NCT04490018

Title Page

Protocol Title:

Immunogenicity and Safety Study of a Quadrivalent Meningococcal Conjugate Vaccine Versus Nimenrix®, and When Administered Alone or Concomitantly with 9vHPV and Tdap-IPV Vaccines in Healthy Adolescents

Study Code: MEQ00071

Protocol Version Number: 5.0

Amendment Number: 1.0

Compound: MenACYW Conjugate Vaccine

Study Phase: Phase IIIb

Short Title:

Study on a Quadrivalent Meningococcal Conjugate Vaccine (MenACYW Conjugate Vaccine) Compared to a Meningococcal Reference Vaccine, and When Given Alone or Concomitantly with Two Other Vaccines in Healthy Adolescents

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Regulatory Agency Identifier Numbers:

EudraCT: 2020-001665-37

WHO UTN: U1111-1249-2973

Approval Date: 19-May-2021

Medical Monitor Name and Contact Information are Provided in the Operating Guidelines.

The study centers, the Investigators at each center, and the Coordinating Investigators are listed in a separate document.

Document History

Previous Versions	Date	Comments
1.0	07 May 2020	Internal version not submitted
2.0	29 May 2020	Updated document with changes in version 2.0 of the Common Protocol Template (CPT) dated 13 May 2020 and released on 19 May 2020
3.0	22 July 2020	IEC/IRB-approved version. Updated in response to comments provided by the Health Authorities prior to study initiation
4.0	08 December 2020	Updated document submitted to the IEC/IRB and the Health Authorities in Italy

Table of Contents

List of Tables

List of Figures

1 Protocol Summary

1.1 Synopsis

Protocol Title:

Immunogenicity and Safety Study of a Quadrivalent Meningococcal Conjugate Vaccine Versus Nimenrix®, and When Administered Alone or Concomitantly with 9vHPV and Tdap-IPV Vaccines in Healthy Adolescents

Short Title:

Study on a Quadrivalent Meningococcal Conjugate Vaccine (MenACYW Conjugate Vaccine) Compared to a Meningococcal Reference Vaccine, and When Given Alone or Concomitantly with Two Other Vaccines in Healthy Adolescents

Rationale:

The purpose of MEQ00071 study will be to compare a quadrivalent meningococcal conjugate vaccine (MenACYW conjugate vaccine) versus a licensed quadrivalent meningococcal polysaccharide (Groups A, C, W-135, Y) conjugate vaccine (Nimenrix®) in the adolescent population. Nimenrix® is a standard of care in several countries and no data of Nimenrix® versus MenACYW conjugate vaccine have been generated in the adolescent population to date.

Until now, co-administration data of MenACYW conjugate vaccine have been generated with other vaccines, ie, 4vHPV (4-valent human papilloma virus) vaccine and Tdap (tetanus, diphtheria, and acellular pertussis) vaccine. In some countries, other vaccines used for adolescents are 9vHPV (9-valent human papilloma virus) vaccine and Tdap-IPV vaccine. This study will generate co-administration data of MenACYW conjugate vaccine with these 2 other adolescent vaccines.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To demonstrate the non-inferiority of the seroprotection rate (serum bactericidal assay using human complement [hSBA] titer ≥ 1:8) to meningococcal serogroups A, C, W, and Y following the administration of a single dose of MenACYW conjugate vaccine (Group 1) compared to a single dose of Nimenrix® (Group 2)	• Seroprotection against meningococcal serogroups A, C, W, and Y measured by hSBA titer ≥ 1:8 in Groups 1 and 2, on Day (D)31 (+14 days)

