NCT number: NCT03547271

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

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

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET58
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, W, and Y) Tetanus Toxoid Conjugate Vaccine
Form / Route:	Liquid solution / Intramuscular (IM)
Indication For This Study:	MenACYW conjugate vaccine administered to healthy infants and toddlers
Version and Date of the SAP Core Body Part:	Version 1.0, 26 April 2024

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List of Abbreviations

µg	Microgram
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CI	confidence interval
CRB	case report book
CRF	case report form
CSR	clinical study report
D	day
DC	diary card
DTaP	diphtheria, tetanus, and acellular pertussis
EU	European Union
FAS	full analysis set
FHA	filamentous hemagglutinin
GCI	Global Clinical Immunology
GM	geometric mean
GMT	geometric mean titer
HB	hepatitis B
HBsAg	hepatitis B surface antigen
Hib	*Haemophilus influenzae* type b
hSBA	serum bactericidal assay using human complement
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IMD	invasive meningococcal disease
IPV	inactivated polio vaccine
IU	international unit
IRT	interactive response technology
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mIU	milli International unit
mL	Milliliter
MMR	measles, mumps, rubella
PCV10	pneumococcal conjugate vaccine (10-valent, adsorbed)

PCV13	pneumococcal conjugate vaccine (13-valent, adsorbed)
PPAS	per-protocol analysis set
PRP	polyribosylribitol phosphate
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
SD	standard deviation
SMT	Safety Management Team
SOC	system organ class (primary)
TC	telephone call
TT	tetanus toxoid
ULOQ	upper limit of quantification
USA	United States of America
V	visit

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. Compared to a previous Sanofi Pasteur meningococcal conjugate vaccine, Menactra® the MenACYW conjugate vaccine is prepared using tetanus toxoid as the carrier protein. Conjugation of polysaccharide antigens to a protein carrier can induce T cell-dependent immune responses, which are anticipated to give rise to higher antibody titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response. The program targets licensure of the MenACYW conjugate vaccine in many countries in North America, Europe, Latin America, Africa, the Middle East, and Asia Pacific.

The MenACYW conjugate vaccine is designed to cover broader age groups than those covered by Menomune® -A/C/Y/W-135 and Menactra®. Menactra® has been very successful since its licensure in 2005; however, it is not licensed in Europe and is not indicated in persons 8 months of age or younger or 56 years of age and older. While Menomune® -A/C/Y/W-135 and Menactra® are currently licensed in different parts of the world, the MenACYW conjugate vaccine is being developed by Sanofi Pasteur to ultimately replace Menomune® -A/C/Y/W-135 and Menactra® in the global market as a quadrivalent meningococcal conjugate vaccine indicated in infants/toddlers, children, adolescents, adults, and older adults > 56 years of age. Meningococcal polysaccharide vaccines have two important limitations: a) the antibody response is age dependent, with infants giving the poorest response; and b) polysaccharides alone are T cell-independent immunogens, and therefore no anamnestic response is seen. The immunogenicity of polysaccharide vaccines in infants and children has been shown to be improved by conjugating the polysaccharides to protein carriers. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of polysaccharide-specific total immunoglobulin G (IgG) and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials including those with the final formulation (MET39 and MET44) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above trials using the final formulation or in the earlier trials.

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

2 Trial Objectives

2.1 Primary Objective

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

2.2 Secondary Objectives

1) To demonstrate the non-inferiority of the antibody response against meningococcal serogroups A, C, W, and Y following the administration of 2 doses in infancy of MenACYW conjugate vaccine compared to 2 doses in infancy of Nimenrix® when each vaccine is administered concomitantly with routine pediatric vaccines (PCV10 and hexavalent vaccine) (Group 1 versus Group 2)
2) To describe the antibody responses against meningococcal serogroups A, C, W, and Y when MenACYW conjugate vaccine is administered in a 3-dose series concomitantly with the routine pediatric vaccines (Group 3)
3) To describe the antibody responses against the antigens of the routine pediatric vaccines administered in a 3-dose series concomitantly with MenACYW conjugate vaccine or Nimenrix® (Groups 1, 2, and 3)
4) To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by hSBA when MenACYW conjugate vaccine or Nimenrix® is administered in a 3-dose series concomitantly with PCV10 and other routine pediatric vaccines (Groups 1 and 2)
5) To describe the antibody responses against meningococcal serogroups A, C, W, and Y measured by hSBA when MenACYW conjugate vaccine is administered in a 4-dose series concomitantly with PCV13 and other routine pediatric vaccines (Group 4)
6) To describe the antibody responses against the antigens of the routine pediatric vaccines administered with MenACYW conjugate vaccine administered in a 4-dose series concomitantly (Group 4)

2.3 Observational Objectives

Immunogenicity

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

Safety

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

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase III, partially modified double-blind (open-label for some of the vaccines / study groups, as detailed in the note below), randomized, parallel-group, active-controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Nimenrix® (Meningococcal group A, C, W-135, and Y conjugate vaccine) when administered as a 3-dose series (ie, 2 doses administered in infancy and 1 dose in the second year of life) concomitantly with routine pediatric vaccines to healthy infants and toddlers in Europe.

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

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

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

Subjects in Finland, Sweden or Poland may have received the licensed rotavirus vaccine concomitantly with study vaccines at study vaccination visits Visit 1 and Visit 2. If not, the rotavirus vaccine could have been administered with a time interval of at least 2 weeks before or 2 weeks after Visit 1 and/or Visit 2. The rotavirus vaccines were sourced by the study sites and administered as per local standard practices. Safety data were collected after the administration of

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

the rotavirus vaccine concomitantly with the study vaccine. No serological testing was done for rotavirus immunogenicity.

