.5 mg AL^{3+} † produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology ‡ adsorbed on aluminium phosphate ($AlPO_4$)..... 0.32 mg Al^{3+} § propagated in VERO cells The vaccine contains the following excipients: lactose anhydrous, sodium chloride, Medium 199 (containing principally amino acids, mineral salts, vitamins), water for injection. The vaccine may contain traces of formaldehyde, neomycin, and polymyxin, which are used during the manufacturing process.
Route:	Deep IM injection

Batch Number:	To be determined
Other Product 2:	**Prevenar 13®**: Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Pfizer Limited, Kent, UK)
Form:	Suspension for injection
Composition:	Each 0.5 mL dose contains: Pneumococcal polysaccharide serotype 1 .....2.2 µg Pneumococcal polysaccharide serotype 3 .....2.2 µg Pneumococcal polysaccharide serotype 4 .....2.2 µg Pneumococcal polysaccharide serotype 5 .....2.2 µg Pneumococcal polysaccharide serotype 6A .....2.2 µg Pneumococcal polysaccharide serotype 6B .....4.4 µg Pneumococcal polysaccharide serotype 7F .....2.2 µg Pneumococcal polysaccharide serotype 9V .....2.2 µg Pneumococcal polysaccharide serotype 14 .....2.2 µg Pneumococcal polysaccharide serotype 18C .....2.2 µg Pneumococcal polysaccharide serotype 19A .....2.2 µg Pneumococcal polysaccharide serotype 19F .....2.2 µg Pneumococcal polysaccharide serotype 23F .....2.2 µg The pneumococcal polysaccharides are conjugated to CRM_{197} carrier protein and adsorbed on aluminum phosphate (0.125 mg aluminum). The vaccine also contains the following excipients: sodium chloride, succinic acid, Polysorbate 80, water for injections.
Route:	IM
Batch Number:	To be determined
Other Product 3:	**Rotarix®**: Human rotavirus RIX4414 strain (live, attenuated [produced on Vero cells]) (GlaxoSmithKline Biological s.a., Rixensart, Belgium)
Form:	Oral suspension in a pre-filled oral applicator
Composition:	Each 1.5 mL dose contains: Human rotavirus RIX4414 strain (live, attenuated)*.....not less than $10^{6.0}$ $CCID_{50}$ *Produced on Vero cells †$CCID_{50}$: 50% cell culture infectious dose The vaccine contains the following excipients: sucrose, di-sodium adipate, Dulbecco's Modified Eagle Medium, sterile water.
Route:	Oral
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 ≥ 56 to ≤ 89 days on the day of the first study visit 2) Born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 2.5 kg (or 5 lb and 8 oz) 3) Informed consent form has been signed and dated by the parent(s) or other legally acceptable representative (and by an independent witness if required by local regulations) 4) Subject and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures

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 (at Visit 1) or planned receipt of any vaccine in the 4 weeks before and/or following any trial vaccination except for influenza vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines 3) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B serogroup-containing vaccine) 4) Previous vaccination before Visit 1 with any pneumococcal, diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b (Hib), poliovirus, and/or rotavirus vaccines. Receipt of BCG vaccine at birth is acceptable 5) Receipt of immune globulins, blood or blood-derived since birth 6) Known or suspected congenital or acquired immunodeficiency, including Severe Combined Immunodeficiency disorder (SCID); or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth 7) History of any neurologic disorders, including any seizures and progressive neurologic disorders or encephalopathy 8) History of *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically 9) History of diphtheria, tetanus, pertussis, poliomyelitis, Hib, hepatitis B, *Streptococcus pneumoniae*, and/or rotavirus infection or disease 10) 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 travelling to countries with high endemic or epidemic disease) 11) History of Guillain-Barré syndrome 12) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances including neomycin, kanamycin, polymyxin, formaldehyde, and latex

	13) Hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency 14) History of intussusception or uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception 15) Verbal report of thrombocytopenia, contraindicating intramuscular vaccination in the investigator's opinion 16) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination 17) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion 18) Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives, including planning to leave the area of the study site before the end of the study 19) Moderate or severe acute illness/infection (according to investigator judgment), or febrile illness (temperature ≥ 38.0°C), or diarrhea or vomiting on the day of vaccination. A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided. 20) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study
Statistical Methods:	All immunogenicity analyses will be performed on the Per-Protocol Analysis Sets (PPAS). Additional immunogenicity analyses will be performed for exploratory purposes on the Full Analysis Set (FAS) according to the randomization group. All safety analyses will be performed on the Safety Analysis Set (SafAS). **Primary Objective** Thirty days after the administration of MenACYW conjugate vaccine alone or concomitantly with Bexsero® in the second year of life (at Visit 5), the percentage of subjects who achieve hSBA titers ≥ 1:8 for meningococcal serogroups A, C, W, and Y in Group 1 are non-inferior to the corresponding percentages in Group 2. Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$ Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$ where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve hSBA titers ≥ 1:8 in Group 1 and Group 2, respectively. Each of the serogroups A, C, W, and Y will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected. **Secondary Objectives** Descriptive statistics will be provided for the antibody titers against meningococcal serogroups A, C, W, and Y for Group 1 and Group 2. In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for

	percentages. For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed. Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups A, C, W, and Y. ***Secondary Objective 1 - Geometric mean titer ratio (GMTR) between Group 1 and Group 2 after the second dose of MenACYW conjugate vaccine*** Thirty days after the administration of MenACYW conjugate vaccine alone or concomitantly with Bexsero® in the second year of life (at Visit 5), the hSBA GMTR between Group 1 and Group 2 for meningococcal serogroups A, C, W, and Y will be calculated and 95% CI will be provided.
	Secondary Objective 2 - Antibody responses of the first and second dose of MenACYW conjugate vaccine: Descriptive analyses on A, C, W, and Y serogroups for all subjects for Group 1 and Group 2 providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4, and Visit 5) using hSBA will include but not be limited to: • GMT and 95% CI • Titer distribution and RCDC • Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI • Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI • Percentage of subjects with hSBA vaccine seroresponse* * hSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as: • For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16. • For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer. Descriptive analyses on A, C, W, and Y serogroups for a subset of subjects in Group 1 and Group 2 providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4 and Visit 5) using rSBA will include but not be limited to: • GMT and 95% CI • Titer distribution and RCDCs • Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI • Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI • Percentage of subjects with rSBA vaccine seroresponse* * rSBA vaccine seroresponse for serogroups A, C, W, and Y is defined as: • For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:32. • For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer.

	Secondary Objective 3 - Antibody persistence after the first dose of MenACYW conjugate vaccine Descriptive analyses on A, C, W, and Y serogroups for all subjects for Group 1 and Group 2 providing a blood sample at Visit 3 and Visit 4 using hSBA will include but not be limited to: • GMT and 95% CI • Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI Descriptive analyses on A, C, W, and Y serogroups for a subset of subjects in Group 1 and Group 2 providing a blood sample at Visit 3 and Visit 4 using rSBA will include but not be limited to: • GMT and 95% CI • Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
	Observational Objectives **Immunogenicity** Descriptive statistics will be provided for the antibody titers against meningococcal serogroups A, C, W, and Y for Group 3. Descriptive analyses on A, C, W, and Y serogroups for all subjects in Group 3 providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4, and Visit 5) using hSBA will include but not be limited to: • GMT and 95% CI • Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI Descriptive analyses on A, C, W, and Y serogroups for a subset of subjects in Group 3 providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4 and Visit 5) using rSBA will include but not be limited to: • GMT and 95% CI • Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI ***Safety*** Safety results will be described for subjects in all study groups after vaccination at 2, 3, 4, and 12 to 13 months of age (Visit 1, Visit 2, Visit 3, and Visit 4, respectively). SAEs will be summarized throughout the trial. The main parameters for the safety endpoints will be described by 95% CIs (Clopper-Pearson method).
	Calculation of Sample Size: Due to the potential impact of COVID-19 pandemic, an additional 100 subjects will be enrolled to maintain sufficient study power for the primary objective. Thus, approximately 800 subjects will be enrolled. An estimated 30% non-adherence rate from enrollment will result in approximately 560 subjects in the per-protocol population available for immunogenicity analyses. Group 1 and Group 2 will have 224 evaluable subjects in each treatment group and Group 3 will have 112 evaluable subjects. The power is calculated with the assumption that the estimate from the evaluation group equals that of the control group. In case of unexpected situation or any study hold resulting in an

unexpected number of unevaluable subjects, total sample size may be increased to replace withdrawn, or unevaluable subjects.

Primary Objective

With 224 evaluable subjects in each of the treatment groups, Group 1 and Group 2, the study will have 88% power to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, and Y antibodies.

Table S2: Power of the study based on the primary objective

Antigen	Endpoint	Non-inferiority Margin	Estimates*	Power (%)
A	hSBA titers ≥ 1:8	10%	92%	95.9
C	hSBA titers ≥ 1:8	10%	90%	92.5
Y	hSBA titers ≥ 1:8	10%	96%	99.8
W	hSBA titers ≥ 1:8	10%	96%	99.8
Overall				88.4

* Estimated responses are based on results observed in MET39, Group 3 (2, 4, 12 months data) (2% had been subtracted from the observed results for serogroups A, Y, and W to provide more conservative estimates)

Table of Study Procedures - Group 1

Phase III Trial, 5 Visits, 4 Vaccination Visits, 4 Telephone Calls, 1 or 3 Blood Samples, 11- to 12-Month Duration per Subject

Visit	**Visit 1**	**Telephone Call (TC) 1***	**Visit 2**	**TC2***	**Visit 3**	**TC3***	**Visit 4†**	**TC4***	**Visit 5‡**
Approximate age of subjects	**2 months**	**-**	**3 months**	**-**	**4 months**		**12-13 months**	**-**	**13-14 months**
Trial timelines (days)	**Day 0**	**Visit 1 + 8 days**	**Visit 1 + 30 days**	**Visit 2 + 8 days**	**Visit 2 + 30 days**	**Visit 3 + 8 days**	**-**	**Visit 4 + 8 days**	**Visit 4 + 30 days**
Time windows (days)	**-**		**+14 days**		**+14 days**				**+21 days**
Informed consent	X								
Inclusion/exclusion criteria	X								
Collection of demographic data	X								
Medical history (including maternal prenatal pertussis vaccination)	X								
Physical examination§	X						X**		
Measurement of temperature††	X		X		X		X		
Contact IRT system for randomization, allocation of subject number, and vaccine assignment	X								
Contact IRT system for vaccine assignment			X		X		X		
Review of temporary contraindications for blood sampling‡‡			X		X				X
Blood sampling (BL)§§			BL1 (3 mL)***		BL2 (3 mL)***				BL3 (6 mL)
					BL1 (3 mL)†††		BL2 (3 mL)†††		
Review of warning and precautions to vaccinations	X		X		X		X		
Review of contraindications to subsequent vaccinations and conditions for withdrawal‡‡‡			X		X		X		
Vaccination with MenACYW conjugate vaccine			X				X		
Vaccination with Bexsero®	X				X		X		

Visit	**Visit 1**	**Telephone Call (TC) 1***	**Visit 2**	**TC2***	**Visit 3**	**TC3***	**Visit 4†**	**TC4***	**Visit 5‡**
Approximate age of subjects	**2 months**	**-**	**3 months**	**-**	**4 months**		**12-13 months**	**-**	**13-14 months**
Trial timelines (days)	**Day 0**	**Visit 1 + 8 days**	**Visit 1 + 30 days**	**Visit 2 + 8 days**	**Visit 2 + 30 days**	**Visit 3 + 8 days**	**-**	**Visit 4 + 8 days**	**Visit 4 + 30 days**
Time windows (days)	**-**		**+14 days**		**+14 days**				**+21 days**
Vaccination with routine pediatric vaccines§§§	X		X		X				
Immediate surveillance (30 minutes) and recording of any immediate unsolicited AEs	X		X		X		X		
Diary card (DC) provided****	DC		DC		DC		DC		
Telephone call		X		X		X		X	
Diary card reviewed and collected			DC		DC		DC		DC
Recording of solicited injection site & systemic reactions	X		X		X		X		
Recording of unsolicited AEs	From Day0 to Day30 after each vaccination								
Reporting of serious adverse events (SAEs, including AESIs)††††	To be reported throughout the trial								
Collection of reportable concomitant medications	X		X		X		X		X
Trial termination record									X

Note: Each visit may be conducted at the site (site visit) or at the subject's home (home visit).