Secondary	
Immunogenicity • To describe the antibody response of meningococcal serogroups A, C, W, and Y measured by hSBA, before and 1 month following meningococcal vaccination administered alone (Groups 1 and 2) or concomitantly with 9vHPV and Tdap-IPV vaccines (Group 3)	• Antibody titers against meningococcal serogroups A, C, W, and Y measured by hSBA in each group assessed before vaccination (D01) and 1 month later (D31 [+14 days]): • ≥ 1:4 and ≥ 1:8 • ≥ 4-fold rise from pre-vaccination to post-vaccination • Vaccine seroresponse defined as follows: • For a participant with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16 • For a participant with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer
• To describe the antibody response of meningococcal serogroup C measured by hSBA and rSBA, before vaccination and at D31 after vaccination with MenACYW conjugate vaccine or Nimenrix® (Groups 1 and 2) according to MenC primed status	• Antibody titer against meningococcal serogroup C measured by hSBA in Groups 1 and 2 according to MenC primed status assessed before vaccination (D01) and at D31 (+14 days) The specific endpoints will be similar to those defined for the first secondary objective. • Antibody titers against meningococcal serogroup C measured by rSBA in a subset of Groups 1 and 2 according to MenC primed status assessed before vaccination (D01) and at D31 (+14 days) The specific endpoints will be similar to those defined for the first observational objective
• To describe the antibody response against antigens of 9vHPV and Tdap-IPV vaccines, before and 1 month following vaccination	• Antibody titers or concentrations against antigens contained in Tdap-IPV measured on D31 (+14 days) and D61 (+14 days) in

	Groups 1 and 2, and on D01 and D31 (+14 days) in Group 3:
	• Anti-tetanus and anti-diphtheria antibody concentrations
	• Anti-tetanus and anti-diphtheria antibody concentrations ratio
	• Anti-tetanus and anti-diphtheria antibody concentrations ≥ 0.1 international units/milliliter (IU/mL) and ≥ 1.0 IU/mL
	• Anti-polio 1, 2, and 3 antibody titers
	• Anti-polio 1, 2, and 3 antibody titers ratio
	• Anti-polio 1, 2, and 3 antibody titers ≥ 1:8
	• Anti-pertussis antibody concentration (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae types 2 and 3 [FIM])
	• Anti-pertussis antibody concentrations ratio (PT, FHA, PRN, FIM)
	• Anti-pertussis vaccine seroresponse (PT, FHA, PRN, FIM), defined as follows:
	  • ≥ 4 × baseline concentration, if the anti-pertussis antibody concentration at baseline (D01) is < 4 × lower limit of quantification (LLOQ)
	  • or ≥ 2 × baseline concentration, if the anti-pertussis antibody concentration at baseline (D01) is ≥ 4 × LLOQ
	• Antibody titers against antigens contained in human papillomavirus (HPV) vaccine measured on D31 (+14 days) and D61 (+14 days) in Groups 1 and 2, and on D01 and D31 (+14 days) in Group 3:

	• Anti-HPV antibody titers for each of the HPV types (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) • Anti-HPV antibody titer ratio for each of the HPV types • Vaccine seroconversion for each of the HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58) by D31 (+14 days) after vaccination, with seroconversion defined as follows: • Changing serostatus from seronegative at baseline (D01) to seropositive by D31 (+14 days) after vaccination. A participant with a titer at or above the serostatus cut-off for a given HPV type is considered seropositive for that type. The serostatus cut-offs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 are 30, 16, 20, 24, 10, 8, 8, 8, and 8 milli-Merck units (mMU)/mL, respectively
Safety • To describe the safety profile in each group after each and any vaccination	The safety profile will be evaluated for each vaccine within 30 days (+14 days) after each vaccination. The following endpoints will be used for the evaluation of safety: • Unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination • Solicited (pre-listed in the participant's diary card and [electronic] Case Report Form [CRF]) injection site and systemic reactions starting any time from the day of vaccination through 7 days after each vaccination • Unsolicited (recorded in a diary card) non-serious AEs reported up to 30 days after each vaccination

	• Serious adverse events (SAEs) (including adverse events of special interest [AESI]) reported throughout the study, ie, from D01 (first vaccination) to the last study day (D61 for Groups 1 and 2 and D31 for Group 3) Depending on the items, the endpoints recorded or derived could include: Nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration/number of days of occurrence, intensity, relationship to the vaccine, whether the AE led to early termination from the study, outcome, and seriousness criterion.