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

3.2 Trial Plan

Approximately 1652 healthy infants aged 6 to 12 weeks at enrollment were to be randomized. Approximately 20% of subjects 6 to 8 weeks of age (≥ 42 to ≤ 59 days) should have been enrolled in Groups 1 and 2 to provide safety and immunogenicity data for this population, as described below:

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

The vaccination and blood sampling schedules are detailed in Table 3.1 and Table 3.2. A detailed summary of study procedures and assessments is provided in Table 3.3 for Group 1, 2 and 3 and Table 3.4 for Group 4.

Vaccinations

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

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

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

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

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

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

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

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

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

Blood sampling

All subjects provide 4 blood samples.

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

- at baseline (pre-primary vaccination 1, Day 0 [D0])
- 30 days (+21 days) after the 2nd dose of MenACYW conjugate vaccine / Nimenrix®

- prior to the 3rd dose (toddler dose) of MenACYW conjugate vaccine / Nimenrix®
- 30 days (+21 days) after the 3rd dose (toddler dose) of MenACYW conjugate vaccine / Nimenrix®

Subjects in Group 4 have provided blood samples for immunogenicity assessment as follows:

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

Collection of safety data

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

Table 3.1: Vaccination and blood sampling schedule in Groups 1, 2, and 3

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

PCV10: Synflorix®

PCV13: Prevenar 13®

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

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

†Blood will be drawn prior to vaccinations

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

Table 3.2: Vaccination and blood sampling schedule in Group 4

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

PCV13: Prevenar 13®

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

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

†Blood will be drawn prior to vaccinations

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

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

Table 3.3: Table of Study Procedures – Groups 1, 2 and 3

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

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

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

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

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

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

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

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

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

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

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

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

††† This call is made 5 months after Visit 3 and at least 14 days before Visit 4. During this telephone call, the staff will find out whether the subject experienced any SAE (including any AESI) not yet reported, will remind the subject's parent / legally acceptable representative that routine vaccinations will be provided in the context of this study and that they should bring back the diary card to the study center at the next visit, and will confirm the date and time of the next visit.

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

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

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

Table 3.4: Table of Study Procedures – Group 4

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

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

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

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

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

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

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

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

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

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

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

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

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

††† This call is made 5 months after Visit 4 and at least 14 days before Visit 5. During this telephone call, the staff will find out whether the subject experienced any SAE (including any AESI) not yet reported, will remind the subject's parent / legally acceptable representative that routine vaccinations will be provided in the context of this study and that they should bring back the diary card to the study center at the next visit, and will confirm the date and time of the next visit.

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

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

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

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

4.1.1 Immunogenicity

4.1.1.1 Immunogenicity Endpoint

The primary endpoint for the evaluation of immunogenicity is:

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

4.1.1.2 Immunogenicity Assessment Methods

All assays will be performed at Global Clinical Immunology (GCI), Swiftwater, PA or at qualified contract laboratories for GCI.
For all samples, hSBA analysis will be done for all four serogroups.

Antibodies to meningococcal antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, W, and Y will be measured in hSBA. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. Serogroup-specific meningococcal bacteria along with human complement are added to the serum dilutions and allowed to incubate. After this incubation period, an agar overlay medium is added to the serum/complement/bacteria mixture, allowed to harden, and then incubated overnight at 37°C with 5% carbon dioxide (CO_2). Bacterial colonies present in the wells are then counted. The endpoint titer is determined by the reciprocal serum dilution yielding ≥ 50% killing as compared to the mean of the complement control wells. The lower limit of quantitation (LLOQ) of the hSBA assay is a titer of 1:4. This method will be performed on all blood samples (refer to Table 9.1 and Table 9.2 of the protocol) for all study groups. In the event of insufficient serum sample volume, the conduct of the hSBA assay is of higher priority than the rSBA assay and the assays for antigens of concomitant vaccines.

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Immunogenicity

4.2.1.1 Immunogenicity Endpoints

1) Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y assessed at 30 days after Dose 2 of MenACYW conjugate vaccine or Nimenrix® measured by hSBA, when administered concomitantly with routine pediatric vaccines (Group 1 versus Group 2)

2) Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y measured by hSBA in Group 3 at the following time points:

   • Day 0 (before Dose 1 of MenACYW conjugate vaccine)

   In addition, the following endpoints will be assessed:

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

   • 30 days after Dose 2 of MenACYW conjugate vaccine in infancy, and before and 30 days after the booster dose (Dose 3)

   In addition, the following endpoints will be assessed:

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

   - Post-vaccination titers ≥ 4 times the latest pre-vaccination titers

   - hSBA vaccine seroresponse for serogroups A, C, W, and Y as defined in section 4.4.2.5

3) To answer the third secondary objective the following endpoints will be used for Group 1, 2 and 3:

   - Antibody titers or concentrations against the antigens of hexavalent vaccine (DTaP-IPV-HB-Hib) in Groups 1, 2, and 3 at the following time points:

     • Day 0 (before Dose 1)

     - Anti-pertussis antibody concentrations (pertussis toxin [PT], filamentous hemagglutinin [FHA])

- 30 days after Dose 2 in infancy

  - Antibody concentrations/titers for all antigens

  - Anti-tetanus antibody concentrations ≥ 0.01 international units (IU)/ milliliter (mL), ≥ 0.1 IU/mL and ≥ 1.0 IU/mL

  - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL

  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8

  - Anti-polyribosyl-ribitol phosphate (PRP) antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL

