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

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET52
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product(s):	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
Version and Date of the SAP core body part:	Version 1.0, 08MAR2023

Table of Contents

List of Tables

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CI	confidence interval
CRF	case report form
CSR	clinical study report
D	day
EDC	electronic data capture
EIA	enzyme immunosorbent assay
ELISA	enzyme linked immunosorbent assay
EDC	electronic data capture
FAS	full analysis set
GM	geometric mean
GMT	geometric mean titer
GMTR	geometric mean titer ratio
hSBA	serum bactericidal assay using human complement
IMD	invasive meningococcal disease
IMP	investigational product
ITP	idiopathic thrombocytopenic purpura
LLOQ	lower limit of quantification
LLT	lowest level term
MD	missing data
MedDRA	medical dictionary for regulatory activities
PPAS	per-protocol analysis set
PT	preferred term
RCDC	reverse cumulative distribution curve
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SOC	system organ class
TLF	table(s), listing(s), and figure(s)
ULOQ	upper limit of quantification

1 Introduction

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 invasive meningococcal disease (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 capsular polysaccharides (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 Menactra® is 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[a] 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. Preclinical 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 (1).

[a] Currently Menomune® -A/C/Y/W-135 is not anymore available in the market.

2 Trial Objectives

2.1 Primary Objectives

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.

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.

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

3 Description of the Overall Trial Design and Plan

3.1 Trial 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: 320 subjects. 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: 320 subjects. MenACYW conjugate vaccine at 3 months and at 12 to 13 months of age; Bexsero® at 2 and 4 months of age

Group 3: 160 subjects. 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 160 subjects in each group will only have 1 blood draw at Visit 5.
- Group 3: all 160 subjects will have 3 blood draws.

All subjects in Group 1 and 2 will have blood draws at Visit 5. 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 in Group 3.

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)

The schedule of vaccination and blood sampling is further detailed in Table 3.1.

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 D7 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 trial will be considered as SAEs.

3.2 Trial Plan

Vaccination and Blood Sampling

A schedule of assessments, study vaccinations, and blood draws is provided in the Table of vaccination and blood sampling schedule in the protocol and in Table 3.1. Subjects in Group 1 and 2 will have 1 or 3 blood draws. Subjects in Group 3 will have 3 blood draws.

Table 3.1: Vaccination and blood sampling schedule

Group	Visit								
	Visit 1 2 months	**Visit 2 3 months**		**Visit 3 4 months**		**Visit 4 12 - 13 months**		**Visit 5 13 - 14 months**	
	Vaccina-tions	**Blood collection**	**Vaccina-tions**	**Blood collection**	**Vaccina-tions**	**Blood collection**	**Vaccin-ation(s)**	**Blood collection**	**Vaccin-ations***
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 D7 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.

Study Procedures

Table 3.2: 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		

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**
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		
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 3.3: 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		

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 Bexsero®	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		
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 3.4: 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) BL1 (3 mL)***		BL2 (3 mL)***		BL3 (6 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		
Telephone call		X		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**
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.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Immunogenicity

4.1.1.1 Immunogenicity Endpoints

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).

4.1.1.2 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.

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Immunogenicity

4.2.1.1 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[a]) 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[b]

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[a]) for Group 1 and Group 2 antibody 9 months 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

4.2.1.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods for the secondary endpoints are the same as those presented in Section 4.1.1.2.

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.

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[a] rSBA data will be generated for all blood draws in a subset of subjects defined as the first 100 subjects randomized to have 3 blood draws in each of the 3 groups (with a 5-digit subject enrollment ID starting with a "98")

[b] 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.

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.

4.3 Observational Endpoints and Assessment Methods

4.3.1 Immunogenicity

4.3.1.1 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[c]) 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

4.3.1.2 Immunogenicity Assessment Methods

The immunogenicity hSBA and rSBA assessment methods for the observational endpoints are the same as those presented in Section 4.1.1.2 and Section 4.2.1.2.

4.3.2 Safety

4.3.2.1 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.