* This call is made 8 days after the respective vaccinations. If day 8 falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported and will remind the subject's parent / legally acceptable representative to continue using the diary card, and confirm the date and time of the next visit.

† Visit 4 may occur anytime from the day the subject becomes 12 months of age until the day before becoming 14 months of age.

‡ Routine pediatric vaccines may be given as per standard of care outside of the study, after all visit procedures have been completed.

§ Physical examination should be performed as per standard of care.

** A health assessment will be performed by a study nurse at Visit 4. A physical examination may be performed on the basis of relevant medical history/study nurse health assessment according to the investigator's clinical judgment.

†† Temperature (route as per standard of care) needs to be measured before each vaccination and recorded in the source documents.

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

§§ Blood sample will be drawn prior to vaccination.

*** Blood samples will be drawn from ~ 70 randomized subjects only (Subset A).

††† Blood samples will be drawn from ~ 90 randomized subjects only (Subset B).

‡‡‡ A physical examination may be performed on the basis of relevant medical history at the time of the visit according to the investigator's clinical judgment.

§§§ Routine pediatric vaccines: At Visit 1: Infanrix hexa®, Rotarix®, Prevenar 13®; at Visit 2: Infanrix hexa®, Rotarix®; at Visit 3: Infanrix hexa®, Prevenar 13®

**** The diary card dispensed to the subject's parent/legally acceptable representative at each visit must correspond to the number of injections given at that 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.

Table of Study Procedures - Group 2

Phase III Trial, 5 Visits, 4 Vaccination Visits, 4 Telephone Calls, 1 or 3 Blood Samples, 11- to 12-Month Duration per Subject

Visit	**Visit 1**	**Telephone Call (TC) 1***	**Visit 2**	**TC2***	**Visit 3**	**TC3***	**Visit 4†**	**TC4***	**Visit 5‡**
Approximate age of subjects	**2 months**	**-**	**3 months**	**-**	**4 months**		**12-13 months**	**-**	**13-14 months**
Trial timelines (days)	**Day 0**	**Visit 1 + 8 days**	**Visit 1 + 30 days**	**Visit 2 + 8 days**	**Visit 2 + 30 days**	**Visit 3 + 8 days**	**-**	**Visit 4 + 8 days**	**Visit 4 + 30 days**
Time windows (days)	**-**		**+14 days**		**+14 days**				**+21 days**
Informed consent	X								
Inclusion/exclusion criteria	X								
Collection of demographic data	X								
Medical history (including maternal prenatal pertussis vaccination)	X								
Physical examination §	X						X**		
Measurement of temperature††	X		X		X		X		
Contact IRT system for randomization, allocation of subject number, and vaccine assignment	X								
Contact IRT system for vaccine assignment			X		X		X		
Review of temporary contraindications for blood sampling‡‡			X		X				X
Blood sampling (BL)§§			BL1 (3 mL)***		BL2 (3 mL)***				BL3 (6 mL)
					BL1 (3 mL)†††		BL2 (3 mL)†††		
Review of warning and precautions to vaccinations	X		X		X		X		
Review of contraindications to subsequent vaccinations and conditions for withdrawal‡‡‡			X		X		X		
Vaccination with MenACYW conjugate vaccine			X				X		
Vaccination with Bexsero®	X				X				

Visit	**Visit 1**	**Telephone Call (TC) 1***	**Visit 2**	**TC2***	**Visit 3**	**TC3***	**Visit 4†**	**TC4***	**Visit 5‡**
Approximate age of subjects	**2 months**	**-**	**3 months**	**-**	**4 months**		**12-13 months**	**-**	**13-14 months**
Trial timelines (days)	**Day 0**	**Visit 1 + 8 days**	**Visit 1 + 30 days**	**Visit 2 + 8 days**	**Visit 2 + 30 days**	**Visit 3 + 8 days**	**-**	**Visit 4 + 8 days**	**Visit 4 + 30 days**
Time windows (days)	**-**		**+14 days**		**+14 days**				**+21 days**
Vaccination with routine pediatric vaccines§§§	X		X		X				
Immediate surveillance (30 minutes) and recording of any immediate unsolicited AEs	X		X		X		X		
Diary card (DC) provided****	DC		DC		DC		DC		
Telephone call		X		X		X		X	
Diary card reviewed and collected			DC		DC		DC		DC
Recording of solicited injection site & systemic reactions	X		X		X		X		
Recording of unsolicited AEs	From Day0 to Day30 after each vaccination								
Reporting of serious adverse events (SAEs, including AESIs)††††	To be reported throughout the trial								
Collection of reportable concomitant medications	X		X		X		X		X
Trial termination record									X

Note: Each visit may be conducted at the site (site visit) or at the subject's home (home visit).

* This call is made 8 days after the respective vaccinations. If day 8 falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported and will remind the subject's parent / legally acceptable representative to continue using the diary card, and confirm the date and time of the next visit.

† Visit 4 may occur anytime from the day the subject becomes 12 months of age until the day before becoming 14 months of age.

‡ Routine pediatric vaccines may be given as per standard of care outside of the study, after all visit procedures have been completed. The 3rd dose of Bexsero® will be provided by the Sponsor to complete the vaccination series.

§ Physical examination should be performed as per standard of care.

** A health assessment will be performed by a study nurse at Visit 4. A physical examination may be performed on the basis of relevant medical history/study nurse health assessment according to the investigator's clinical judgment.

†† Temperature (route as per standard of care) needs to be measured before each vaccination and recorded in the source documents.

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

§§ Blood sample will be drawn prior to vaccination.

*** Blood samples will be drawn from ~70 randomized subjects only (Subset A).

††† Blood samples will be drawn from ~ 90 randomized subjects only (Subset B).

‡‡‡ A physical examination may be performed on the basis of relevant medical history at the time of the visit according to the investigator's clinical judgment.

§§§ Routine pediatric vaccines: At Visit 1: Infanrix hexa®, Rotarix®, Prevenar 13®; at Visit 2: Infanrix hexa®, Rotarix®; at Visit 3: Infanrix hexa®, Prevenar 13®

**** The diary card dispensed to the subject's parent/legally acceptable representative at each visit must correspond to the number of injections given at that 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.

Table of Study Procedures - Group 3

Phase III Trial, 5 Visits, 4 Vaccination Visits, 4 Telephone Calls, 3 Blood Samples, 11- to 12-Month Duration per Subject

Visit	**Visit 1**	**Telephone Call (TC) 1***	**Visit 2**	**TC2***	**Visit 3**	**TC3***	**Visit 4†**	**TC4***	**Visit 5‡**
Approximate age of subjects	**2 months**	**-**	**3 months**	**-**	**4 months**		**12-13 months**	**-**	**13-14 months**
Trial timelines (days)	**Day 0**	**Visit 1 + 8 days**	**Visit 1 + 30 days**	**Visit 2 + 8 days**	**Visit 2 + 30 days**	**Visit 3 + 8 days**	**-**	**Visit 4 + 8 days**	**Visit 4 + 30 days**
Time windows (days)	**-**		**+14 days**		**+14 days**				**+21 days**
Informed consent	X								
Inclusion/exclusion criteria	X								
Collection of demographic data	X								
Medical history (including maternal prenatal pertussis vaccination)	X								
Physical examination§	X						X**		
Measurement of temperature††	X		X		X		X		
Contact IRT system for randomization, allocation of subject number, and vaccine assignment	X								
Contact IRT system for vaccine assignment			X		X		X		
Review of temporary contraindications for blood sampling‡‡			X		X				X
Blood sampling (BL)§§			BL1 (3 mL)		BL2 (3 mL)				BL3 (6 mL)
					BL1 (3 mL)***		BL2 (3 mL)***		
Review of warning and precautions to vaccinations	X		X		X		X		
Review of contraindications to subsequent vaccinations and conditions for withdrawal†††			X		X		X		
Vaccination with Bexsero®	X				X		X		
Vaccination with routine pediatric vaccines‡‡‡	X		X		X				
Immediate surveillance (30 minutes) and recording of any immediate unsolicited AEs	X		X		X		X		
Diary card (DC) provided§§§	DC		DC		DC		DC		

Visit	**Visit 1**	**Telephone Call (TC) 1***	**Visit 2**	**TC2***	**Visit 3**	**TC3***	**Visit 4†**	**TC4***	**Visit 5‡**
Approximate age of subjects	**2 months**	**-**	**3 months**	**-**	**4 months**		**12-13 months**	**-**	**13-14 months**
Trial timelines (days)	**Day 0**	**Visit 1 + 8 days**	**Visit 1 + 30 days**	**Visit 2 + 8 days**	**Visit 2 + 30 days**	**Visit 3 + 8 days**	**-**	**Visit 4 + 8 days**	**Visit 4 + 30 days**
Time windows (days)	**-**		**+14 days**		**+14 days**				**+21 days**
Telephone call		X		X		X		X	
Diary card reviewed and collected			DC		DC		DC		DC
Recording of solicited injection site & systemic reactions	X		X		X		X		
Recording of unsolicited AEs	From Day0 to Day30 after each vaccination								
Reporting of serious adverse events (SAEs, including AESIs)****	To be reported throughout the trial								
Collection of reportable concomitant medications	X		X		X		X		X
Trial termination record									X

Note: Each visit may be conducted at the site (site visit) or at the subject's home (home visit).

* This call is made 8 days after the respective vaccinations. If day 8 falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported and will remind the subject's parent / legally acceptable representative to continue using the diary card, and confirm the date and time of the next visit.

† Visit 4 may occur anytime from the day the subject becomes 12 months of age until the day before becoming 14 months of age.

‡ Routine pediatric vaccines may be given as per standard of care outside of the study, after all visit procedures have been completed.

§ Physical examination should be performed as per standard of care.

**A health assessment will be performed by a study nurse at Visit 4. A physical examination may be performed on the basis of relevant medical history/study nurse health assessment according to the investigator's clinical judgment.

†† Temperature (route as per standard of care) needs to be measured before each vaccination and recorded in the source documents.

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

§§ Blood sample will be drawn prior to vaccination.

*** Blood samples will be drawn from ~ 70 randomized subjects only (Subset A).

††† Blood samples will be drawn from ~ 90 randomized subjects only (Subset B).

‡‡‡ A physical examination may be performed on the basis of relevant medical history at the time of the visit according to the investigator's clinical judgment.

§§§ Routine pediatric vaccines: At Visit 1: Infanrix hexa®, Rotarix®, Prevenar 13®; at Visit 2: Infanrix hexa®, Rotarix®; at Visit 3: Infanrix hexa®, Prevenar 13®. Licensed ACWY conjugate meningococcal vaccine (Nimenrix®) will be offered 30 days after the last study visit (Visit 5) at an additional optional visit..

**** The diary card dispensed to the subject's parent/legally acceptable representative at each visit must correspond to the number of injections given at that 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.