  - Pertussis vaccine seroresponse for anti-PT and anti-FHA, defined in section 4.4.2.6

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

- Before and 30 days after the booster dose (Dose 3):

  - Antibody concentrations/titers for all antigens

  - Anti-tetanus antibody concentrations ≥ 0.01 IU/mL ≥ 0.1 IU/mL and ≥ 1.0 IU/mL

  - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL

  - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8

  - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL

  - Pertussis vaccine seroresponse for anti-PT and anti-FHA as defined in section 4.4.2.6

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

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

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

  - Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and ≥ 1.0 µg/mL for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F

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

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

- Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and ≥ 1.0 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

- Antibody concentrations against the antigens of MMR vaccine 30 days after the MMR vaccine injection[a]
  - Antibody concentrations for all antigens
  - Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL)
  - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
  - Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)

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

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

   • Day 0 (before Dose 1 of MenACYW conjugate vaccine)

   In addition, the following endpoints will be assessed:
   - Antibody titers ≥ 1:4 and titers ≥ 1:8

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

   In addition, the following endpoints will be assessed:
   - Antibody titers ≥ 1:4 and titers ≥ 1:8
   - Post-vaccination titers ≥ 4 times the latest pre-vaccination titers
   - hSBA vaccine seroresponse for serogroups A, C, W, and Y is defined in section 4.4.2.5

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

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

- Antibody titers or concentrations against the antigens of hexavalent vaccine (DTaP-IPV-HB-Hib)
  - Pre-booster dose:
    - Anti-pertussis antibody concentrations anti-PT, anti-FHA
  - 30 days after the booster dose (Dose 4):
    - Antibody concentrations/titers for all antigens
    - Anti-tetanus antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
    - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
    - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
    - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
    - Pertussis vaccine seroresponse for anti-PT and anti-FHA as defined in section 4.4.2.6
    - Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Antibody concentrations against the antigens of PCV13 in Group 4, 30 days after the booster dose (Dose 4):
    - Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
    - Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and ≥ 1.0 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Antibody concentrations against the antigens of MMR vaccine 30 days after the MMR vaccine injection[a]
    - Antibody concentrations for all antigens
    - Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL)
    - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
    - Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)

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

4.2.1.2 Immunogenicity Assessment Methods

See Section 9.2.2.2 of the protocol.

4.2.2 Efficacy

No clinical efficacy data were obtained in the study.

4.2.3 Safety

There are no secondary objectives for safety.

4.3 Observational Endpoints and Assessment Methods

4.3.1 Immunogenicity

4.3.1.1 Immunogenicity Endpoints

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

- Antibody titers ≥ 1:8, and titers ≥ 1:128
- Post-vaccination titers ≥ 4 times the latest pre-vaccination titers
- rSBA vaccine seroresponse for serogroups A, C, W, and Y as defined in section 4.4.2.7

4.3.1.2 Immunogenicity Assessment Methods

See Section 9.3.1.2 of the protocol.

[a] The rSBA subset will comprise:
- Group 1 and Group 2: 100 subjects in each group
- Group 3 and Group 4: 50 subjects in each group

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

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.
Therefore an AE may be:

- A new illness
- The worsening of a pre-existing condition
- An effect of the vaccination, including the comparator
- A combination of the above
- All AEs include serious and non-serious AEs.

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

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the Investigator there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (eg, asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious* which is based on subject / event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[a]

[a] The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization[a]
- Results in persistent or significant disability / incapacity[b]
- Is a congenital anomaly / birth defect
- Is an important medical event (IME)

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These IMEs should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new-onset diabetes, or autoimmune disease.

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered an 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" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (eg, injection site tenderness or irritability occurring between D0 and D07 post-vaccination).

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

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

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[a] 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.

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

Unsolicited AE / AR:

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

Injection Site Reaction:

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

Systemic AE:

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

Adverse Event of Special Interest (AESI):

An AESI is an event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

4.3.2.2 Safety Endpoints

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

- Unsolicited systemic AEs reported in the 30 minutes after each vaccination, including occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken, relationship to the product administered, and whether the event caused termination from the study.
- Solicited (prelisted in the subject's diary card and CRB) injection site and systemic reactions starting any time from Day 0 (day of vaccination) through Day 7 after each vaccination, including occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction caused termination from the study.
- Unsolicited non-serious AEs reported up to 30 days after each vaccination, including occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to the product administered, and whether the event caused termination from the study.

- SAEs (including AESIs) reported throughout the study, ie, from Visit 1 (first vaccination) to the last study visit (Visit 5 for Groups 1, 2, and 3 and Visit 6 for Group 4, occurring 30 days [+21 days] after the last vaccination), including occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to the product administered, whether the event caused termination from the study, outcome, elapsed time from last administration (if less than 24 hours), relationship to study procedures, and seriousness criterion.

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 SAE.

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

After each vaccination, subjects' parents / legally acceptable representatives will be provided with a diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (ie, D0 to D07) until resolution:

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

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

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

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

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

Table 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 rectal, oral or axillary according to local practices, with the rectal route preferred for infants and the axillary route preferred for toddlers. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic thermometers must not be used.

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 from Day 0 to Day 30 or until the subject returns for the next study visit, whichever comes first. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from Visit 1 until 30 days after the last vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE case report form (CRF) and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports). In case a subject experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE.

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 4.1and Table 4.2).

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

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

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

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

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

- Action taken for each AE (eg, medication)

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

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

- Whether the AE was serious

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

- Whether the AE caused study discontinuation

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 EU regulators.