[c] rSBA data will be generated for all blood draws in a subset of subjects defined as the first 100 subjects randomized to have 3 blood draws in each of the 3 groups (with a 5-digit subject enrollment ID starting with a "98").

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[d]
- Requires inpatient hospitalization or prolongation of existing hospitalization[e]
- Results in persistent or significant disability / incapacity[f]
- 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

[d] 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.

[e] 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.

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

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 reaction (AR).

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

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

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

Solicited Reaction:

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

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

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

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

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., pre-listed 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.

4.3.2.2 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, relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) injection site reactions occurring up to D07 after each vaccination
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRB) systemic reactions occurring up to D07 after each vaccination
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to D30 after each vaccination
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) after vaccination(s) from D0 through the end of the trial.

4.3.2.3 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.

4.3.2.3.1 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 the protocol.

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

After the first vaccination, 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 subject's parent / legally acceptable representative in the diary card on the day of each vaccination and for the next 7 days (i.e., D0 to D07) until resolution:

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

  The action(s) taken by the parent or 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 4.1 and Table 4.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

Table 4.1: 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 4.2: 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.

4.3.2.3.3 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 following 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 CRF. 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 the protocol 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 4.1 and Table 4.2).

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

  - Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

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

- Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described Section 4.3.2.3.5.

- 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

4.3.2.3.4 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)
- Kawasaki disease
- Guillain-Barré syndrome
- Idiopathic thrombocytopenic purpura (ITP)

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 the protocol. Further

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

4.3.2.3.5 Assessment of Causality

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

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

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

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

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

All daily records for solicited injection site and systemic reactions will be derived into daily intensity scales according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

For the derivation of daily intensities, the following sequential steps will be applied:

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as "No" and with all daily records missing (Unknown), then all daily intensities will be derived as None.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator.

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.4.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Presence

Presence is derived from the maximum overall intensity on the period considered:

None: No presence

Grade 1, Grade 2, or Grade 3: Presence

Missing or Unknown: Missing presence

Subjects with at least one non-missing presence for a specific endpoint will be included in the safety analysis tables. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

The time period is displayed as D0-D3, D4-D7, D8 and later.

Note: solicited reactions with Missing presence will not be included in the safety analysis tables but will be listed separately in separate listings.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3 during the solicited period (D0 to D7) after each vaccination.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence during the solicited period (D0 to D7) after each vaccination.

Time of onset is presented as D0-D3, D4-D7.

4.4.1.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the solicited period (D0 to D7) considered is derived from the daily intensities as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity (e.g., Grade 3) may also be derived.

4.4.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence after each vaccination is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

> (End date – last vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1

If the end date of the solicited reaction is missing or is incomplete (contains missing data), the overall number of days of occurrence will be considered as Missing.

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period as described in Section 4.4.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables).

4.4.1.2 Unsolicited AEs

4.4.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a None intensity event.

Note: Unsolicited AEs with None intensity for a specific endpoint will not be included in the safety analysis tables but will be included in separate listings.

4.4.1.2.2 Intensity

Intensity for unsolicited AE will be derived according to the following classification:

> None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator.

Intensity for the other unsolicited AEs will correspond to the value reported in the CRF.

The maximum intensity corresponds to the highest intensity for a unique term.

4.4.1.2.3 Last Vaccination

Last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the CRF and is calculated as follows:

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE.
- If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" is used to determine the last vaccination before the unsolicited AE.

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE provided in the clinical database and the date of last vaccination as described in Section 4.4.1.2.3:

Time of Onset = start date of the unsolicited AE - date of last vaccination before the unsolicited AE

The time of onset is considered as missing only if one or both dates are missing or partially missing.

The unsolicited AEs will be analyzed "Within 30 days" after each vaccination, which corresponds to AEs with a time of onset between 0 and 30 days after each vaccination or missing onset date. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the Section 4.4.1.2.3), so will be included in these tables.

Time of onset period is displayed as D0-D3, D4-D7, D8-D14, D15 or later, and Missing.

The unsolicited AEs will also be analyzed "Within 30 days" after any vaccination.