List of Abbreviations

µg	microgram
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sampling
CDM	Clinical Data Management
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
EDC	electronic data capture
FAS	full analysis set
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMT	geometric mean titers
GPV	Global Pharmacovigilance
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	intramuscular
IME	important medical event
IRB	Institutional Review Board
IRT	interactive response technology
LCLS	last contact, last subject
LLOQ	lower limit of quantitation
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter

NIMP	non-investigational medicinal products
NSAID	non-steroidal anti-inflammatory drug
PPAS	per-protocol analysis set
PRN	pertactin
PRP	polyribosyl-ribitol phosphate
PS	polysaccharide
PV	Pharmacovigilance
RCDC	reverse cumulative distribution curves
RMO	Responsible Medical Officer
RV	rotavirus vaccine
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SCID	severe combined immunodeficiency disorder
SOC	system organ class
SMT	Safety Management Team
TBD	to be determined
TC	telephone call
TMF	trial master file
UK	United Kingdom
US	United States

1 Introduction

1.1 Background

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria meningitidis (N. Meningitidis)*, a Gram-negative diplococcus found exclusively in humans. Symptoms may include intense headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, myalgia, and a characteristic petechial rash (1). At least 12 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 (UK), 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 United States (US) and more recently in Canada and Europe (17) (18) (19). The Y serogroup is commonly associated with meningococcal pneumonia, particularly in older adults ≥ 65 years of age (20). Outbreaks of serogroup B meningococcal disease have also been reported on college campuses in the US during the last 5-year period: a prolonged outbreak of serogroup B on a university campus in Ohio from 2008 – 2010 and 2 universities in New Jersey and California in 2013 (21) (22).

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

Surveillance data from England and Wales showed an increase in endemic meningococcal serogroup W disease across all age groups, accounting for 15% of all IMD cases in 2013 - 2014 compared with an average of 1% to 2% of all IMD cases in earlier years (24). A gradual increase in serogroup Y IMD has also been recently reported in Sweden during 2005 – 2012 (25) (26). Nearly 50% of all IMD was caused by serogroup Y in 2012 (25). Similarly, an increase in the proportion of IMD caused by serogroup Y has been observed in other Nordic countries, accounting for 31% in Norway in 2009 – 2010 (27) and 38% in Finland in 2010 (28).

The MenACYW conjugate vaccine is being developed for the immunization of individuals of all ages (infants 6 weeks of age and older through and including older adults > 56 years of age)

against IMD. The purpose of the vaccine is to provide broad coverage against circulating meningococcal strains from serogroups A, C, W, and Y.

The MET52 trial will evaluate the safety and immunogenicity of the MenACYW conjugate vaccine given as a 2-dose series when introduced into an existing immunization schedule containing a meningococcal B vaccine, Bexsero®, in infants and toddlers in the UK.

1.2 Background of the Investigational Product

1.2.1 Clinical

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

The formulation has been evaluated in around 7115 subjects (infants, toddlers, adolescents, and adults > 56 years of age) in 10 completed studies: 4 Phase II studies, MET39, MET44, MET50, conducted in the USA, and MET54 conducted in Finland, and 6 Phase III studies, MET35, MET43, MET49 and MET56, conducted in the USA, MET51 conducted in EU region (Spain, Germany, Hungary and Finland), and MET57 conducted in Thailand, South Korea, Russia, and Mexico. The vaccine is currently approved under the brand name MenQuadfi for use as single dose in ages 12 months and older in the EU, Canada, Australia and Brazil. The vaccine is also approved for use as single dose in ages 2 years and older in the USA.

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

1.2.1.1 Study MET39 (Phase II)

MET39 was a Phase II, randomized, open-label, multi-center study conducted in the US for which 580 healthy subjects from 2 to 15 months of age were enrolled. This study evaluated the optimal vaccination schedule in the infant/toddler population. Subjects in Group 1 through Group 4 received 1, 2, or 3 primary doses plus an additional dose of the MenACYW conjugate vaccine in the second year of life, concomitantly with routine pediatric vaccines at several different vaccination schedules. Subjects in Group 5 received 1 dose of the MenACYW conjugate vaccine concomitantly with routine pediatric vaccines. The routine pediatric vaccines given concomitantly with MenACYW conjugate vaccine at various schedules included Prevnar® (pneumococcal conjugate vaccine) or Prevnar 13® (pneumococcal 13-valent conjugate vaccine [PCV13]) , Pentacel® (diphtheria, tetanus, pertussis [acellular, component]-poliovirus [inactivated]//*Haemophilus influenzae* type b [DTaP-IPV//Hib]), Rotarix® (monovalent rotavirus vaccine [RV1]) or RotaTeq® (pentavalent rotavirus vaccine [RV5]), hepatitis B [HB] vaccine, M-M-R® II vaccine (measles, mumps, and rubella vaccine [MMR]) , and Varivax® (varicella vaccine).

Immunogenicity

After the primary series consisting of 1, 2, or 3 doses of MenACYW conjugate vaccine, protective serum bactericidal assay using human complement (hSBA) threshold titers of ≥ 1:8 were attained by > 88% of subjects for serogroup C and by 62% to 74% for serogroup A. For serogroups Y and W, ≥ 90% achieved the threshold titer after 3 doses, 75% to 84% after 2 doses, but only 25% after a single dose administered at 6 months of age.

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

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 hSBA. MenACYW conjugate vaccine immune responses evaluated by rSBA and hSBA were generally comparable to Nimenrix® immune responses with some variation by serogroup.

hSBA

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

rSBA

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

Safety

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

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

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

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

MenACYW conjugate vaccine is an investigational vaccine that is undergoing active clinical investigation. There may be no direct benefit from receiving the MenACYW conjugate vaccine. However, based on the data generated from previous studies, the immunogenicity profile of the

MenACYW conjugate vaccine in different age groups shows that the majority of subjects developed seroprotective levels of antibodies after vaccination. The safety evaluation indicates that the vaccine is well-tolerated, and no safety issues have been detected to date. In all, the data support further evaluation of the MenACYW conjugate vaccine in humans.

As with any vaccine, MenACYW conjugate vaccine may not protect 100% of individuals against the disease it is designed to prevent.

Following completion of the trial, subjects who received only licensed pediatric vaccines (Group 3) will be offered vaccination with a UK licensed quadrivalent ACWY conjugated meningococcal vaccine (Nimenrix®) to provide protection against meningococcal infection as a benefit for participation in this trial. This vaccine will be offered outside the scope of the study, free of charge.

1.3.2 Potential Risks to Subjects

Like other vaccines, MenACYW conjugate vaccine or Bexsero® 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 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 (29). A retrospective cohort study carried out in the US using healthcare claims data found no evidence of increased risk associated with the use of that vaccine. The study was able to exclude all but relatively small incremental risks (30).

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 (31). The IOM found evidence for a causal relation between tetanus toxoid-containing vaccines and brachial neuritis (32). Arthus reactions are rarely reported after vaccination and can occur after tetanus-toxoid containing vaccines (33).

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

The potential risk listed here are not exhaustive. Refer to the Investigator's Brochure of the investigational vaccine and to the package insert for Bexsero® (34) (35) and concomitant routine pediatric vaccines for additional information regarding potential risks.

1.4 Rationale for the Study

The MenACYW conjugate vaccine is designed for the immunization of individuals of all ages (infants 6 weeks of age and older through and including older adults > 56 years of age) against IMD. The purpose of the vaccine is to provide broad coverage against circulating meningococcal strains from serogroups A, C, W, and Y. 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 (MCV4) indicated in infants/toddlers, children, adolescents, adults, and older adults > 56 years of age. Meningococcal PS vaccines have 2 important limitations: a) the antibody response is age-dependent, with infants giving the poorest response; and b) PS alone are T-cell independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of PS vaccines in infants and children has been shown to be improved by conjugating the PS to protein carriers. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of PS-specific total immunoglobulin (Ig) G and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials including those with the final formulation (MET39 and MET44) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above trials using the final formulation or in the earlier trials.

The MET52 trial will support licensure of MenACYW conjugate vaccine in the EU. This is a Phase III study designed to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine when administered concomitantly with a meningococcal serogroup B vaccine as part of a routine immunization program in healthy infants and toddlers. The UK was selected as the country in which the study will be conducted based on the national immunization program including a meningococcal serogroup B vaccine (Bexsero®). Bexsero® was licensed in Europe in 2013, and since July 2015 has been introduced into the UK's routine childhood immunization at 2, 4, and between 12 and 13 months of age (36).

2 Study Objectives

2.1 Primary Objective

To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, W, and Y in terms of hSBA vaccine seroprotection (antibody titer ≥ 1:8) when MenACYW conjugate vaccine is administered concomitantly with Bexsero® in the second year of life compared to when MenACYW conjugate vaccine is given alone.

The endpoint for the primary objective is presented in Section 9.1.2.1

2.2 Secondary Objectives

1) To compare the hSBA antibody response in terms of geometric mean titers (GMTs) against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine is administered concomitantly with Bexsero® or when MenACYW conjugate vaccine is given alone in the second year of life.
2) To describe the hSBA and rSBA antibody responses against meningococcal serogroups A, C, W, and Y before and after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age, before and after the 2nd dose of MenACYW conjugate vaccine administered at 12 to 13 months of age for Group 1 and Group 2
3) To describe the hSBA and rSBA antibody persistence against meningococcal serogroups A, C, W, and Y after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age for Group 1 and Group 2

The endpoints for the secondary objectives are presented in Section 9.2.2.1

2.3 Observational Objectives

Immunogenicity

1) To describe the prevalence of antibodies against meningococcal serogroups A, C, W, and Y in Group 3 after Bexsero® administration

Safety

1) To describe the safety of MenACYW conjugate vaccine when given alone and when administered concomitantly with Bexsero® at 12 to 13 months of age
2) To describe the safety of Bexsero® when given alone and when administered concomitantly with MenACYW conjugate vaccine at 12 to 13 months of age
3) To describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine vaccines at 3 months of age
4) To describe the safety of routine vaccines when given alone or administered concomitantly with MenACYW conjugate vaccine at 3 months of age

5) To describe the safety profile of routine vaccines and Bexsero® administered concomitantly at 2 and 4 months of age

The endpoints for the observational objectives are presented in Section 9.3

3 Investigators and Study Organization

This study will be conducted in multiple centers in the UK. 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].

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 serious adverse events (SAEs) occurring during the study that are related to the product administered will be reported by the Sponsor or 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, open-label, randomized, parallel-group, active-controlled, multi-center study to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine when administered concomitantly with a meningococcal group B vaccine (Bexsero®) and other routine pediatric vaccines as part of the National Immunization Schedule in healthy infants and toddlers in the UK.

Approximately 800 healthy infants aged ≥ 56 to ≤ 89 days (approximately 2 months of age) will be randomized 2:2:1 to the following 3 groups:

Group 1: MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero® at 2, 4, and 12 to 13 months of age

Group 2: MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero® at 2 and 4 months of age

Group 3: Bexsero® at 2, 4, and 12 to 13 months of age

Routine pediatric vaccines will be given to subjects in all groups according to the UK immunization schedule:

- Infanrix hexa® (Combined Diphtheria-Tetanus-acellular Pertussis [DTPa], Hepatitis B, Inactivated Poliovirus and *Haemophilus influenzae* type b Vaccine; DTPa-HBV-IPV+Hib) at 2, 3, and 4 months of age
- Rotarix® (rotavirus vaccine; RV) at 2 and 3 months of age
- Prevenar 13® (pneumococcal 13-valent conjugate vaccine; PCV13) at 2 and 4 months of age

The routine vaccines (Infanrix hexa®, Rotarix®, and Prevenar 13®) will be sourced by the investigators and administered as per the standard practices. MenACYW conjugate vaccine and Bexsero® will be provided by the Sponsor.

The routine pediatric vaccines administered in the second year of life (Menitorix®, Priorix®/M-M-RVAXPRO®, and PCV13 [for all groups], and Bexsero® [for Group 2]) may be given as per standard of care at the last study visit after completion of study procedures (Visit 5 at 13 to 14 months). For Group 2, Bexsero® will be provided by the Sponsor to complete the vaccination series for subjects enrolled in this group. Subjects in Group 3 will be offered a single dose of the licensed ACWY conjugate meningococcal vaccine (Nimenrix®). This is a non-study vaccine to be administered 30 days after the last study visit (Visit 5) at an additional optional visit, and will be outside the scope of the study evaluations. No immunogenicity and safety data will be collected after the administration of these vaccines.

Note: Each visit may be conducted at the site (site visit) or at the subject's home (home visit).