No safety concerns relating to these AESIs have been identified with the use of MenACYW conjugate vaccine in the completed clinical trials. Because of their medical importance and to ensure expedited communication to the Sponsor, these AESIs are to be considered and collected as SAEs and reported to the Sponsor. 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 either ***not related*** or ***related***, based on the following definitions:

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

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

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

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 reactions will be derived into daily intensity 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 Overall Intensity

Maximum overall intensity is derived from the daily intensities computed 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 over the time period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing or Unknown: Missing presence

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis. 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.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed 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.

Note: If a reaction is not continuous (ie, 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.

Time of onset period is displayed 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 computed 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 (eg, 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 presence is derived from the daily intensities and the end date of the reaction after the end of the solicited period. The overall number of days of presence is:

- (End date - last vaccination date) + (number of days of presence within the solicited period) - length of the solicited period + 1

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

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed 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 Grade 0 intensity event.

Grade 0 events are not included in safety analysis but are included in separate listings.

4.4.1.2.2 Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing

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" or similar field, 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 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 Day 0 and Day 30.

Unsolicited AE that occurred before vaccination (negative time of onset) will not be included in analysis but will be listed separately.

Unsolicited AE which is non-serious, non-AESI and non-MAAE that occurred with a time of onset higher than defined above will not be included in analysis but will be listed separately.

- For unsolicited AE with missing day, month and year, the unsolicited AE will be classified as "Within 30 days"
- For unsolicited AE with partially missing start date, the partial available information will be used to determine if this AE is classified "Within 30 days" or "Not within 30 days". An AE will be categorized as "Not within 30 days" only if there is clear evidence from the partially missing start date that this AE happens before the first vaccination or after the last vaccination + 30 days. In all other situations, this AE is considered as "Within 30 days". Situations may happen as:

    - If the start date of AE has missing Day and non-missing Month and Year
        - If the "Month/Year of AE start date" < "Month/Year of first vaccination date", then it is clear that this unsolicited AE happened before the first vaccination and this unsolicited AE will not be included in the analysis but will be listed separately.

- Else if the "Month/Year of last vaccination date" <= "Month/Year of AE start date" <= "Month/Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "Within 30 days".
- Else if the "Month/Year of AE start date" > "Month/Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "not within 30 days". If the AE is non-serious, non-AESI and non-MAAE, then it will not be included in the analysis but will be listed separately.

- If the start date of AE has missing Day and Month and non-missing Year:
  - If the "Year of AE start date" < "Year of first vaccination date", then it is clear that this unsolicited AE happens before the first vaccination and this unsolicited AE will not be included in the analysis but will be listed separately.
  - Else if the "Year of last vaccination date" <= "Year of AE start date" <= "Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "Within 30 days".
  - Else if the "Year of AE start date" > "Year of (last vaccination date + 30 days)", then this unsolicited AE will be categorized as "not within 30 days". If the AE is non-serious, non-AESI and non-MAAE, then it will not be included in the analysis but will be listed separately.

A few examples of missing time of onset with start date of AE partially missing:

First injection date	Last injection date	Start date of the AE	Injection date + 30	Will be analyzed "Within 30 days" ?
16Oct2023	16Oct2023	Missing	N/A	Y
16Oct2023	16Oct2023	Sep2023	N/A	N
16Oct2023	16Oct2023	Oct2023	15Nov2023	Y
16Oct2023	16Oct2023	Nov2023	15Nov2023	Y
16Oct2023	16Oct2023	Dec2023	15Nov2023	N
05Jan2023	05Jan2023	2022	N/A	N
16Oct2023	16Oct2023	2023	15Nov2023	Y
08Dec2023	08Dec2023	2024	07Jan2024	Y
16Oct2023	16Oct2023	2024	15Nov2023	N

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

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
- Within 30 days
- During the study (ie, all SAEs occurred during the study)
- From D31 after vaccination injection to next visit (for SAE overview only)

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
- Within 30 days
- During the study (ie, all AESIs occurred during the study)
- From D31 after vaccination injection to next visit (for SAE overview only)

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 Causal 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 Nimenrix®, "relationship to non-investigational product (non-IMP)" which refers to the relationship with routine vaccines from the study (only collected for unsolicited injection site reactions), and "relationship to study procedures" which is applicable for SAEs only.

The information will be summarized as collected in those fields.

Missing causal relationship will be handled as described in Section 5.3.1.2. Relationship to study procedure is only presented in the listing.

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 before the end of active phase.

In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Study" form question "What was the participant's status?" has "Adverse Event" checked.
- Safety overview table: A participant 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 (undetectable responses < the lower limit of quantitation [LLOQ] and ≥ the 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 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

4.4.2.2 Seroprotection

If the computed value is ≥ to a predefined cutoff, then the derived seroprotection indicator will be "Yes" for that test, otherwise seroprotection will be "No". Note: If the computed value is missing, seroprotection will be missing.

hSBA vaccine seroprotection is defined as: hSBA titers ≥ 1:8.

4.4.2.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows:

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

Note: If baseline or post-baseline is missing, then fold-rise is missing.

4.4.2.4 Seroconversion

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

Note: If baseline or post-baseline is missing, then fold-rise is missing.

Using the calculation method described in section 4.4.2.3, the ≥ 4-fold rises indicator evaluated after the last dose in infancy for hSBA titers and rSBA titers will be derived as follows:

- Using values of BL0002 (Visit 3 for Groups 1, 2 ,3 and Visit 4 for Groups 4) as post-baseline values and values of BL0001 (Visit 1 for all groups) as baseline values.