Overall Design:

Type of design	Parallel, multi-center, multinational
Phase	IIIb
Control method	Active-controlled (control = licensed quadrivalent meningococcal polysaccharide conjugate vaccine [Nimenrix®])
Study population	Healthy adolescents aged 10 to 17 years
Countries	Countries in Europe (Spain, Italy and Hungary) and Countries in Asia (Singapore, potential other countries to be determined)
Level and method of blinding	Partially observer-blind (open-label for one of the study groups)
Study intervention assignment method	Randomization

Disclosure Statement: This is a parallel group prevention study with 2 groups that are observer-blind (only the person administering the vaccine is unblinded), and 1 group that is open-label.

Number of Participants:

A total of 464 participants are expected to be randomized.

Intervention Groups and Duration:

Eligible participants will be randomized in a 3:3:2 ratio in the following study groups:

- Group 1 (investigational group – sequential administration): MenACYW conjugate vaccine on Day (D) 01 and 9vHPV* + Tdap-IPV vaccines on D31: n=174
- Group 2 (control group – sequential administration): Nimenrix® on D01 and 9vHPV* + Tdap-IPV vaccines on D31: n=174
- Group 3 (investigational group – concomitant administration): MenACYW conjugate vaccine + 9vHPV* + Tdap-IPV vaccines on D01: n=116

***Note:** This is the first dose of 9vHPV, of the 2-dose or 3-dose series according to the national recommendations and age of the participant. These additional vaccinations for the completion of 9vHPV schedule will take place outside of the objectives and scope of this study and thus will not be described in this protocol.

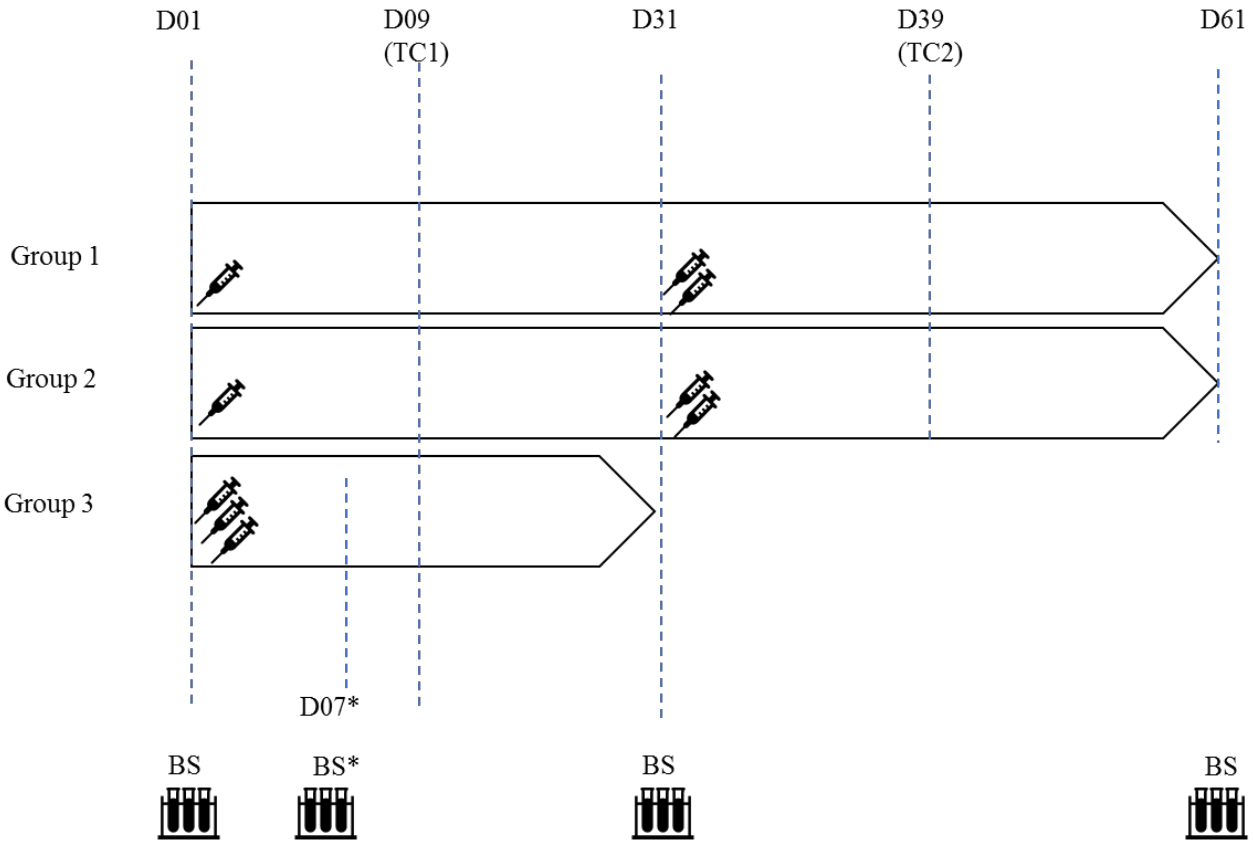
All injections will be given via intramuscular route. The duration of study participation for each participant will be approximately 30 to 60 days.