Blood Sampling

Subjects will provide the following blood samples:

- Groups 1 and 2: 160 subjects in each group will be randomized to have 3 blood draws at the intervals mentioned below. The remaining subjects will only have 1 blood draw at Visit 5.
- Group 3: all 160 subjects will have 3 blood draws.

For the subjects randomized to have 3 blood draws in Group 1 and Group 2, the first 2 blood draws will be performed in a staggered way – approximately half of the subjects (~70 subjects in each group) will have blood draws at Visit 2 and Visit 3 (subset A), and the remaining half (~90 subjects in each group) will have blood draws at Visit 3 and Visit 4 (subset B). The third blood draw will be performed at Visit 5 for all subjects.

Subset A (~70 subjects in each group):

- a pre-vaccination blood sample at Visit 2
- a blood sample at Visit 3 (30 days after vaccination at Visit 2)
- a blood sample at Visit 5 (30 days after vaccination at Visit 4)

Subset B (~90 subjects in each group):

- a blood sample at Visit 3 (30 days after vaccination at Visit 2)
- a pre-vaccination blood sample at Visit 4
- a blood sample at Visit 5 (30 days after vaccination at Visit 4)

For the subjects randomized to Group 3, the first 2 blood draws will be performed in a staggered way – approximately half of the subjects (~70 subjects) will have blood draws at Visit 2 and Visit 3 (subset A), and the remaining half (~90 subjects) will have blood draws at Visit 3 and Visit 4 (subset B). The third blood draw will be performed at Visit 5 for all subjects.

Subset A (~70 subjects):

- a pre-vaccination blood sample at Visit 2
- a blood sample at Visit 3 (30 days after vaccination at Visit 2)
- a blood sample at Visit 5 (30 days after vaccination at Visit 4)

Subset B (~90 subjects):

- a blood sample at Visit 3 (30 days after vaccination at Visit 2)
- a pre-vaccination blood sample at Visit 4
- a blood sample at Visit 5 (30 days after vaccination at Visit 4)

Safety data will be collected as follows: Immediate unsolicited systemic AEs will be collected within 30 minutes after each vaccination. Solicited AEs will be collected from Day (D) 0 to D07 after each vaccination; unsolicited AEs will be collected from D0 to D30 after each vaccination; SAEs (including adverse events of special interest [AESIs]) will be collected throughout the study from D0 to Visit 5. All AESIs collected in this trial will be considered as SAEs.

5.1.2 Justification of the Study Design

The MET52 will be evaluating the safety and immunogenicity of the MenACYW conjugate vaccine given as a 2-dose series when introduced into an existing immunization schedule containing a meningococcal B vaccine. The study will be used to support licensure of MenACYW conjugate vaccine in the EU, evaluating concomitant administration of MenACYW conjugate vaccine and routine pediatric vaccines including the meningococcal B vaccine, Bexsero®, in infants and toddlers in the UK when receiving the routine vaccinations according to the UK immunization schedule.

The study is designed to evaluate any possible interference with the immunogenicity of MenACYW conjugate vaccine when given on the background of the UK routine vaccinations, including Bexsero®. Accordingly, the immunogenicity assessments will be conducted at the time points when MenACYW conjugate vaccine is administered (before and 30 days after administration at 3 months of age, and before and 30 days after administration at 12 to 13 months of age). The safety evaluation will assess any potential interference with the safety of MenACYW conjugate vaccine when given as above, and also any potential interference of MenACYW conjugate vaccine on the safety of the routine vaccines, including Bexsero®. The study also aims to evaluate the persistence of immune response following administration of the dose of the MenACYW conjugate vaccine in the first year of life (3 months of age).

Given that the meningococcal vaccines (MenACYW conjugate vaccine and Bexsero®) used in this study have different appearances, and individual group vaccination schedule differs in the number of vaccines administered and timing of their administration, the study has an open-label design.

5.1.3 Study Plan

Vaccination and Blood sampling

A schedule of assessments, study vaccinations, and blood draws is provided in the Tables of Study Procedures and in Table 5.1. Subjects in Group 1 and 2 will have 1 or 3 blood draws. Subjects in Group 3 will have 3 blood draws.

Table 5.1: Schedule of vaccination and blood draws

Group	Visit								
	Visit 1 **2 months**	**Visit 2** **3 months**		**Visit 3** **4 months**		**Visit 4** **12 - 13 months**		**Visit 5** **13 - 14 months**	
	Vaccinations	**Blood collection**	**Vaccinations**	**Blood collection**	**Vaccinations**	**Blood collection**	**Vaccination(s)**	**Blood collection**	**Vaccinations***
1 **(N=320)**	Infanrix hexa Rotarix Bexsero PCV13	**BL1** (n=70)†	Infanrix hexa Rotarix **MenACYW**	**BL2** (n=70)†	Infanrix hexa Bexsero PCV13		Bexsero **MenACYW**	**BL3** (n=320)	*PCV13* *Menitorix* *Priorix/M-M-RVAXPRO*
				BL1 (n=90)‡		**BL2** (n=90)‡			
2 **(N=320)**	Infanrix hexa Rotarix Bexsero PCV13	**BL1** (n=70)†	Infanrix hexa Rotarix **MenACYW**	**BL2** (n=70)†	Infanrix hexa Bexsero PCV13		**MenACYW**	**BL3** (n=320)	*PCV13* *Menitorix* *Bexsero*§ *Priorix/M-M-RVAXPRO*
				BL1 (n=90)‡		**BL2** (n=90)‡			
3** **(N=160)**	Infanrix hexa Rotarix Bexsero PCV13	**BL1** (n=70)†	Infanrix hexa Rotarix	**BL2** (n=70)†	Infanrix hexa Bexsero PCV13		Bexsero	**BL3** (n=160)	*PCV13* *Menitorix* *Priorix/M-M-RVAXPRO*
				BL1 (n=90)‡		**BL2** (n=90)‡			

* Routine vaccines to be given after study visit procedures are completed. No immunogenicity or safety data will be collected after the administration of these vaccines.

†The first ~70 subjects randomized to have 2 blood draws at Visit 2 and Visit 3 (Subset A)

‡The last ~90 subjects randomized to have 2 blood draws at Visit 3 and Visit 4 (Subset B)

§For Group 2, the 3rd dose of Bexsero® will be provided by Sponsor for completion of the Bexsero vaccination series.

**Licensed ACWY conjugate meningococcal vaccine (Nimenrix®) will be offered at least 30 days after the last study visit (Visit 5) at an additional optional visit.

BL: Blood draw prior to vaccination; N: number of subjects randomized in each group; n: number of subjects randomized to have blood draws in each group at the given visit

Collection of safety data

- All subjects will be observed for 30 minutes after each vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the electronic case report book (CRB).
- The subject's parent / legally acceptable representative will record information in a diary card about solicited reactions from D0 to D07 after all vaccinations and unsolicited AEs from D0 until the next study visit. SAEs (including AESIs) will be recorded throughout the study.
- The subject's parent / legally acceptable representative will record information in a diary card about SAEs (including AESIs) 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.
- The subject's parent/ legally acceptable representative will be asked to notify the site immediately about any potential SAEs at any time during the trial.
- Staff will contact the subject's parent/ legally acceptable representative by telephone 8 days after vaccination(s) at Visit 1, Visit 2, Visit 3 and Visit 4 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.
- The completed diary cards will each be collected and reviewed with the subject's parent/ legally acceptable representative at the subsequent visit.

5.1.4 Visit Procedures

Each visit may be conducted at the site (site visit) or at the subject's home (home visit). Study staff will contact the subject's parent / legally acceptable representative to confirm upcoming visits.

Visit 1 (Day 0): Inclusion, and Vaccination

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

2) Check inclusion and exclusion criteria for eligibility.

3) Collect demographic data.

4) Obtain verbal medical history about the subject, including ongoing medication. Collect maternal prenatal immunization with pertussis vaccine (Section 5.2.7).

5) Conduct a physical examination as per standard of care.

6) Take the subject's temperature. If the temperature is ≥38°C, postpone vaccination until the condition is resolved.

7) Call the interactive response technology (IRT) system for randomization, allocation of subject number and vaccine assignment.

8) Review warnings and precautions to vaccinations.

9) Administer the following vaccines. Each vaccine should be administered in the assigned location and documented appropriately:

   a) Bexsero®: inject deep IM into the anterolateral area of the thigh

   b) Infanrix hexa®: inject deep IM into the anterolateral area of the thigh

   c) Prevenar 13®: inject IM into the anterolateral area of the thigh

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

   If multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are given in the same limb, the injection sites should be separated by 1 inch or more, so that any local reactions can be differentiated.

10) Keep the subject under observation for 30 minutes and record any adverse reaction in the source document.

11) Give the parent / legally acceptable representative a diary card (the diary card should match the number of injections given at this visit, 3 injections for all groups), a thermometer, and a ruler, and go over the instructions for their use. Instruct the parent / legally acceptable representative to retain the thermometer and ruler throughout the duration of the study. At each subsequent visit, confirm that the parent / legally acceptable representative has retained the thermometer and ruler, replace only as necessary.

12) Remind the parent / legally acceptable representative to expect a telephone call 8 days after Visit 1.

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

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

Telephone Call 1 (8 days after Visit 1)

Note: If day 8 falls on a weekend or a holiday, the telephone call may be made on the following business day.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE, including an AESI occurred, follow the instructions in Section 10 for reporting it.

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

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

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

2) Measure temperature. If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.

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

4) Collect 3 mL of blood from the subjects in Subset A (BL1) (see Section 5.1.2 and Section 5.1.3 for definition of Subset A and details of the sample schedule, and Section 7.1 for detailed instructions regarding the handling of blood samples). All attempts should be made to obtain a blood sample; however, if the attempts are unsuccessful, the subject could continue in the study with all the study procedures including vaccination.

5) Review warnings and precautions to vaccinations.

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

7) Contact the IRT system for vaccine assignment.

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

   - MenACYW conjugate vaccine: inject IM into the anterolateral area of the thigh
   - Infanrix hexa®: inject deep IM into the anterolateral area of the thigh
   - Rotarix®: administer orally per instructions in the package insert

   It is recommended that MenACYW conjugate vaccine and Infanrix hexa® be administered in opposite limbs. If multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are given in the same limb, the injection sites should be separated by 1 inch or more, so that any local reactions can be differentiated.

9) 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.

10) Give the parent / legally acceptable representative a diary card (the diary card should match the number of injections given during this visit, 2 injections for Groups 1 and 2, and 1 injection for Group 3).

11) Remind the parent / legally acceptable representative to expect a telephone call 8 days after Visit 2.

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

13) Complete the relevant CRFs for this visit.

Telephone Call 2 (8 days after Visit 2)

Refer to steps in Telephone Call 1.

Visit 3 (30 [+14] days after Visit 2): Collection of Safety Information, Vaccination, and Blood Sample

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

2) Measure temperature. If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.

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

4) Collect 3 mL of blood from subjects in Subset A (BL2), and from subjects in Subset B (BL1) (see Section 5.1.2 and Section 5.1.3 for definition of Subset A and Subset B and details of the sample schedule, and Section 7.1 for detailed instructions regarding the handling of blood samples).

5) Review warnings and precautions to vaccinations.

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

7) Contact the IRT system for vaccine assignment.

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

   - Bexsero®: inject deep IM into the anterolateral area of the thigh.
   - Infanrix hexa®: inject deep IM into the anterolateral area of the thigh
   - Prevenar 13®: inject IM into the anterolateral area of the thigh

   If multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are given in the same limb, the injection sites should be separated by 1 inch or more, so that any local reactions can be differentiated.

9) 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.

10) Give the parent / legally acceptable representative a diary card (the diary card should match the number of injections given during this visit, 3 injections for all groups)

11) Remind the parent / legally acceptable representative to expect a telephone call 8 days after Visit 3.

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

13) Complete the relevant CRFs for this visit.

Telephone Call 3 (8 days after Visit 3)

Refer to steps in Telephone Call 1.

Visit 4 (12 to 13 months): Collection of Safety Information, Vaccination

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

2) A physical examination may be performed as per standard of care on the basis of relevant medical history/study nurse health assessment according to investigator's clinical judgment.