For the booster series, two ≥ 4-fold rises indicators for hSBA and rSBA titers will be presented and derived as follows:

- Using values of BL0004 (Visit 5 for Groups 1, 2, 3 and Visit 6 for Groups 4) as post-baseline values and values of BL0001 (Visit 1 for all groups) as baseline values.
- Using values of BL0004 (Visit 5 for Groups 1,2, 3 and Visit 6 for Groups 4) as post-baseline values and values of BL0003 (Visit 4 for Groups 1, 2, 3 and Visit 5 for Groups 4) as baseline values.

4.4.2.5 hSBA Vaccine Seroresponse

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

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

For the vaccine seroresponse evaluated after the last dose in infancy, the post-vaccination titer corresponds to BL0002 (Visit 3 for Groups 1, 2, 3 and Visit 4 for Groups 4) and the pre-vaccination titer corresponds to BL0001 (Visit 1 for all groups).

For the vaccine seroresponse evaluated after the booster dose, two seroresponse indicators will be defined as follows:

- The post-vaccination titer corresponds of BL0004 (Visit 5 for Groups 1, 2, 3 and Visit 6 for Groups 4) and the pre-vaccination titer corresponds to BL0001 (Visit 1 for all groups).

- The post-vaccination titer corresponds of BL0004 (Visit 5 for Groups 1, 2, 3 and Visit 6 for Groups 4) and the pre-vaccination titer corresponds to BL0003 (Visit 4 for Groups 1, 2, 3 and Visit 5 for Groups 4).

4.4.2.6 Pertussis vaccine seroresponse for anti-PT and anti-FHA

For Groups 1, 2, and 3, 30 days after Dose 2 in infancy, Pertussis vaccine seroresponse for anti-PT and anti-FHA is defined as:

- If the pre-primary vaccination concentration is $< 4 \times$ LLOQ, post-primary vaccination concentration $\geq 4 \times$ LLOQ
- If the pre-primary vaccination concentration is $\geq 4 \times$ LLOQ, post-primary vaccination concentration $\geq$ pre-primary vaccination concentration

For Groups 1, 2, and 3, before and 30 days after the booster dose (Dose 3) and for Group 4, before and 30 days after the booster dose (Dose 4), Pertussis vaccine seroresponse for anti-PT and anti-FHA is defined as:

- If the pre-booster vaccination concentration is $< 4 \times$ LLOQ, post-booster vaccination concentration $\geq 4 \times$ pre-booster concentration
- If the pre-booster vaccination concentration is $\geq 4 \times$ LLOQ, post-booster vaccination concentration $\geq 2 \times$ pre-booster concentration

4.4.2.7 rSBA Vaccine Seroresponse

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

- 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 at least 4-fold greater than the pre-vaccination titer.

For the vaccine seroresponse evaluated after the last dose in infancy, the post-vaccination titer corresponds to BL0002 (Visit 3 for Groups 1, 2, 3 and Visit 4 for Groups 4) and the pre-vaccination titer corresponds to BL0001 (Visit 1 for all groups).

For the vaccine seroresponse evaluated after the booster dose, two seroresponse indicators will be defined as follows:

- The post-booster vaccination titer corresponds of BL0004 (Visit 5 for Groups 1, 2, 3 and Visit 6 for Groups 4) and the pre-primary vaccination titer corresponds to BL0001 (Visit 1 for all groups).

- The post- booster vaccination titer corresponds of BL0004 (Visit 5 for Groups 1, 2, 3 and Visit 6 for Groups 4) and the pre- booster vaccination titer corresponds to BL0003 (Visit 4 for Groups 1, 2, 3 and Visit 5 for Groups 4).

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 is the calendar age in day at the time of inclusion. Age will also be presented using a categorical variable with two categories: ≥ 42 to ≤ 59 days and ≥ 60 to 89 days.

4.4.4.2 Duration of the Study

The duration is computed in days as follows: Latest period date - earliest period date + 1.

4.4.4.3 Subject Duration

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

Maximum (Visit dates, Termination date, Last contact date) – V01 date + 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.

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 (1).

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.

The results of the statistical analysis will be available in the final clinical study report (CSR).

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 (seroprotection, seroconversion, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / data)	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).

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method), quoted by Newcombe (1), ie, using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (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.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

5.1.1.1 Hypotheses

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

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

H_0 *(Null hypothesis)*:

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

H_1 *(Alternative hypothesis)*:

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

5.1.1.2 Statistical Methods

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

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

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

5.1.2 Hypotheses and Statistical Methods for Secondary Objective 1

5.1.2.1 Hypotheses

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

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

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

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

5.1.2.2 Statistical Methods

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

5.1.3 Statistical Methods for Secondary Objectives 2, 3 and 4

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

In general, categorical variables will be summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions. For GMTs and geometric mean concentrations (GMCs), 95% CIs of point estimates will be calculated using a normal approximation assuming they are log-normally distributed.