Note: Unsolicited AEs that occurred before vaccination (negative time of onset) or with onset higher than defined above (e.g, >30 days after each vaccination for non-serious AE) will not be included in analysis, but will be listed separately.

4.4.1.2.5 Duration

Duration is derived from the start and end dates of the unsolicited AE:

Duration = End date of unsolicited AE - start date of unsolicited AE + 1.

The duration is considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

4.4.1.2.6 Serious Adverse Events

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF.

SAEs will be analyzed throughout the study using the following periods:

- Within 7 days after each vaccination
- Within 30 days after each vaccination
- During the study (i.e., all SAEs occurred during the study)

4.4.1.2.7 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF. AESIs will be analyzed throughout the study using the following periods:

- Within 7 days after each vaccination
- Within 30 days after each vaccination
- During the study (i.e., all AESIs occurred during the study)

4.4.1.3 Other Safety Endpoints

4.4.1.3.1 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.4.1.3.2 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.3.3 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.3.4 Causality Relationship

There are three original relationship terms collected in this study indicating if there is a causal relationship between one AE and study vaccines or study procedures (SAEs only). It includes "relationship to investigational product (IMP)" which refers to the relationship with MenACYW or Bexsero, "relationship to non-investigational product (non-IMP)" which refers to the relationship with routine vaccines from the study, and "relationship to study procedures" which is applicable for SAEs only.

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis. Missing relationship to non-IMP with a start date on or after 20DEC2019[b] will be considered related to non-IMP vaccine.
- The missing relationship to study procedures for SAEs will not be imputed. The relationship with study procedures (SAEs only) will not be included in analysis, but will be listed separately.

The original relationship information will be presented as collected in the AE listings with relationship collected.

4.4.1.3.5 Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who, on the "Completion at End of Study" form question "What was the subject's status?" has "Adverse Event" checked.
- Safety overview table: A subject who has either on the "Completion at End of Study" form, question "What was the participant's status?" has "Adverse Event" checked or lists a solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.
- System Organ Class (SOC)/Preferred Term (PT) table: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

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

If a value is < LLOQ, then use the computed value LLOQ/2

If a value is between ≥ LLOQ and < ULOQ, then use the value

If a value is ≥ ULOQ, then use the computed value ULOQ

[b] 20DEC2019 corresponds to the start date of collection in database of the relationship for non-IMP unsolicited systemic AEs.

4.4.2.2 hSBA Vaccine Seroprotection

The derived seroprotection indicator for hSBA will be "Yes" if hSBA titer is ≥ 1:8, otherwise seroprotection will be "No". Note: If hSBA titer is missing, the seroprotection for hSBA will be missing.

4.4.2.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline/pre-vaccination and post-baseline/post-vaccination computed values (as described in Section 4.4.2.1) and is computed as follows:

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

If the computed fold-rise value is ≥ 4, then the derived ≥ 4-fold rise indicator will be "Yes", otherwise ≥ 4-fold rise will be "No".

Note: If baseline/pre-vaccination or post-baseline/post-vaccination computed value is missing, then fold-rise is missing.

4.4.2.4 hSBA Vaccine Seroresponse

The derived seroresponse indicator for hSBA will be "Yes" if

- 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.

4.4.2.5 rSBA Vaccine Seroresponse

The derived seroresponse indicator for rSBA will be "Yes" if

- 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

4.4.3 Efficacy

Not applicable

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

The age of a subject in the study was the calendar age in day at the time of inclusion.

Duration of a Subject in the Trial

The duration of a subject in the study is computed as follows:

Maximum (date of last visit, date of termination) – date of V01 of that subject +1.

Duration of the Study

The duration of study is computed in days as follows:

Maximum of all subjects (date of last visit, date of termination) – Minimum of all subjects (date of V01) + 1

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 software or later. The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics in Table 5.1 will be presented. The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (2)). For immunogenicity results, assuming that Log_{10} transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log_{10} (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (seroresponse, ≥ 4-fold rise, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / concentration)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

5.1.1.1 Hypotheses

Thirty days[c] 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 (hSBA vaccine seroprotection) in Group 1 and Group 2, respectively.