3) Measure temperature. If the temperature is ≥ 38°C, postpone vaccination until the condition is resolved.

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

5) Collect 3 mL of blood from the subjects in Subset B (BL2) (see Section 5.1.2 and Section 5.1.3 for definition of Subset B and details of the sample schedule, and Section 7.1 for detailed instructions regarding the handling of blood samples).

6) Review warnings and precautions to vaccinations.

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

8) Contact the IRT system for vaccine assignment.

9) Administer the study vaccines. The vaccine should be administered in the assigned location and documented, appropriately.

   Group 1:

   - MenACYW conjugate vaccine: inject IM into the anterolateral area of the thigh
   - Bexsero®: inject deep IM into the anterolateral area of the thigh

   It is recommended that MenACYW conjugate vaccine and Bexsero® be administered in opposite limbs. If vaccines are given in the same limb, the injection sites should be separated by 1 inch or more, so that any local reactions can be differentiated.

   Group 2:

   - MenACYW conjugate vaccine: inject IM into the anterolateral area of the thigh

   Group 3:

   - Bexsero®: inject deep IM into the anterolateral area of the thigh

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 / legally acceptable representative a diary card (the diary card should match the number of injections given during this visit, 2 injections for Group 1, and 1 injection for Groups 2 and 3).

12) Remind the parent / legally acceptable representative to expect a telephone call 8 days after Visit 4.

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

14) Complete the relevant CRFs for this visit.

Telephone Call 4 (8 days after Visit 4)

Refer to steps in Telephone Call 1.

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

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

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

3) Collect 6 mL of blood (BL3) from all subjects (see Section 7.1 for detailed instructions regarding the handling of blood samples).

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

5) Complete the relevant CRFs for this visit.

6) Complete the trial termination record.

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

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): Q4 2018 to Q4 2022

Planned inclusion period - FVFS to FVLS (first visit, last subject): Q4 2018 to Q3 2021

Planned end of study – LVLS (last visit, last subject): Q4 2022

Planned date of final clinical study report: Q3 2023

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 / an appropriate and legally acceptable representative voluntarily confirms his or her willingness to participate in a particular study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF.

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

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

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

Informed consent forms will be provided in duplicate, or a photocopy of the signed consent will be made. The original will be kept by the Investigator, and the copy will be kept by the subject's parent / legally acceptable representative.

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 ≥ 56 to ≤ 89 days on the day of the first study visit[a]

2) Born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 2.5 kg (or 5 lb and 8 oz)

3) Informed consent form has been signed and dated by the parent(s) or other legally acceptable representative (and by an independent witness if required by local regulations)

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

5.2.5 Exclusion Criteria

An individual fulfilling *any* of the following criteria is to be excluded from 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 (at Visit 1) or planned receipt of any vaccine in the 4 weeks before and/or following any trial vaccination except for influenza vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

3) Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B serogroup-containing vaccine)

4) Previous vaccination (before Visit 1) with any pneumococcal, diphtheria, tetanus, pertussis, hepatitis B, Haemophilus influenzae type b (Hib), poliovirus, and/or rotavirus vaccines. Receipt of BCG vaccine at birth is acceptable.

5) Receipt of immune globulins, blood or blood-derived since birth

6) Known or suspected congenital or acquired immunodeficiency, including Severe Combined Immunodeficiency disorder (SCID); 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

[a] ≥ 56 to ≤ 89 days" means from the 56th day after birth to the day before the 90th day after birth

7) History of any neurologic disorders, including any seizures and progressive neurologic disorders or encephalopathy

8) History of Neisseria meningitidis infection, confirmed either clinically, serologically, or microbiologically

9) History of diphtheria, tetanus, pertussis, poliomyelitis, Hib, hepatitis B, Streptococcus pneumoniae, and/or rotavirus infection or disease

10) 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 travelling to countries with high endemic or epidemic disease)

11) History of Guillain-Barré syndrome

12) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances including neomycin, kanamycin, polymyxin, formaldehyde, and latex[a]

13) Hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency

14) History of intussusception or uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception

15) Verbal report of thrombocytopenia, contraindicating intramuscular vaccination in the investigator's opinion

16) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination

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

18) Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives, including planning to leave the area of the study site before the end of the study

19) Moderate or severe acute illness/infection (according to investigator judgment), or febrile illness (temperature ≥ 38.0°C), or diarrhea or vomiting on the day of vaccination. A

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[a] The components of all vaccines are listed in Section 6. The components of the MenACYW conjugate vaccine are also listed in the Investigator's Brochure

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

prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.

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

If the subject has a primary physician who is not the Investigator, the site must contact this physician with the parent's / legally acceptable representative's consent to inform him / her of the subject's participation in the study.

5.2.6 Medical History

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

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

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

The reporting of signs and symptoms in lieu of a diagnosis is strongly discouraged.

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

In addition, maternal vaccination against pertussis while pregnant with the subject enrolled in the study will be collected in the CRB (including date of vaccination).

The information collected will not be coded. This information will further assist with the interpretation of data collected during the trial.

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 ≥ 38.0°C) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment. The presence of a minor infection is not a contraindication.

- The administration of Rotarix® should be postponed in subjects suffering from diarrhea or vomiting.
- Receipt of any vaccine (other than the study vaccine[s]) in the 4 weeks preceding the first study vaccination (at Visit 1) or planned receipt of any vaccine in the 4 weeks before and/or following any study vaccination except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

The following is a temporary contraindication to blood draw:

- Receipt of oral or injected antibiotic therapy within the 72 hours (3 days) prior to a study blood draw. If a subject receives oral or injectable antibiotic therapy within 3 days prior to a blood draw, the investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw. If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

5.2.7.2 Warnings and Precautions to Vaccination

Prior to vaccination, check the warnings and precautions for individual vaccines administered. For the licensed vaccines, refer to the individual package inserts (34) (37) (38) (39). For MenACYW conjugate vaccine, refer to the Investigator's Brochure.

5.2.7.3 Definitive Contraindications

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

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

MenACYW conjugate vaccine:

1) MenACYW conjugate vaccine should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine or after previous administration of the vaccine or a vaccine containing the same components or constituents.
2) MenACYW conjugate vaccine should not be administered to anyone with a history of Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine, or a history of Arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid-containing vaccine.

Bexsero®:

3) Hypersensitivity to the active substances or to any of the excipients.

Infanrix hexa®:

4) Hypersensitivity to the active substances or to any of the excipients, or formaldehyde, neomycin and polymyxin.
5) Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.
6) Infanrix hexa® is contraindicated if the infant or toddlers has experienced an encephalopathy of unknown etiology, occurring within 7 days following previous vaccination with pertussis containing vaccine.

Prevenar 13®:

7) Hypersensitivity to the active substances, to any of the excipients, or to diphtheria toxoid.

Rotarix®:

8) Hypersensitivity to the active substance or to any of the excipients.
9) Children with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not receive the rotavirus vaccine as this contains sucrose as an excipient.
10) Hypersensitivity after previous administration of rotavirus vaccines.
11) History of intussusception.
12) Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception.
13) Subjects with SCID disorder.

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.

5.2.8 Conditions for Withdrawal

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

A subject may be withdrawn from the study:

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

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

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

Withdrawn subjects will not be replaced.

5.2.9 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 CRB completion instructions for additional details and examples):

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.3.2.1 This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject 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 subject or parent/ legally acceptable representative did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (e.g., deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • If the subject experiences a definitive contraindication that is a protocol deviation. • The parent/ legally acceptable representative signed the certified letter sent by the investigator but did not give any other news and did not come to any following visit.
Withdrawal by Parent / Legally Acceptable Representative	To be used: • When the parent/ legally acceptable representative indicated unwillingness to continue in the study • When the parent/ legally acceptable representative 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 any subject who has prematurely terminated the study because of an AE, a protocol deviation, or loss of eligibility, including definitive contraindications.

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

5.3 Safety Emergency Call

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

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

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. Administrative changes do not require IEC / IRB approval; however, the IEC / IRB must be notified whenever one is made.

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 organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the study subjects' parents/legally acceptable representative and should assure appropriate subject therapy and/or follow-up.

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

6 Vaccines Administered

MenACYW conjugate vaccine and Bexsero® will be provided by the Sponsor while the routine vaccines (Infanrix hexa®, Rotarix®, and Prevenar 13®) will be sourced by the investigators from the National Immunization Program and administered as per the standard practices. MenACYW conjugate vaccine and Bexsero® are classified as investigational medicinal products (IMP) and routine vaccines as non-investigational medicinal products (NIMP).

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product

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

Form: Liquid solution
Dose: 0.5 milliliter (mL)
Route: IM
Batch number: To be determined (TBD)

6.1.1.1 Composition

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

Meningococcal capsular polysaccharides:

Serogroup A ..... 10 µg
Serogroup C ..... 10 µg
Serogroup Y ..... 10 µg
Serogroup W ..... 10 µg

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

6.1.1.2 Preparation and Administration

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

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

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

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 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 2 doses of MenACYW conjugate vaccine administered concomitantly with routine pediatric vaccines (1st dose at 3 months of age) or with Bexsero® (2nd dose at 12 to 13 months of age).
- Subjects in Group 2 will receive 2 doses of MenACYW conjugate vaccine administered concomitantly with routine pediatric vaccines (1st dose at 3 months of age) or alone (2nd dose at 12 to 13 months of age).

6.1.2 Identity of Control Product

Bexsero®: Meningococcal group B Vaccine (rDNA, component, adsorbed)

Form: Suspension for injection in pre-filled syringe

Dose: 0.5 milliliter (mL)

Route: Deep IM

Batch number: TBD

6.1.2.1 Composition

Each 0.5 mL dose contains:

Recombinant Neisseria (N) meningitidis group B NHBA fusion protein[abc]	50 µg
Recombinant N meningitidis group B NadA protein[abc]	50 µg
Recombinant N meningitidis group B fHbp fusion protein[abc]	50 µg
Outer membrane vesicles from N meningitidis group B strain NZ98/254 measured as amount of total protein containing the PorA Pl.4[b]	25 µg

[a] Produced in *E. coli* cells by recombinant DNA technology

[b] Adsorbed on aluminium hydroxide (0.5 mg Al^{3+})

[c] NHB (Neisseria Heparin Binding Antigen), NadA (Neisserial adhesin A), fHbp (factor H binding protein)

The vaccine contains the following excipients: sodium chloride, histidine, sucrose, water for injections.

6.1.2.2 Preparation and Administration

Bexsero® is supplied in single dose (0.5 mL) pre-filled syringes.

A single dose of Bexsero® should be given by deep intramuscular injection, preferably in the anterolateral aspect of the thigh in infants. See the Bexsero® package insert (34).

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

6.1.2.3 Dose Selection and Timing

- Subjects in Group 1 will receive 3 doses of Bexsero® administered at 2, 4 and 12 to 13 months of age.
- Subjects in Group 2 will receive 2 doses of Bexsero® administered at 2 and 4 months of age. (Note: The 3rd dose of Bexsero® will be given at 13 to 14 months of age [Visit 5] after completion of study procedures, and will be provided by the Sponsor in order to complete the vaccination series).
- Subjects in Group 3 will receive 3 doses of Bexsero® administered at 2, 4 and 12 to 13 months of age.