Objective 2 (Group 3) and objective 4 (Groups 1 and 2)

The meningococcal serogroups A, C, Y, and W measured by hSBA, for Groups 1, 2, and 3, before Dose 1 of MenACYW conjugate vaccine, 30 days after Dose 2 of MenACYW conjugate vaccine in infancy, and before and 30 days after the booster dose (Dose 3) will be described with:

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

Objective 3 (Groups 1, 2 and 3)

The antibody titers or concentrations against the antigens of hexavalent vaccine (DTaP-IPV-HB-Hib) will be described:

- At Day 0 (before Dose 1)
  - GMT and 95% CI for Pertussis antigens (pertussis toxin [PT], filamentous hemagglutinin [FHA])

- At 30 days after Dose 2 in infancy
  - GMT and 95% CI
  - *RCDCs*
  - Percentage of subjects with titer ≥ cutoff:
    - Anti-tetanus antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
    - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
    - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
    - Anti-polyribosyl-ribitol phosphate (PRP) antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
    - Anti-hepatitis B surface antigen (HBsAg) antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
  - Pertussis vaccine seroresponse for anti-PT and anti-FHA

- Before and 30 days after the booster dose (Dose 3)
  - GMT and 95% CI
  - Titer distribution and RCDCs
  - Percentage of subjects with concentrations/titers ≥ cut-off:
    - Anti-tetanus antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
    - Anti-diphtheria antibody concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
    - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
    - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
    - Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
  - Pertussis vaccine seroresponse for anti-PT and anti-FHA

The antibody concentrations against the antigens of PCV10 (Anti-pneumococcal antibody concentrations for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) in Groups 1 and 2, 30 days after Dose 2 in infancy and 30 days after the booster dose (Dose 3) will be described:

- GMT and 95% CI
- Titer distribution and RCDCs
- Percentage of subjects with Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and ≥ 1.0 µg/mL

Antibody concentrations against the antigens of PCV13 (Anti-pneumococcal antibody concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in Group 3, 30 days after Dose 2 in infancy and 30 days after the booster dose (Dose 3):

- GMT and 95% CI
- RCDCs
- Percentage of subjects with Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and ≥ 1.0 µg/mL

The Antibody concentrations against the antigens of MMR vaccine 30 days after the MMR vaccine injection[a] will be described:

- GMT and 95% CI
- RCDCs
- Percentage of subjects with titer ≥ cutoff
    - Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL)
    - Anti-mumps antibody concentrations (serostatus cutoff: 10 Mumps Ab units/mL)
    - Anti-rubella antibody concentrations (serostatus cutoff: 10 IU/mL)

5.1.4 Statistical Methods for Secondary Objectives 5 and 6

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

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

Objective 5 (Group 4)

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

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

Objective 6 (Group 4)

The antibody titers or concentrations against the antigens of DTaP-IPV-HB-Hib vaccine before and 30 days after the booster dose (Dose 4), the antibody concentrations against the antigens of PCV13 vaccine 30 days after the booster dose (Dose 4), and the antibody concentrations against the antigens of MMR vaccine 30 days after vaccination[a] will be described:

- At Day 0 (before Dose 1)
  - GMT and 95% CI for Pertussis antigens (pertussis toxin [PT], filamentous hemagglutinin [FHA])

- 30 days after the booster dose (Dose 4)
  - GMT and 95% CI for all antigens
  - RCDCs for all antigens[b]
  - Percentage of subjects with titer ≥ cutoff:
    - Anti-tetanus antibody concentrations ⩾ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
    - Anti-diphtheria antibody concentrations ⩾ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
    - Anti-poliovirus types 1, 2, and 3 antibody titers ≥ 1:8
    - Anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
    - Anti-HBsAg antibody concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
    - Anti-pneumococcal antibody concentrations ≥ 0.35 µg/mL and ⩾ 1.0 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
    - Anti-measles antibody concentrations (serostatus cutoff: 255 mIU/mL)

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

[b] Including MMR only if MMR vaccine has been administered concomitantly with the study vaccines

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

- Pertussis vaccine seroresponse for anti-PT and anti-FHA

The analyses described above include MMR antigens only if the MMR vaccine has been administered concomitantly with the study vaccines.

5.1.5 Statistical Methods for Observational Objective(s)

5.1.5.1 Immunogenicity

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

The meningococcal serogroups A, C, Y, and W measured by rSBA in a subset of subjects in all groups at Day 0 (before Dose 1) (all groups), 30 days after Dose 2 (Groups 1, 2, and 3) or 30 days after Dose 3 (Group 4) in infancy, and before and 30 days after the booster dose (all groups) will be described with:

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

5.1.5.2 Safety

Safety results will be described for subjects in all study groups after any and each vaccination at 2, 4, 6 (only for Group 4) and 12 to 18 months of age (Visits 1, 2, and 4 for Groups 1, 2 and 3, and Visits 1, 2, 3 and 5 for Group 4). The main parameters for the safety endpoints will be described by 95% CI using the exact binomial method (Clopper-Pearson method).

At least the following parameters will be presented:

- Unsolicited systemic AEs reported in the 30 minutes after each vaccination, including occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken, relationship to the product administered, and whether the event caused termination from the study.
- Solicited (prelisted in the subject's diary card and CRB) injection site and systemic reactions starting any time from Day 0 (day of vaccination) through Day 7 after each vaccination,

including occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction caused termination from the study.

- Unsolicited non-serious AEs reported up to 30 days after each vaccination, including occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to the product administered, and whether the event caused termination from the study.
- SAEs (including AESIs) reported throughout the study, ie, from Visit 1 (first vaccination) to the last study visit (Visit 5 for Groups 1, 2, and 3 and Visit 6 for Group 4, occurring 30 days [+21 days] after the last vaccination), including occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to the product administered, whether the event caused termination from the study, outcome, elapsed time from last administration (if less than 24 hours), relationship to study procedures, and seriousness criterion.

5.1.6 Complementary Output

5.1.6.1 Sensitivity Analysis due to COVID-19 Pandemic

The impact of COVID-19 pandemic situation on study conduct will be summarized through impact on visit procedures, study completion and major/critical protocol deviations due to COVID-19.