Data Monitoring Committee: No

1.2 Schema

The study design of MEQ00071 study is presented in Figure 1.1.

Figure 1.1 – Study design



BS: blood sample; D: day; TC: telephone call
*D07 visit and BS is applicable for a subset of participants (N=60) in Group 3. For this subset in Group 3, TC1 discussions can occur during Day 07 visit and TC1 is therefore optional.

Group 1: MenACYW conjugate vaccine on D01 + 9vHPV on D31 + Tdap-IPV on D31
Group 2: Nimenrix® on D01 + 9vHPV on D31 + Tdap-IPV on D31
Group 3: MenACYW conjugate vaccine + 9vHPV + Tdap-IPV on D01

1.3 Schedule of Activities (SoA)

Visits procedures are detailed in the Operating Guidelines.

The schedule of activities for Group 1 and Group 2 are given in Table 1.1 and for Group 3 are given in Table 1.2.

Table 1.1: Schedule of activities for Group 1 and Group 2

Phase IIIb Study, 3 Visits, 2 Vaccination Visits, 2 Telephone Calls, 3 Vaccine Injections, 3 Blood Collections, 60 Days Duration Per Participant

Visit/Contact	*Collection of information in the CRF*	Visit 1	TC 1	Visit 2	TC2	Visit 3
Study timelines (days)		Day 01	Day 09 (Visit 1 + 8 days)	Day 31 (Visit 1 + 30 days)	Day 39 (Visit 2 + 8 days)	Day 61 (Visit 2 + 30 days)
Time windows (days)			+2 days	+14 days	+2 days	+14 days
Visit procedures:						
ICF and AF	*X*	X				
Inclusion/exclusion criteria	*X*	X				
Collection of demographic data	*X*	X				
Urine pregnancy test (if applicable)		X		X		
Collection of medical history	*X*	X				
Physical examination (including temperature)*		X		X		X
Contact IRT system for participant number allocation and vaccine dose randomization	*X*	X				
Review of temporary contraindications for blood sampling†		X		X		X

Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**TC 1**	**Visit 2**	**TC2**	**Visit 3**
Study timelines (days)		Day 01	Day 09 (Visit 1 + 8 days)	Day 31 (Visit 1 + 30 days)	Day 39 (Visit 2 + 8 days)	Day 61 (Visit 2 + 30 days)
Time windows (days)			+2 days	+14 days	+2 days	+14 days
Visit procedures:						
Blood sampling		BL01AA or BL01AR ¥ (5 mL)‡		BL02AA or BL02AR ¥ (8 mL)‡		BL03AA (8 mL)
Review warnings and precautions to vaccination		X		X		
Review of contraindications to subsequent vaccination				X		
Vaccination with MenACYW conjugate vaccine or Nimenrix® (IM in deltoid muscle)		**X**				
Vaccination with 9vHPV and Tdap-IPV vaccines (IM in deltoid muscle of contralateral arm, with the 2 injections separated by minimum 2.5 cm)				**X**		
Immediate surveillance (30 minutes)	*X*	X		X		
Diary card provided		DC1		DC2		
Telephone call			X§		X§	
Diary card reviewed and collected				DC1		DC2
Collection of solicited injection site and systemic reactions	*X*	X**		X**††		X††
Collection of unsolicited non-serious AEs	*X*	Day of vaccination to 30 days after vaccination				
Collection of SAEs, including AESI‡‡	*X*	To be reported at any time during the study				

Visit/Contact	*Collection of information in the CRF*	Visit 1	TC 1	Visit 2	TC2	Visit 3
Study timelines (days)		Day 01	Day 09 (Visit 1 + 8 days)	Day 31 (Visit 1 + 30 days)	Day 39 (Visit 2 + 8 days)	Day 61 (Visit 2 + 30 days)
Time windows (days)			+2 days	+14 days	+2 days	+14 days
Visit procedures:						
Collection of reportable concomitant medications	*X*	X		X		X
Collection of pregnancies	*X*	To be reported at any time during the study				
End of Active Phase participation record	*X*					X

Abbreviations: AE: adverse event; AESI: adverse events of special interest; AF: Assent Form; BL: blood sampling; CRF: Case Report Form; DC: diary card; ICF: Informed Consent Form; IM: intramuscular; IRT: interactive response technology; SAE: serious adverse event; TC: telephone call

* Physical examination should be performed as per standard of care including, but not limited to, a general examination of the main body systems of interest (ie, heart, lung, skin, neurologic, muscular-skeletal, lymphatic system, etc). Temperature to be measured by oral (preferred route), rectal, or axillary route using a digital thermometer before vaccination and daily during the 7 days after vaccination and recorded in the diary card. 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.

† Should a participant 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 participant 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.

¥ Blood sample corresponding to the rSBA subset of participants.

‡ Blood sample at Day 01 and Day 31 will be drawn before administration of the vaccines.

§ This call is made 8 days to 10 days after the respective vaccinations. If Day 09 (+2 days) or Day 39 (+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 participant experienced any SAE (including any AESI) not yet reported, and will remind the participant'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.

** Solicited injection site and systemic reactions will be recorded from the day of vaccination through 7 days after each vaccination.

†† Solicited injection site and systemic reactions will be recorded during the review and collection of DC1 and DC2 at Day 31 (+14 days) and Day 61 (+14 days).

‡‡ AESI 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 causal relationship.

Table 1.2: Schedule of activities for Group 3

Phase IIIb Study, 2-3 Visits, 1 Vaccination Visit, 0-1 Telephone Call, 3 Vaccine Injections, 2-3 Blood Collections, 30 Days Duration Per Participant

Visit/Contact	*Collection of information in the CRF*	Visit 1	Visit 2*	TC 1†	Visit 3
Study timelines (days)		Day 01	Day 07 (Visit 1 + 6 days)	Day 09 (Visit 1 + 8 days)	Day 31 (Visit 1 + 30 days)
Time windows (days)			+2 days	+2 days	+14 days
Visit procedures:					
ICF and AF	*X*	X			
Inclusion/exclusion criteria	*X*	X			
Collection of demographic data	*X*	X			
Urine pregnancy test (if applicable)		X			
Collection of medical history	*X*	X			
Physical examination (including temperature)‡		X			X
Contact IRT system for participant number allocation and vaccine dose randomization	*X*	X			
Review of temporary contraindications for blood sampling§		X	X		X
Blood sampling		BL01BB or BL01BR ¥ (8 mL)**	BL02D7 (5 mL)		BL03BB or BL03BR ¥ (8 mL)
Vaccination with MenACYW conjugate vaccine (IM in deltoid muscle)		**X**			
Vaccination with 9vHPV and Tdap-IPV vaccines (IM in deltoid muscle of contralateral arm, with the 2 injections separated by minimum 2.5 cm)		**X**			