5.1.1.2 Statistical Methods

Each of the serogroups A, C, W, and Y will be tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is > -10%, the inferiority assumption will be rejected. For the 4 non-inferiority hypotheses using the vaccine seroprotection 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 (3).

Let $\hat{\theta} = p_1 - p_2$, then $L = \hat{\theta} - \delta$ and $U = \hat{\theta} + \varepsilon$ are respectively the lower and the upper limits of the CI, where:

$$\delta = Z_{0.025}\sqrt{\left\{\frac{l_1(1-l_1)}{n_1} + \frac{u_2(1-u_2)}{n_2}\right\}}$$

$$\varepsilon = Z_{0.025}\sqrt{\left\{\frac{l_2(1-l_2)}{n_2} + \frac{u_1(1-u_1)}{n_1}\right\}}$$

l_1 and u_1 are calculated from the CI of the single proportion in Group 1 given by:

$$\frac{(2n_1p_1 + Z^2_{0.025} \pm Z_{0.025}\sqrt{(Z^2_{0.025} + 4n_1p_1(1-p_1))})}{2(n_1 + Z^2_{0.025})}$$

[c] D30 (+21 days)

l_2 and u_2 are calculated from the CI of the single proportion in Group 2 given by:

$$\frac{(2n_2p_2 + Z^2_{0.025} \pm Z_{0.025}\sqrt{(Z^2_{0.025} + 4n_2p_2(1-p_2))}}{2(n_2 + Z^2_{0.025})}$$

where $Z_{0.025}$ is the upper 97.5th percentile of the standard normal distribution.

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

5.1.2 Hypotheses and Statistical Methods for Secondary Objective(s)

5.1.2.1 Hypotheses

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

5.1.2.2 Statistical Methods

Descriptive statistics will be provided for the antibody titers against meningococcal serogroups A, C, W, and Y for each group. 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 (2). For GMTs, 95% CIs of point estimates will be calculated using normal approximation assuming they are log-normally distributed ($\log_{10}$ scale).

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

Logarithm transformation of the individual titers will be calculated. Assuming that individual $\log_{10}$(titer) is normally distributed, the 95% CI for the difference in $\log_{10}$(GMT) between Group 1 and Group 2 will be in the form:

$$\bar{X}_1 - \bar{X}_2 \pm t(1-\alpha/2, n_1 + n_2 - 2) \cdot S\sqrt{1/n_1 + 1/n_2}$$

where $\bar{X}_i = \log_{10}(\text{GMT})$ is the mean of $\log_{10}$(titer) of Group i, $S^2 = [(n_1 - 1)\, S_1{}^2 + (n_2 - 1)\, S_2{}^2] / (n_1 + n_2 - 2)$ is the pooled sample variance, n_i and S_i^2 are the sample size and sample variance of

[d] D30 (+21 days)

Group i, $t(1-\alpha/2, n_1 + n_2 - 2)$ is the 100(1-α/2) percentile of the *t*-distribution with degrees of freedom $df = n_1 + n_2 - 2$.

The 95% CI for the hSBA GMTR between Group 1 and Group 2 will be formed by taking the antilogarithms of the lower and upper limits of the 95% CI for the difference in log(GMT) between both vaccine groups.

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, within the time window for each time point) 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
- Percentages of subjects with titer ≥ 4-fold rise from Visit 2 to Visit 3, from Visit 2 to Visit 5, from Visit 4 to Visit 5, and corresponding 95% CIs
- Percentages of subjects with hSBA vaccine seroresponse[e] from Visit 2 to Visit 3, and from Visit 2 to Visit 5, from Visit 4 to Visit 5, and corresponding 95% CIs

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 RCDC
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
- Percentages of subjects with titer ≥ 4-fold rise from Visit 2 to Visit 3, from Visit 2 to Visit 5, from Visit 4 to Visit 5, and corresponding 95% CIs
- Percentages of subjects with rSBA vaccine seroresponse[f] from Visit 2 to Visit 3, from Visit 2 to Visit 5, from Visit 4 to Visit 5, and corresponding 95% CIs

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 in Group 1 and Group 2 providing a blood sample at corresponding time points (Visit 3 and Visit 4, within the time

[e] 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.