The 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 COVID-19 pandemic will be based on but not limited to the following analysis:

- 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/not impacted by COVID-19
- To summarize baseline demographics by randomized group for subjects impacted /not 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

The main immunogenicity and safety endpoints that might be summarized are described as follows:

Immunogenicity analyses

The sensitivity analyses due to COVID-19 Pandemic in immunogenicity will be performed on PPAS and full analysis set (FAS).

1) The primary endpoint for immunogenicity will be assessed:
   - GMTs against meningococcal serogroups A, C, W, and Y measured by hSBA a 3-dose series vaccination at 12 to 18 months of age (Group 1 versus Group 2)
2) The secondary endpoint for immunogenicity will be assessed:
   - Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y measured by hSBA assessed after a 2-dose series at 5 months of age (Group 1 and 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 4 months of age – Safety Analysis Set 2

Safety overview after vaccine injection at 6 months of age – Safety Analysis Set 3

Safety overview after vaccine injections at 12 through 18 months of age – Safety Analysis Set 4

5.1.6.2 Subgroup analysis

Additional subgroup analyses by gender, age group and pre-term/full term birth based on PPAS will be provided for primary and main secondary immunogenicity endpoints.

The gender subgroup analyses will have two categories (Female and Male). For the age group analysis, two categories will be used (≥ 42 to ⩽ 59 days vs ≥60 to 89 days). Pre-term birth will be defined as birth with a gestational age <37 weeks.

The following parameters will be assessed 30 days after the last vaccination in the second year and 30 days after the last vaccination in infant series:

1) The primary endpoint for immunogenicity will be assessed:
   - GMTs against meningococcal serogroups A, C, W, and Y measured by hSBA a 3-dose series vaccination at 12 to 18 months of age (Group 1 versus Group 2)
2) The secondary endpoint for immunogenicity will be assessed:
   - Antibody titers ≥ 1:8 against meningococcal serogroups A, C, W, and Y measured by hSBA assessed after a 2-dose series at 5 months of age (Group 1 and Group 2)

The safety overview after any vaccine injections will be also described.

The subgroup analysis by pre-term/full term birth will be carried out only if there is minimum of 30 pre-term birth in the PPAS.

5.2 Analysis Sets

The study vaccines refer to MenACYW conjugate vaccine, Nimenrix® vaccine and concomitant routine vaccines in the pre-defined vaccination schedule from Visit 1 to Visit 4/Visit 5.

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

5.2.1 Full Analysis Set

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

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

5.2.2 Per-Protocol Analysis Set

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

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

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria

- Subject did not complete the vaccination schedule
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
    - Visit 2: Visit 1 + 60 days (+14 days)
    - Visit 3 (Group 4 only): Visit 2 + 60 days (+14 days)
- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
    - Blood sampling 2 (BL0002):
        - Visit 3: Visit 2 + 30 days [+21 days] (Group 1, 2, 3)
        - Visit 4: Visit 3 + 30 days [+21 days] (Group 4)
- Subject received a protocol-prohibited therapy / medication / vaccine (identified among category 2 / category 3, not including the rotavirus vaccine administered at V1 and V2)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database

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

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

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

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

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window for the booster dose at 12 to 18 months of age (all groups) and at least 180 days after Visit 2 (Group 1,2 3) or after Visit 3 (Group 4)

- Subject did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
    - Blood sampling 4 (BL0004):
        - Visit 5: Visit 4 + 30 days [+21 days] (Group 1, 2, 3)
        - Visit 6: Visit 5 + 30 days [+21 days] (Group 4)
- Subject received a protocol-prohibited therapy / medication / vaccine (identified among category 2 / category 3)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database

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

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

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) and have any safety data available. Specific safety analysis set will be defined and used after each vaccination. All subjects will have their safety analyzed after each dose according to the vaccine they received, and after any dose according to the vaccine received at the first dose. As participants in Group 3 and 4 have the same vaccines administered at 2, 4 and at 12 to 18 months of age, those two groups cannot be differentiated according to the vaccine received at the corresponding visit. Hence, for those two groups the following rules will be applied to determine the analysis actual treatment group for the first dose at 2 month of age and the second dose at 4 months of age:

- If the subject has received a dose of MenACYW at Visit 3 then the actual vaccination group is "Group 4"
- Else if the subject has received a dose of Group 3 study vaccines at Visit 4 then the actual vaccination group is "Group 3"
- Else, if the subject only received vaccination at 2 and/or 4 months of age, then the randomization group will be used to determine the actual vaccination group.

To determine the analysis actual treatment group for the vaccination at 12 to 18 months of age, the following rule will be used:

- If the subject has received a dose of study vaccines at Visit 5 then the actual vaccination group is "Group 4", otherwise if the study vaccines are given at Visit 4 then the actual vaccination group is "Group 3".

For each safety analysis set, safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

5.2.3.1 Overall Safety Analysis Set for Any Dose

The overall SafAS is defined as those subjects who have received at least one dose of the study vaccines and have any safety data available. All subjects will have their safety analyzed after any dose according to the vaccine received at the first dose. Actual vaccination groups for Group 3 and Group 4 will be determined using the rule presented in section 5.2.3.

5.2.3.2 Safety Analysis Set for Vaccination at 2 Months of Age

The SafAS 1 for vaccination at around 2 months of age is defined as those subjects who have received the study vaccine at Visit 1 and have any safety data available. Subjects in Group 1 and 2 will have their safety analyzed after the Visit 1 dose according to the vaccines they actually received at Visit 1. Actual vaccination groups for Group 3 and Group 4 will be determined using the rule presented in section 5.2.3.