6.2 Identity of Other Products

6.2.1 Identity of Other Product 1

Infanrix hexa®: Diphtheria (D), tetanus (T), pertussis (acellular component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and *Haemophilus influenzae* type b (Hib) conjugate vaccine (adsorbed) (GlaxoSmithKline UK, Middlesex, UK)

Form:	Powder and suspension for suspension injection
Dose:	0.5 mL
Route:	Deep IM
Batch number:	TBD

6.2.1.1 Composition

After reconstitution, each 0.5 mL dose contains:

Diphtheria toxoid[a] ..... not less than 30 International Units (IU)

Tetanus toxoid[a] ..... not less than 40 IU

Bordetella pertussis antigens:

- Pertussis toxoid[a] ..... 25 µg
- Filamentous hemagglutinin (FHA)[a] ..... 25 µg
- Pertactin (PRN) ..... 8 µg

Hepatitis B surface antigen (HBs)[bc] ..... 10 µg

Poliovirus (inactivated) (IPV)

- type 1 (Mahoney strain)[d] ..... 40 D-antigen unit
- type 2 (MEF-1 strain)[a] ..... 8 D-antigen unit
- type 3 (Saukett strain)[a] ..... 32 D-antigen unit

Haemophilus influenzae type b polysaccharide ..... 10 µg
(polyribosylribitol phosphate, PRP) [e]
conjugated to tetanus toxoid as carrier protein ..... approximately 25 µg

The vaccine contains the following excipients: lactose anhydrous, sodium chloride, Medium 199 (containing principally amino acids, mineral salts, vitamins), water for injection.

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

6.2.1.2 Preparation and Administration

Infanrix hexa® is supplied as a suspension (DTaP-HBV-IPV component) that is reconstituted with a lyophilized powder of adsorbed Hib, both in single dose vials. The vaccine is reconstituted by adding the entire contents of the syringe (DTaP-HBV-IPV component) to the vial containing the Hib pellet.

A single dose after reconstitution is 0.5 mL. See the Infanrix hexa® package insert (37).

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[a] adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 mg AL^{3+}

[b] produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

[c] adsorbed on aluminium phosphate ($AlPO_4$) 0.32 mg Al^{3+}

[d] propagated in VERO cells

[e] adsorbed on aluminium phosphate ($AlPO_4$) 0.32 mg Al^{3+}

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

6.2.1.3 Dose Selection and Timing

All subjects will receive 3 doses of Infanrix hexa® at 2, 3, and 4 months of age according to the UK immunization schedule.

6.2.2 Identity of Other Product 2

PREVENAR 13®: Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Pfizer Limited, Kent, UK)

Form: Suspension for injection

Dose: 0.5 mL

Route: IM

Batch number: TBD

6.2.2.1 Composition

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

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

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

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

6.2.2.2 Preparation and Administration

Prevenar 13® is supplied in a single-dose prefilled syringe. See the Prevenar 13® package insert (38).

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

6.2.2.3 Dose Selection and Timing

All subjects will receive 2 doses of Prevenar 13® at 2 and 4 months of age according to the UK immunization schedule.

The vaccine dose administered in the second year of life may be given as per standard of care at the last study visit after completion of study procedures (Visit 5 at 13 to 14 months).

6.2.3 Identity of Other Product 3

Rotarix®: Human rotavirus RIX4414 strain (live, attenuated [produced on Vero cells]) (GlaxoSmithKline Biological s.a., Rixensart, Belgium)

Form: Oral Suspension

Dose: 1.5 mL

Route: Oral

Batch number: TBD

6.2.3.1 Composition

Each 1.5 mL dose contains:

Human rotavirus RIX4414 strain
(live, attenuated)[a]..... not less than $10^{6.0}$ $CCID_{50}$[b]

The vaccine contains the following excipients: sucrose, di-sodium adipate, Dulbecco's Modified Eagle Medium, sterile water.

6.2.3.2 Preparation and Administration

Rotarix® is available in single-dose vials of lyophilized vaccine, accompanied by a prefilled oral applicator of liquid diluent (1 mL) with a plunger stopper, and a transfer adapter for reconstitution. See the Rotarix® package insert (39).

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

6.2.3.3 Dose Selection and Timing

All subjects will receive 2 doses of Rotarix® at 2 and 3 months of age according to the UK immunization schedule.

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[a] Produced on Vero cells

[b] $CCID_{50}$: 50% cell culture infectious dose

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 detachable label will be attached to the source documents by the sites. See the Operating Guidelines for additional label detail.

The investigational and control products are not blinded.

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 investigational product, MenACYW conjugate vaccine (single-dose vials), and control product will be supplied by the Sponsor.

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

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

The concomitant products will be sourced locally by the Investigational sites.

6.3.2.2 Product Storage

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

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C and should be protected from light. The vaccines must not be frozen.

For the investigational and control products, 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.

For concomitant products, the temperature will be monitored according to local standard practices.

6.3.2.3 Product Accountability

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

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

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

Concomitant products accountability will be managed according to local standard practices.

6.3.3 Replacement Doses

If a replacement dose of the investigational and/ or control product is required (e.g., because the syringe broke or particulate matter was observed in the syringe), the site personnel must either contact the IRT 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 investigational and control 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

Blinding and code-breaking procedures are not applicable to this study.

Given that the meningococcal vaccines (investigational and control) used in this study have different appearances, and individual group vaccination schedule differs in the number of vaccines administered and timing of their administration, the study has an open-label design. The laboratory personnel involved in testing the samples will be blinded.

6.5 Randomization and Allocation Procedures

On the day of Visit 1, subjects who meet the inclusion/exclusion criteria and whose parent / legally acceptable representative signs the ICF will be randomly assigned to Groups 1 through 3 in a 2:2:1 ratio, such that Group 1 will have approximately 320 subjects, Group 2 will have approximately 320 subjects, and Group 3 will have approximately 160 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 prompts. The IRT system will then provide the group 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 826000100005 is the fifth subject enrolled in Center Number 1 in the UK (826 being the UK 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, 2, and 3 as detailed below). Those will include Category 1, 2, and 3 medications ongoing at the time of inclusion in the study, or started at any time during the subject's participation in the trial. For category 3 medication, the period of reporting in CRB will be restricted to only 3 days (72 hours) prior to each blood sampling time point.

Collection period in source documents

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

Categories of Reportable medications and reporting period

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

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

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

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

- Category 2: Reportable medications with potential impact on immune response of the study vaccines and used to define the PPAS. For example:
  - Flu vaccines administered within 14 days pre or post each trial vaccination, including the day of the study vaccination visit
  - Any vaccine other than study vaccines (vaccines non-described in the Protocol) within the 28 days (4 weeks) preceding or after the trial vaccination, including the day of the study vaccination visit.
  - Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
  - Immunosuppressive therapy such as immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks) within past 3 months, anti-cancer chemotherapy, anti-proliferative drugs such as DNA synthesis inhibitors, or radiation therapy: used in the 6 months preceding the first trial vaccination, and up to the last blood draw.
    - Category 2 medications will be reported in the CRB according to the collection period detailed above up to the last blood draw.

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

- Category 3: Antibiotics that the subject received within 72 hours preceding each visit for blood draw related to IMP assessment (meningococcal vaccines) and used to define the PPAS.
    - Category 3 medications will be reported in the CRB for the period of 3 days (72 hours) before each blood draw.

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

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

- Trade name
- Rationale for the origin of prescription: Whether it was a prophylactic[a] medication? Prophylactic medications will be recorded in the Action Taken section of the AE collection tables.
- Medication category (1, 2, or 3)
- Start and stop dates

Dosage and administration route, homeopathic medication, will not be recorded.

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

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

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected:

- Groups 1 and 2: 160 subjects in each group will be randomized to have 3 blood draws at the intervals mentioned below. The remaining subjects will only have 1 blood draw at Visit 5.
- Group 3: all subjects will have 3 blood draws.

For the subjects randomized to have 3 blood draws in Group 1 and Group 2, the first 2 blood draws will be performed in a staggered way – approximately half of the subjects (~70 subjects in each group) will have blood draws at Visit 2 and Visit 3 (subset A), and the remaining half (~90 subjects in each group) will have blood draws at Visit 3 and Visit 4 (subset B). The third blood draw will be performed at Visit 5 for all subjects.

Subset A (~70 subjects in each group):

- a pre-vaccination blood sample at Visit 2

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

- a blood sample at Visit 3 (30 days after vaccination at Visit 2)
- a blood sample at Visit 5 (30 days after vaccination at Visit 4)

Subset B (~90 subjects in each group):

- a blood sample at Visit 3 (30 days after vaccination at Visit 2)
- a pre-vaccination blood sample at Visit 4
- a blood sample at Visit 5 (30 days after vaccination at Visit 4)

For the subjects randomized to Group 3, the first 2 blood draws will be performed in a staggered way – approximately half of the subjects (~70 subjects) will have blood draws at Visit 2 and Visit 3 (subset A), and the remaining half (~90 subjects) will have blood draws at Visit 3 and Visit 4 (subset B). The third blood draw will be performed at Visit 5 for all subjects.

Subset A (~70 subjects):

- a pre-vaccination blood sample at Visit 2
- a blood sample at Visit 3 (30 days after vaccination at Visit 2)
- a blood sample at Visit 5 (30 days after vaccination at Visit 4)

Subset B (~90 subjects):

- a blood sample at Visit 3 (30 days after vaccination at Visit 2)
- a pre-vaccination blood sample at Visit 4
- a blood sample at Visit 5 (30 days after vaccination at Visit 4)

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

7.1 Sample Collection

At Visits 2, 3 and 4, 3 mL of blood will be collected and at Visit 5, 6 mL of blood will be collected in tubes provided by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity; will verify the assigned subject's number on the pre-printed label that contains that subject's number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

7.2 Sample Preparation

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

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

The samples are then centrifuged, and the serum is transferred to the appropriate number of aliquoting tubes. These tubes must be pre-labeled with adhesive labels that identify the study code, the subject's number and the sampling stage or visit number.

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

7.3 Sample Storage and Shipment

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C or below. The temperature will be monitored and documented on the appropriate form during the entire study. If it rises above -10°C for any period of time, the Clinical Logistics Coordinator must be notified. See the Operating Guidelines for further details.

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

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

Blood samples for the assessment of antibody responses to the study vaccines will be stored for up to 25 years after the end of the study. It can take many years for a vaccine to be developed and approved for use. Even after the vaccine is made available to the public, we continue to gain more knowledge of the vaccine's benefits and risk or improve the methods we use to measure the efficacy of the vaccine. It is for this reason that it is important we retain these blood samples so that we can go back and confirm the results of this study if new information or improved methods become available.

7.4 Future Use of Stored Serum Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur R&D Global Operations for at least 25 years after the last license approval in the relevant market areas has been obtained for the vaccine being tested.

Subjects' parents / legally acceptable representatives will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

8 Clinical Supplies

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

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

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

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

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

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Safety

There are no primary objectives for safety.

9.1.2 Immunogenicity

9.1.2.1 Immunogenicity Endpoint

The primary endpoint for the evaluation of immunogenicity is:

Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y measured by hSBA assessed 30 days after vaccination(s) at 12 to 13 months of age (Group 1 versus Group 2)

9.1.2.2 Immunogenicity Assessment Methods

The hSBA testing will be performed at GCI, Swiftwater, PA.

Antibodies to meningococcal antigens (hSBA Method)

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

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Safety

There are no secondary objectives for safety.

9.2.2 Immunogenicity

9.2.2.1 Immunogenicity Endpoints

1) Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA 30 days after vaccinations with MenACYW conjugate vaccine concomitantly with Bexsero® or alone at 12 to 13 months of age (Group 1 vs Group 2)
2) Before and 30 days after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age, before and 30 days after the 2nd dose of MenACYW conjugate vaccine administered at 12 to 13 months of age, the following endpoints against meningococcal serogroups A, C, W, and Y will be assessed using hSBA and rSBA (subset) for Group 1 and Group 2:
   - hSBA and rSBA antibody titer (GMT)
   - titer distribution and RCDC
   - hSBA antibody titer ≥ 1:4 and titers ≥ 1:8
   - rSBA antibody titer ≥ 1:8 and titers ≥ 1:128
   - antibody titer ≥ 4-fold rise from pre-vaccination to post-vaccination

- hSBA and rSBA vaccine seroresponse[a]

3) 30 days after the 1st dose of MenACYW conjugate vaccine administered at 3 months of age, and before the 2nd dose of MenACYW conjugate vaccine administered at 12 to 13 months of age, the following endpoints against meningococcal serogroups A, C, W, and Y will be assessed using hSBA and rSBA (subset) for Group 1 and Group 2 antibody persistence evaluation:
   - hSBA and rSBA antibody titer (GMT)
   - hSBA antibody titer ≥ 1:4 and titers ≥ 1:8
   - rSBA antibody titer ≥ 1:8 and titers ≥ 1:128

9.2.2.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the secondary endpoints are the same as those presented in Section 9.1.2.2.