[f] 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.

window for each time point) 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 all subjects in Group 1 and Group 2 providing a blood sample at corresponding time points (Visit 3 and Visit 4, within the time window for each time point) 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

5.1.3 Statistical Methods for Observational Objective(s)

5.1.3.1 Hypothesis

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

5.1.3.2 Statistical Methods

5.1.3.2.1 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, within the time window for each time point) 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

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
- Titer distribution and RCDC
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI

5.1.3.2.2 Safety

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

5.1.4 Complementary Output

5.1.4.1 Sensitivity Analysis due to COVID-19 Pandemic

As this study was conducted during Coronavirus Disease 2019 (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 subset of subjects who were impacted by COVID-19 is 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, baseline and demographics characteristics, and the main immunogenicity and safety endpoints will also be summarized in the subsets of subjects impacted / non-impacted subjects to assess the potential impact of COVID-19 situation on study outcome. The outputs will be provided in Appendix 15 of the CSR.

The assessment of the impact of COVID-19 pandemic will be based on but not limited to the following analyses:

- To summarize the impact of COVID-19 on the overall study conduct
    - Early termination due to COVID-19
    - Impact on visit conduct (visit not done, partially done, data collection method/procedure change)
    - Major and critical protocol deviations due to COVID-19
- To summarize disposition across study visits for subjects impacted by COVID-19
- To summarize baseline demographics for subjects impacted / non-impacted by COVID-19
- To provide an individual listing of subjects impacted by COVID-19 and how they were impacted
- To provide a listing of visits impacted by COVID-19 and how they were impacted
- To assess the potential impact of COVID-19 on the main immunogenicity and safety endpoints in the subsets of impacted / non-impacted subjects

Immunogenicity analyses

The sensitivity analyses in immunogenicity will be performed based on PPAS and FAS.

1) The primary endpoint for immunogenicity will be assessed:
    - 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 and Group 2)
2) To evaluate the baseline immunogenicity, the following endpoint at D0 before the vaccination at 3 months of age will also be assessed:
    - Percentage of subjects with hSBA ≥ 1:8, and 95% CI (Group 1 and Group 2)
3) To assess the GMTR between Group 1 and Group 2 after the second MenACYW vaccination:
    - GMTs against meningococcal serogroups A, C, W, and Y measured by hSBA 30 days after vaccinations at 12 to 13 months of age (Group 1 versus Group 2)

Safety analyses

Safety overview after any vaccine injections – Overall Safety Analysis Set

Safety overview after vaccine injections at 2 months of age – Safety Analysis Set 1

Safety overview after vaccine injections at 3 months of age – Safety Analysis Set 2

Safety overview after vaccine injections at 4 months of age – Safety Analysis Set 3

Safety overview after vaccine injections at 12 through 13 months of age – Safety Analysis Set 4

5.1.4.2 Subgroup Analysis

Additional subgroup analyses by gender based on PPAS will be provided for primary and main secondary immunogenicity endpoints and will be described in Appendix 15 of the CSR.

The gender subgroup analyses will have two categories (Female and Male).

The following immunogenicity parameters will be assessed:

1) Primary parameter:
   - Percentage of subjects with hSBA titers ≥ 1:8 and 95% CI against meningococcal serogroups A, C, W, and Y 30 days after vaccination(s) at 12 to 13 months of age (Group 1 and Group 2)
2) GMTR between Group 1 and Group 2 after the second MenACYW vaccination:
   - GMTs against meningococcal serogroups A, C, W, and Y measured by hSBA 30 days after vaccinations at 12 to 13 months of age (Group 1 versus Group 2)
3) Immunogenicity response after the second MenACYW vaccination in the second year of life for Group 1 and Group 2:
   - Percentage of subjects with hSBA vaccine seroresponse and 95% CI from pre-first MenACYW vaccination at 3 months of age (Visit 2) to 30 days post second MenACYW vaccination in the second year of life (Visit 5)