5.2.3.3 Safety Analysis Set for Vaccination at 4 Months of Age

The SafAS 2 for vaccination as those subjects who have received the study vaccine at Visit 2 and have any safety data available. Subjects in Group 1 and 2 will have their safety analyzed after the Visit 2 dose according to the vaccines they actually received at Visit 2. Actual vaccination groups for Group 3 and Group 4 will be determined using the rule presented in section 5.2.3.

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

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

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

The SafAS 4 for vaccination as those subjects who have received the study vaccine at Visit 4 / 5 (depending on the schedule) and have any safety data available. All subjects will have their safety analyzed after the Visit 4 / 5 dose according to the vaccines they actually received at Visit 4 / 5. Actual vaccination groups for Group 3 and Group 4 will be determined using the rule presented in section 5.2.3.

5.2.4 Other Analysis Set(s)

Enrolled study participants: Enrolled study participants are study participants for whom a CRF has been created.

Randomized study participants: A randomized study participant is a study participant for whom an injection group has been allocated.

5.2.5 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS analysis set (PPAS1 or PPAS2).

If the difference between PPAS1 and FAS1 (or PPAS2 and FAS2) is greater than 10%, a supplemental analysis based on FAS1 (or FAS2) will be performed to evaluate consistency of the results for the main immunogenicity analyses.

The difference is computed as: (total number of subjects in FAS1 – total number of subjects in PPAS1) / number of subjects in FAS1.

In the FAS1 and FAS2, subjects will be analyzed by the vaccine group to which they were randomized.

The safety analysis will be performed on the overall SafAS, SafAS1 to SafAS 4. Subjects will be analyzed according to the rules derived in section 5.2.3.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

No replacement will be done.

In all subject listings, partial and missing data will be clearly indicated as missing.

5.3.1.1 Immediate

For unsolicited 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.

5.3.1.2 Causality

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the 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 to investigational product will be considered as related to study vaccine at the time of analysis.

- The missing relationship to study procedures for SAEs will not be imputed.

5.3.1.3 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.

5.3.1.4 Start Date and Stop 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 within or not within the defined time window (according to the Section 4.4.1.2.4), according to the last vaccination (computed according to the Section 4.4.1.2.3). If either the start date or end date is missing or partially missing, the duration will be considered missing.

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

5.3.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

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

5.4 Interim / Preliminary Analysis

No planned interim / preliminary analyses were performed.

5.5 Determination of Sample Size and Power Calculation

Approximately a total of 1652 subjects was planned to be enrolled.

For the Primary Objective

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

- An estimated 26.2% dropout rate from the PPAS (528 subjects evaluable by group),
- a 1-sided alpha level of 2.5%,

- a non-inferiority margin of 1.5 (GMT ratio),
- a standard deviation (SD) of log10-transformed titers of 0.7 for serogroups A and C, 0.5 for serogroup Y, and 0.6 for serogroup W.

The calculated power for the primary objective of the study using those parameters is presented in the Table 5.2 below.

Table 5.2: Power of the study based on the primary objective

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

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

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

For the Secondary Objective

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

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

The calculated power for the secondary objective of the study using those parameters is presented in the Table 5.3 below.

Table 5.3: Power of the study for the secondary objective

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

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

* Percentages of subjects with an hSBA titer ≥ 1:8 are based on the MET39 (NCT01049035) MenACYW 2/4/12 months schedule (Group 3) post dose 2 results using estimates 2% lower than in the MenACYW group. The power

is calculated with the assumption that the estimates from the investigational group equal that of the control group corresponding to the estimated percentages in the Nimenrix® group described above.

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

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

5.6 Data Review for Statistical Purposes

A blind 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.

The safety of the investigational product was continuously monitored by the Sponsor. Periodic blinded (when applicable) safety data review was performed by the Sponsor's Safety Management Team (SMT).

5.7 Changes in the Conduct of the Trial or Planned Analyses

The protocol stipulated that "The main immunogenicity analysis will be performed on the PPAS analysis set including PPAS2 for the primary objective and PPAS1 for secondary objective 1 and will be confirmed on the FAS2 and FAS1". However, due to an internal change of analysis process, the main immunogenicity analysis will be confirmed on the FAS2 and FAS1 only if the difference between PPAS1 and FAS1 (or PPAS2 and FAS2) is greater than 10%, as described in section 5.2.5.

Concomitant medications category fields were inactivated, and concomitant medications were coded with WHODrug dictionary by the coding specialists.

Also, as participants in Group 3 and 4 have the same vaccines administered at 2, 4 and at 12 to 18 months of age, actual treatment group derivation for the Safety analysis sets for those groups had been specified in section 5.2.3.

Finally, several analysis cut-offs for some concentrations have been considered in addition to the one already defined in the protocol:

- For anti-diphtheria antibody concentrations, the cut-off $\geqslant$ 1.0 IU/mL has been added for secondary objective 3 (30 days after Dose 2) and the cut-off $\geqslant$ 0.01 IU/mL has been added for secondary objective 3 (Before and 30 days after the booster dose) and secondary objective 6
- For anti-polyribosyl-ribitol phosphate (PRP) antibody concentrations, the cut-off $\geqslant$ 1.0 µg/mL has been added for secondary objective 3 (30 days after Dose 2)

- For anti-tetanus antibody concentrations, the cut-off ⩾ 1.0 IU/mL has been added for secondary objective 3 (30 days after Dose 2) and the cut-off ⩾ 0.01 IU/mL has been added for secondary objective 3 (Before and 30 days after the booster dose) and secondary objective 6
- For anti-pneumococcal antibody concentrations for serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, the cut-off ⩾ 1.0 µg/mL has been added for secondary objective 3 and secondary objective 6

6 References List

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