The rSBA testing is planned to take place at the Public Health England, Manchester, UK laboratory of Prof. Ray Borrow. Only a subset of samples in each group will be tested by rSBA (first 100 subjects randomized to have 3 blood draws in each of the 3 groups).

Antibodies to meningococcal antigens (rSBA Method)

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

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

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[a] hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer.

rSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:32.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer.

9.3 Observational Endpoints and Assessment Methods

9.3.1 Immunogenicity

9.3.1.1 Immunogenicity Endpoints

1) At 3 months of age, 4 months of age, at before and 30 days after vaccination with Bexsero® at 12 to 13 months of age, the following endpoints against meningococcal serogroups A, C, W, and Y will be assessed using hSBA and rSBA (subset) for Group 3:
   - hSBA and rSBA antibody titer (GMT)
   - hSBA antibody titer ≥ 1:4 and titers ≥ 1:8
   - rSBA antibody titer ≥ 1:8 and titers ≥ 1:128

9.3.1.2 Immunogenicity Assessment Methods

The immunogenicity hSBA and rSBA assessment methods for the observational endpoints are the same as those presented in Section 9.1.2.2 and Section 9.2.2.2.

9.3.2 Safety

9.3.2.1 Safety Definitions

The following definitions are taken from the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Adverse Event (AE):

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the

Investigator there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (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 adverse reactions (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" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (e.g., 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.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if headache between D0 and D07 is a solicited reaction (i.e., prelisted in the protocol and CRB), then a headache starting on D07 is a solicited reaction, whereas headache starting on D08 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

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

Systemic AE:

Systemic AEs are all AEs that are not injection or administration site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination or administration site (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.

9.3.2.2 Safety Endpoints

The following endpoints will be used for all subjects for the evaluation of the Safety Objectives:

- 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(s)

- 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(s)
- 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(s)
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination(s)
- 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) after vaccination(s) from D0 through the end of the trial

9.3.2.3 Safety Assessment Methods

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

9.3.2.3.1 Immediate Post-vaccination Observation Period

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

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

9.3.2.3.2 Reactogenicity (Solicited Reactions from Day 0 to Day 07 after Each Vaccination)

After the first vaccination, subject's parents / legally acceptable representatives will be provided with a diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (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 / legally acceptable representative to treat and/or manage any **solicited reactions** will be classified in the CRB using the following list (all applicable items should be checked):

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

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

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

Table 9.1 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 / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 9.2: 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 / legally acceptable representatives will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

Parents / legally acceptable representatives are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is axillary (as per standard of care). Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic thermometers must not be used.

9.3.2.3.3 Unsolicited Adverse Events

In addition to recording solicited reactions, parents / legally acceptable representatives will be instructed to record any other medical events that may occur 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 Visit 1 until 30 (±21) days after the last vaccination (end of study). 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 adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

[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 adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

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

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

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

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

- Whether the AE was serious

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

- Whether the AE caused study discontinuation

9.3.2.3.4 Adverse Events of Special Interest

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

- Generalized seizures (febrile and non-febrile) (40) (41)
- Kawasaki disease (42) (43) (44)
- Guillain-Barré syndrome (45)
- Idiopathic thrombocytopenic purpura (ITP) (46) (47)

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

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

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

9.3.2.3.5 Assessment of Causality

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

- Not related – The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the first vaccination (screening phase, if applicable)
- Related – There is a "reasonable possibility" that the AE was caused by the product administered, meaning that there is evidence or arguments to suggest a causal relationship

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

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

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

Serious adverse events occurring during a subject's participation in the study or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The investigator (licensed physician [M.D. or D.O.]) must validate the information entered on the AE CRF by completing the investigator validation form.

The Investigator must indicate on the AE CRF that the event was serious and must complete the relevant SAE section of this form as well as the appropriate Safety Complementary Information

CRFs. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the CTL with relevant SAE information details.

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

The Investigator must complete the paper copies of the AE CRF and of the appropriate Safety Complementary Information CRFs and send them to the Sponsor by one of the following means:

- By fax, to the following number: 570-957-2782

In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com

- By express mail, to the following address:

Sanofi Pasteur Inc.
Reception and Triage – Case Management
Global Pharmacovigilance
Mail Drop: 45D38
Discovery Drive
Swiftwater, PA 18370

When the EDC system becomes available, the Investigator must transcribe the information from the paper forms into the EDC system.

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

10.2 Follow-up Reporting by the Investigator

The AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (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 9.3.2.3.5.

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

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

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

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

The Sponsor's RMO [redacted] will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the 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 9.3.2.3. These diary cards will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Parents / legally acceptable representatives will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct parents / legally acceptable representatives on how to correctly use these tools.

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

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

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

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

11.2 Data Management

Management of SAE Data

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

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

Management of Clinical and Laboratory Data

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

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

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

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 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 Primary Objective

12.1.1.1 Hypotheses

Thirty days after the administration of MenACYW conjugate vaccine alone or concomitantly with Bexsero® in the second year of life (at Visit 5), the percentage of subjects who achieve hSBA titers ≥ 1:8 for meningococcal serogroups A, C, W, and Y in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$
Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve hSBA titers ≥ 1:8 in Group 1 and Group 2, respectively. Each of the serogroups A, C, W, and Y will be tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected.

12.1.1.2 Statistical Methods

For the 4 non-inferiority hypotheses using the vaccine response rates, the 95% CI of the difference in proportions between Group 1 and Group 2 will be computed using the Wilson Score method without continuity correction (48).

The overall non-inferiority of primary objective will be demonstrated if all 4 individual null hypotheses are rejected.

12.1.2 Hypotheses and Statistical Methods for Secondary Objective

12.1.2.1 Hypotheses

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

12.1.2.2 Statistical Methods

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups A, C, W, and Y for Group 1 and Group 2. In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages (49). For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed.

Reverse cumulative distribution curve (RCDC) figures will be provided for the antibody titers against meningococcal serogroups A, C, W, and Y.

Secondary Objective 1 – Geometric mean titer ratio (GMTR) between Group 1 and Group 2 after the second dose of MenACYW conjugate vaccine:

Thirty days after the administration of MenACYW conjugate vaccine alone or concomitantly with Bexsero® in the second year of life (at Visit 5), the hSBA GMTR between Group 1 and Group 2 for meningococcal serogroups A, C, W, and Y will be calculated and 95% CI will be provided.

Assuming that $\log_{10}$ transformation of the data follows a normal distribution, the $\log_{10}$ (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMTRs.

For each of the GMTRs, the statistical methodology will be based on the use of the 2-sided 95% CI of difference in means of post-vaccination $\log_{10}$ transformed concentrations between the 2 groups with normal approximation.

Secondary Objective 2 - Antibody responses of the first and second dose of MenACYW conjugate vaccine:

Descriptive analyses on A, C, W, and Y serogroups for all subjects in Group 1 and Group 2 providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4 and Visit 5) using hSBA will include but not be limited to:

- GMT and 95% CI
- Titer distribution and RCDC
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI

- Percentage of subjects with hSBA vaccine seroresponse[a]

Descriptive analyses on A, C, W, and Y serogroups for a subset of subjects in Group 1 and Group 2 providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4, and Visit 5) using rSBA will include but not be limited to:

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

Secondary Objective 3 – Antibody persistence after the first dose of MenACYW conjugate vaccine:

To evaluate antibody persistence after the first dose of MenACYW conjugate vaccine administered at 3 months of age, descriptive analyses on A, C, W, and Y serogroups for all subjects in Group 1 and Group 2 providing a blood sample at Visit 3 and Visit 4 using hSBA will include but not be limited to:

- GMT and 95% CI
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI

To evaluate antibody persistence after the first dose of MenACYW conjugate vaccine administered at 3 months of age, descriptive analyses on A, C, W, and Y serogroups for a subset of subjects in Group 1 and Group 2 providing a blood sample at Visit 3 and Visit 4 using rSBA will include but not be limited to:

- GMT and 95% CI
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI

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[a] hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer.

[b] rSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:32.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the pre-vaccination titer.

12.1.3 Statistical Methods for Observational Objectives

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

Immunogenicity

Descriptive analyses on A, C, W, and Y serogroups for all subjects in Group 3 providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4, and Visit 5) using hSBA will include but not be limited to:

- GMT and 95% CI
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI

Descriptive analyses on A, C, W, and Y serogroups for a subset of subjects in Group 3 providing a blood sample at corresponding time points (Visit 2, Visit 3, Visit 4 and Visit 5) using rSBA will include but not be limited to:

- GMT and 95% CI
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI

Safety

Safety results will be described for subjects in all study groups after vaccination at 2, 3, 4, and 12 to 13 months of age (Visit 1, Visit 2, Visit 3, and Visit 4, respectively). SAEs will be summarized throughout the trial. The main parameters for the safety endpoints will be described by 95% CIs (Clopper-Pearson method).

12.1.4 Sensitivity analysis due to COVID-19 pandemic

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

12.2 Analysis Sets

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

The study vaccines refer to MenACYW conjugate vaccine, Bexsero® vaccine and concomitant routine vaccines in the pre-defined vaccination schedule from Visit 1 to Visit 4.

The investigational product only refers to MenACYW conjugate vaccine or Bexsero® vaccine.

12.2.1 Full Analysis Set

There will be 3 Full Analysis Sets (FASs) for this study. Immunogenicity analyses will be performed on the 3 FASs for exploratory purposes.

12.2.1.1 Full Analysis Set 1 (FAS1) for Infant Vaccination (< 12 Months of Age):

The FAS1 is defined as the subset of all randomized subjects who received at least 1 dose of the study vaccine in infancy (at Visit 1 to Visit 3, <12 months of age), and have a valid post-vaccination serology result at Visit 3 in infancy. All subjects will be analyzed according to the treatment group to which they were randomized.

12.2.1.2 Full Analysis Set 2 (FAS2) for Persistence after Infant Vaccination (< 12 Months of Age):

The FAS2 is defined as the subset of all randomized subjects who received at least 1 dose of the study vaccine in infancy (at Visit 1 to Visit 3, <12 months of age), and have a valid post-vaccination serology result at Visit 4 (12 to 13 months of age). All subjects will be analyzed according to the treatment group to which they were randomized.

12.2.1.3 Full Analysis Set 3 (FAS3) for Second Year of Life Vaccination (12 to 13 Months of Age):

The FAS3 is defined as the subset of all randomized subjects who received at least 1 dose of the study vaccines at Visit 4 (12 to 13 month of age) in the second year of life, and have a valid post-vaccination serology result at Visit 5 in the second year of life (13 to 14 months of age). All subjects will be analyzed according to the treatment group to which they were randomized.

12.2.2 Safety Analysis Set

The Safety Analysis Set (SafAS) is defined as those subjects who have received at least one dose of the study vaccine(s)[a] and have any safety data available. Specific safety analysis will be defined and used after each vaccination. All subjects will have their safety analyzed after each dose according to the vaccine they actually received at each visit, and after any dose according to the vaccine received through Visit 1 to Visit 4.

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

There will be five SafASs for this study.

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

12.2.2.1 Overall Safety Analysis Set for Any Dose (SafAS)

The overall SafAS is defined as those subjects who have received at least one dose of the study vaccine and have any safety data available.

All subjects will have their safety analyzed after any dose according to the vaccine received from Visit 1 (2 months) to Visit 4 (12 through 13 months).