Safety analyses

The safety overview will be also described by gender:

Safety overview after any vaccine injections – Overall Safety Analysis Set

Safety overview after vaccine injections at 2 months of age – Safety Analysis Set 1

Safety overview after vaccine injections at 3 months of age – Safety Analysis Set 2

Safety overview after vaccine injections at 4 months of age – Safety Analysis Set 3

Safety overview after vaccine injections at 12 through 13 months of age – Safety Analysis Set 4

5.1.4.3 Sensitivity Analysis due to Blood Sample Issues

If applicable and necessary, additional immunogenicity sensitivity analyses will be performed for subjects with blood samples potentially handled incorrectly during collection, processing, storage or shipment, and may have potential impact on the analysis results (e. g., blood samples stored out

of temperature after a power outage) based on the PPASs. The outputs will be provided in Appendix 15 of the CSR.

The endpoint for the sensitivity analyses will be the GMT.

- hSBA GMTs and 95% CI at each time point for each group by blood sample status – Per-Protocol Analysis Set 1
- hSBA GMTs and 95% CI at each time point for each group by blood sample status – Per-Protocol Analysis Set 3

5.1.4.4 Sensitivity Analysis due to study vaccine non-suitability for use issues

During a data review, it was reported that a significant amount of subjects received study vaccines that were not suitable for use. Additional immunogenicity sensitivity analyses will be conducted for subjects who received an unacceptable IMP due to study vaccine non-suitability for use issues. These subjects will be excluded from PPAS3 due to the exclusion criterion "Preparation and / or administration of vaccine was not done as per-protocol for infant stage or second year of life, from Visit 1 to Visit 4". The sensitivity analyses will be conducted on PPAS4. PPAS4 is defined the same as PPAS3, except for the PPAS3 exclusion criterion "Preparation and / or administration of vaccine was not done as per-protocol for infant stage or second year of life, from Visit 1 to Visit 4". PPAS4 will not exclude the subjects with this criterion. The output will be provided in Appendix 15 of the CSR.

The following immunogenicity parameters will be assessed:

1) Primary parameter:
    - Percentage of subjects with hSBA titers ≥ 1:8 and 95% CI against meningococcal serogroups A, C, W, and Y 30 days after vaccination(s) at 12 to 13 months of age (Group 1 and Group 2)
2) GMTR between Group 1 and Group 2 after the second MenACYW vaccination:
    - GMTs against meningococcal serogroups A, C, W, and Y measured by hSBA 30 days after vaccinations at 12 to 13 months of age (Group 1 versus Group 2)
3) Immunogenicity response after the second MenACYW vaccination in the second year of life for Group 1 and Group 2:
    - Percentage of subjects with hSBA vaccine seroresponse and 95% CI from pre-first MenACYW vaccination at 3 months of age (Visit 2) to 30 days post second MenACYW vaccination in the second year of life (Visit 5)

5.2 Analysis Sets

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

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS according to the randomization

group. All safety analyses will be performed on the SafAS according to the vaccine they actually received.

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.

5.2.1 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.

5.2.1.1 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.

5.2.1.2 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.

5.2.1.3 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.

5.2.2 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)
- PPAS for sensitivity analyses (PPAS4)

5.2.2.1 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 vaccine or coronavirus vaccine, subjects who receive 1 or more doses of a pandemic influenza vaccine or coronavirus vaccine, or the vaccine listed above at any time during the study will not be withdrawn from the study.

5.2.2.2 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 vaccine or coronavirus vaccine, subjects who receive 1 or more doses of a pandemic influenza vaccine or coronavirus vaccine, or the vaccine listed above at any time during the study will not be withdrawn from the study.

5.2.2.3 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 PPAS3

- 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 (reportable concomitant medication of category 2 and / or category 3) 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 and the dose of Bexsero® for Group 1, the dose of MenACYW conjugate vaccine 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 vaccine or coronavirus vaccine, subjects who receive 1 or more doses of a pandemic influenza vaccine or coronavirus vaccine, or the vaccine listed above at any time during the study will not be withdrawn from the study.