1) If one subject received both MenACYW conjugate vaccine and Bexsero® vaccine at Visit 4, the actual vaccination group is "Group 1".
2) Else if one subject only completed Visit 1 and received Bexsero® at Visit 1, the actual vaccination group will be classified as "Group 1", "Group 2" or "Group 3" according to the randomization group.
3) Else if one subject did not receive both MenACYW conjugate vaccine and Bexsero® vaccine at Visit 4, but received at least one dose of MenACYW from Visit 1 to Visit 4, the actual vaccination group is either "Group 1" or "Group 2" based on the randomization group.
4) Else if one subject did not receive MenACYW conjugate vaccine but received at least one dose of Bexsero® vaccine from Visit 1 to Visit 4, the actual vaccination group is "Group 3".
5) Else if one subject did not receive MenACYW conjugate vaccine and Bexsero® vaccine from Visit 1 to Visit 4, but received at least one dose of routine vaccines from Visit 1 to Visit 4, the actual vaccination group is "Other"

The safety analysis tables will not present data for 'Other' group, and the safety data for 'Other' group will be listed only.

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 (SafAS1)

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

The subjects received at least one dose of study vaccines but out of the planned vaccination schedule at Visit 1 will be classified to "Other" group. The safety analysis tables will not present data for 'Other' group at Visit 1, and the safety data for 'Other' group at Visit 1 will be listed only.

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

12.2.2.3 Safety Analysis Set for Vaccination at 3 Months of Age (SafAS2)

The SafAS2 for vaccination at 3 months of age is defined as those subjects who have received at least one dose of the study vaccines at Visit 2 around 3 months of age and have any safety data

available. All subjects will have their safety analyzed after Visit 2 dose according to the vaccines they actually received at Visit 2.

The subjects received at least one dose of study vaccines but out of the planned vaccination schedule at Visit 2 will be classified to "Other" group. The safety analysis tables will not present data for 'Other' group at Visit 2, and the safety data for 'Other' group at Visit 2 will be listed only.

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

12.2.2.4 Safety Analysis Set for Vaccination at 4 Months of Age (SafAS3)

The SafAS3 for vaccination at 4 months of age is defined as those subjects who have received at least one dose of the study vaccines at Visit 3 around 4 months of age and have any safety data available. All subjects will have their safety analyzed after Visit 3 dose according to the vaccines they actually received at Visit 2 and Visit 3. For subjects who received Bexsero® vaccine and at least one dose of routine vaccines at Visit 3, who received MenACYW conjugate vaccine and at least one dose of routine vaccines at Visit 2 will be analyzed under "Group 1 + Group 2" combined group, while subjects who received Bexsero® and at least one dose of routine vaccines at Visit 3 but only received at least one dose of routine vaccines without MenACYW conjugate vaccine at Visit 2 will be analyzed under "Group 3".

The subjects received at least one dose of study vaccines but out of the planned vaccination schedule at Visit 3 will be classified to "Other" group. The safety analysis tables will not present data for 'Other' group at Visit 3, and the safety data for 'Other' group at Visit 3 will be listed only.

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 12-13 Months of Age (SafAS4)

The SafAS4 for vaccination at months of age is defined as those subjects who have received at least one dose of the study vaccines at Visit 4 around 12 to13 months of age and have any safety data available. All subjects will have their safety analyzed after Visit 4 dose according to the vaccine(s) they actually received at Visit 4.

The subjects received at least one dose of study vaccines but out of the planned vaccination schedule at Visit 4 will be classified to "Other" group. The safety analysis tables will not present data for 'Other' group at Visit 4, and the safety data for 'Other' group at Visit 4 will be listed only.

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

12.2.3 Per-Protocol Analysis Set

The per-protocol analysis set (PPAS) is a subset of the FAS. Immunogenicity analyses will primarily be performed on PPAS. There will be three Per-Protocol Sets (PPASs) for this study according to the three FASs:

- PPAS for immunogenicity evaluation after infant vaccination (4 months of age, PPAS1)
- PPAS for immunogenicity persistence evaluation after infant vaccination (12 to 13 months of age, PPAS2)
- PPAS for second year of life vaccination (PPAS3)

12.2.3.1 Per-Protocol Set for immunogenicity evaluation after infant vaccination (4 months of Age, PPAS1):

The PPAS1 is a subset of the FAS1.

Post-vaccination serology obtained at Visit 3 (4 months of age) for all meningococcal antigens (A, C, W and Y) will be used for immunogenicity analyses of infant stage of the study.

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule for infant stage from Visit 1 to Visit 3
- Subject received a vaccine other than the one that he / she was randomized to receive for infant stage from Visit 1 to Visit 3
- Preparation and / or administration of vaccine was not done as per-protocol for infant stage from Visit 1 to Visit 3
- Subject did not receive vaccine in the proper time window for infant stage from Visit 1 to Visit 3:
    - Visit 1: ≥56 to ≤89 days of age
    - Visit 2: Visit 1 + 30 days (+14 days)
    - Visit 3: Visit 2 + 30 days (+14 days)
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn at Visit 3:
    - Blood sampling Visit 3: Visit 2 + 30 days (+14 days)
- Subject received a protocol-prohibited therapy / medication / vaccine (reportable concomitant medication of category 2 and / or category 3)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

In addition to the reasons listed above, subjects will also be excluded from the PPAS1 if their serology sample did not produce a valid test result at Visit 3.

Vaccine correctness required by the PPAS1 includes not only the 1 dose of MenACYW conjugate vaccine for Group 1 and Group 2, and the 2 doses of Bexsero® for Groups 1 to 3, but also the concomitant routine vaccines as scheduled (Infanrix hexa®, Rotarix®, and Prevenar 13®) for Groups 1 to 3 during infant stage from Visit 1 to Visit 3.

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

12.2.3.2 Per-Protocol Set for immunogenicity persistence evaluation after infant vaccination (12 to 13 Months of Age, PPAS2)

The PPAS2 is a subset of the FAS2.

Post-vaccination (after infant vaccination) serology obtained at Visit 4 (12 to 13 months of age) prior to toddler vaccination for all meningococcal antigens (A, C, W and Y) will be used for immunogenicity persistence analyses of infant stage of the study.

The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS2:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule for infant stage from Visit 1 to Visit 3
- Subject received a vaccine other than the one that he / she was randomized to receive for infant stage from Visit 1 to Visit 3
- Preparation and / or administration of vaccine was not done as per-protocol for infant stage from Visit 1 to Visit 3
- Subject did not receive vaccine in the proper time window for infant stage from Visit 1 to Visit 3:
    - Visit 1: ≥56 to ≤89 days of age
    - Visit 2: Visit 1 + 30 days (+14 days)
    - Visit 3: Visit 2 + 30 days (+14 days)
- Subject did not provide a post-dose (after infant vaccination) serology sample in the proper time window or a post-dose serology sample was not drawn at Visit 4:
    - Blood sampling Visit 4: 12 to 13 months of age prior to toddler vaccination
- Subject received a protocol-prohibited therapy / medication / vaccine (reportable concomitant medication of category 2 and / or category 3)

- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

In addition to the reasons listed above, subjects will also be excluded from the PPAS2 if their serology sample did not produce a valid test result at Visit 4.

Vaccine correctness required by the PPAS2 includes not only the 1 dose of MenACYW conjugate vaccine for Group 1 and Group 2, and the 2 doses of Bexsero® for Groups 1 to 3, but also the concomitant routine vaccines as scheduled (Infanrix hexa®, Rotarix®, and Prevenar 13®) for Groups 1 to 3 during infant stage from Visit 1 to Visit 3.

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

12.2.3.3 Per-Protocol Set for Second Year of Life Vaccination (12 to 13 Months of Age, PPAS3):

The PPAS3 is a subset of the FAS3.

During the second year of life, the immunogenicity analyses for meningococcal antigens (A, C, W and Y) are performed on serology obtained at Visit 5, which is 30 days after the administration of study vaccine(s) at Visit 4.

The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS2:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule, including the infant schedule and the 12 to 13 months vaccination in second year of life, from Visit 1 to Visit 4
- Subject received a vaccine other than the one that he / she was randomized to receive during the infant stage or second year of life, from Visit 1 to Visit 4
- Preparation and / or administration of vaccine was not done as per-protocol during the infant stage or second year of life, from Visit 1 to Visit 4
- Subject did not receive vaccine in the proper time window during the second year of life:
  - Visit 4: 12 to 13 months of age
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn at Visit 5 in the second year of life:
  - Blood sampling 3 (Visit 5): Visit 4 + 30 days (+21 days)
- Subject received a protocol-prohibited therapy / medication / vaccine during the infant stage or second year of life prior to or at Visit 5

- Subject had other protocol violations during the infant stage or second year of life from Visit 1 to Visit 5, which affected the subject's immune response, as determined by the clinical team before locking the database

In addition to the reasons listed above, subjects will also be excluded from the PPAS3 if their serology sample did not produce a valid test result at Visit 5 in the second year of life.

Vaccine correctness required by the PPAS3 includes the dose of MenACYW conjugate vaccine for Group 1, the dose of MenACYW conjugate vaccine and the dose of Bexsero® for Group 2, and the dose of Bexsero® for Group 3 in the second year of life at Visit 4.

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

12.2.4 Populations Used in Analyses

Immunogenicity analyses will be primarily performed on the PPAS, including PPAS1, PPAS2 and PPAS3 (immunogenicity persistence analyses after infant vaccination will be performed on the PPAS2). Additional immunogenicity analyses will be performed for exploratory purposes on the FAS, including FAS1, FAS2 and FAS3 (immunogenicity persistence analyses after infant vaccination will be performed on the FAS2). In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

The safety analysis will be performed on the SafAS, including SafAS, and SafAS1 through SafAS4. Subjects will be analyzed according to the vaccine(s) they actually received.

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done.

12.3.2 Immunogenicity

Missing data will not be imputed. No test or search for outliers will be performed.

12.4 Interim / Preliminary Analysis

No interim analyses are planned.

12.5 Determination of Sample Size and Power Calculation

Due to the potential impact of COVID-19 pandemic, an additional 100 subjects will be enrolled to maintain sufficient study power for the primary objective. Thus, approximately 800 subjects will be enrolled. An estimated 30% non-adherence rate from enrollment will result in approximately

560 subjects in the per-protocol population available for immunogenicity analyses. Group 1 and Group 2 will have 224 evaluable subjects in each treatment group and Group 3 will have 112 evaluable subjects. The power is calculated with the assumption that the estimate from the evaluation group equals that of the control group.

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

For the Primary Objective

With 224 evaluable subjects in each of the treatment groups, Group 1 and Group 2, the study will have 88% power to declare the non-inferiority of Group 1 versus Group 2 based on A, C, W, and Y antibodies.

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

Antigen	Endpoint	Non-inferiority Margin	Estimates*	Power (%)
A	hSBA titers ≥ 1:8	10%	92%	95.9
C	hSBA titers ≥ 1:8	10%	90%	92.5
Y	hSBA titers ≥ 1:8	10%	96%	99.8
W	hSBA titers ≥ 1:8	10%	96%	99.8
Overall				**88.4**

*Estimated responses are based on results observed in MET39, Group 3 (2, 4, 12 months data) (2% had been subtracted from the observed results for serogroups A, W, and Y to provide more conservative estimates)

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 forms, telephone contact logs, and worksheets. The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

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

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

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

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

13.3 Confidentiality of Data, Data Protection, and Access to Subject Records

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur. In the event a subject's medical records are not at the investigational site, it is the responsibility of the investigator to obtain those records if needed.

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

Subject's race and ethnicity will be collected in this study because these data are required by regulatory agencies to submit demographic data and summarize effectiveness and safety data for important subgroups, including gender, and race and/or ethnicity (50).

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 which 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.

[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.

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

The following instruction manuals will be provided: the Operating Guidelines for detailed study procedures such as the product management and sample-handling procedures.

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

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (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 samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

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

13.4.3 Archiving

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

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

13.5 Financial Contract and Insurance Coverage

A Clinical Trial Agreement 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 / legally acceptable representative may be provided with a stipend according to local practice to compensate for the time and travel required for study visits and procedures, if any.

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

Document Number	Version Number
CLI_00002404	6.0
Project Code MenQuad TT	
Artifact Name Protocol Body	

	Approver Name	Date (Universal Time)	Reason for Signature
Approval	[redacted]		