5.2.2.4 Per-Protocol Set for Second Year of Life Vaccination (12 to 13 Months of Age, PPAS4)

PPAS4 is defined the same as PPAS3, except for the PPAS3 exclusion criterion "Preparation and / or administration of vaccine was not done as per-protocol for infant stage or second year of life, from Visit 1 to Visit 4". PPAS4 will not exclude the subjects with study vaccine non-suitability for use issues.

5.2.3 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)[ga] 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.

5.2.3.1 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 vaccines 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 complete Visit 01 and received Bexsero at Visit 01, the actual vaccination group will be classified to "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 from Visit 1 to Visit 4 and didn't receive 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"

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

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).

5.2.3.2 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 Bexsero® vaccine and at least one dose of schedule routine vaccines will be analyzed under "Group 1 + Group 2 + Group 3" combined group.

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).

5.2.3.3 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 who received MenACYW and at least one dose of routine vaccines will be analyzed under "Group 1 + Group 2" combined group, while the subjects didn't receive MenACYW but received at least one dose of routine vaccines 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 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).

5.2.3.4 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 the Subjects received Bexsero ® vaccine and at least one dose of routine vaccines at Visit 3, who had received MenACYW and at least one dose of routine vaccines at Visit 2 will be analyzed under "Group 1 + Group 2" combined group, while subjects 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 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 2 or 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).

5.2.3.5 Safety Analysis Set for Vaccination at 12-13 Months of Age (SafAS4)

The SafAS4 for vaccination at 12-13 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 under "Group 1", "Group 2", or "Group 3".

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).

Other Analysis Set(s)

Enrolled / Screened subjects

As this study has no screening visit, enrolled subjects are subjects for whom signed off the inform consent form (ICF) and a CRF has been created.

Randomized subjects

A randomized subject is an enrolled subject for whom an injection group has been allocated and with any available data in CRF.

5.2.4 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.

5.2.5 Handling of Missing Data and Outliers

5.2.6 Safety

Generally, no replacement will be done for safety missing data and outliers. In all subject listings, partial and missing data will be clearly indicated as missing.

5.2.6.1 Immediate

For unsolicited non-serious systemic AEs, a missing response to the "Immediate" field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

5.2.6.2 Causal Relationship

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be imputed as in Section 4.4.1.3.4.

5.2.6.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

5.2.6.4 Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the last vaccination (computed according to the Section 4.4.1.2.3.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

5.2.6.5 Action Taken

Missing actions taken will remain missing and not be imputed.

5.2.7 Immunogenicity

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

The computational rule for undetectable responses < LLOQ and ≥ ULOQ is described in Section 4.4.2.1.

5.2.8 Efficacy

Not applicable.

5.3 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

5.4 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% drop-out 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.

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 5.2: 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)

In case the drop-out rate exceeds 30%, with 209 evaluable subjects in each treatment group, the overall power to declare the non-inferiority for Group 1 versus Group 2 will be 85%. With 191 evaluable subjects in each treatment group, the overall power to declare the non-inferiority for Group 1 versus Group 2 will be 80%.

5.5 Data Review for Statistical Purposes

A review of the data has been anticipated through the data review process led by data management before database lock. This review of the data included a statistical review.

Besides, 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.

5.6 Changes in the Conduct of the Trial or Planned Analyses

Two sensitivity analyses are added to the planned analyses. One is for the subjects with blood samples potentially handled incorrectly during collection, processing, storage or shipment, and may have potential impact on the analysis results (e. g., blood samples stored out of temperature after a power outage). The other one is for the subjects who received an unacceptable IMP for use due to study vaccine non-suitability for use issues.

6 References List

1 Payne J. Meningococcal vaccination. Patient. https://patient.info/doctor/meningococcalvaccination#ref-2. Updated 20 August 2015. Accessed 15 August 2017.

2 Newcombe R.G., Two-sided confidence intervals for the single proportion: comparison of seven methods, Statistics in Medicine, (1998) 17, 857-872.

3 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998; 17(8):873-90.