Visit/Contact	*Collection of information in the CRF*	Visit 1	Visit 2*	TC 1†	Visit 3
Study timelines (days)		Day 01	Day 07 (Visit 1 + 6 days)	Day 09 (Visit 1 + 8 days)	Day 31 (Visit 1 + 30 days)
Time windows (days)			+2 days	+2 days	+14 days
Visit procedures:					
Immediate surveillance (30 minutes)	*X*	X			
Diary card provided		DC1			
Telephone call				X††	
Diary card reviewed and collected					DC1
Collection of solicited injection site and systemic reactions	*X*	X‡‡			X§§
Collection of unsolicited non-serious AEs	*X*	Day of vaccination to 30 days after vaccination			
Collection of SAEs, including AESI***	*X*	To be reported at any time during the study			
Collection of reportable concomitant medications	*X*	X	X		X
Collection of pregnancies	*X*	To be reported at any time during the study			
End of Active Phase participation record	*X*				X

Abbreviations: AE: adverse event; AESI: adverse events of special interest; AF: Assent Form; BL: blood sampling; CRF: Case Report Form; DC: diary card; ICF: Informed Consent Form; IM: intramuscular; IRT: interactive response technology; SAE: serious adverse event; TC: telephone call

* Visit at Day 07 (+2 days) is applicable only for a subset of participants, N=60. This subset of participants will have 3 blood samplings. All other participants in Group 3 will have only 2 study visits and 2 blood samplings.
† For a subset of participants (N=60) who have Day 07 (+2 days) visit, TC1 discussions can occur during Day 07 visit and TC1 at Day 09 (+2 days) is therefore optional.

‡ Physical examination should be performed as per standard of care including, but not limited to, a general examination of the main body systems of interest (ie, heart, lung, skin, neurologic, muscular-skeletal, lymphatic system, etc). Temperature to be measured by oral (preferred route), rectal, or axillary route using a digital thermometer before vaccination and daily during the 7 days after vaccination and recorded in the diary card. 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.

§ Should a participant 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 participant 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.

¥ Blood sample corresponding to the rSBA subset of participants.

** Blood sample at Day 01 will be drawn before administration of the vaccines.

†† This call is made 8 days to 10 days after the vaccinations and is optional for the subset of participants (N=60) who have TC1 discussions during the Day 07 visit. For the remaining participants who have TC1 at Day 09 (+2 days), if this day 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 participant experienced any SAE (including any AESI) not yet reported, and will remind the participant'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.

‡‡ Solicited injection site and systemic reactions will be recorded from the day of vaccination through 7 days after vaccination

§§ Solicited injection site and systemic reactions will be recorded during the review and collection of DC1 at Day 31 (+14 days).

*** AESI 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 causal relationship

2 Introduction

2.1 Study Rationale

The purpose of MEQ00071 study will be to compare a quadrivalent meningococcal conjugate vaccine (MenACYW conjugate vaccine) versus a licensed quadrivalent meningococcal polysaccharide (Groups A, C, W-135, Y) conjugate vaccine (Nimenrix®) in the adolescent population. Nimenrix® is a standard of care in several countries and no data of Nimenrix® versus MenACYW conjugate vaccine has been generated in the adolescent population to date.

Until now, co-administration data of MenACYW conjugate vaccine have been generated with other vaccines, ie, 4vHPV (4-valent human papilloma virus) vaccine and Tdap (tetanus, diphtheria, and acellular pertussis) vaccine. In some countries, other vaccines used for adolescents are 9vHPV (9-valent human papilloma virus) vaccine and Tdap-IPV vaccine. This study will also generate co-administration data of MenACYW conjugate vaccine with these 2 other adolescent vaccines.

2.2 Background

Invasive meningococcal disease (IMD) is a serious illness caused by the bacterium *Neisseria meningitidis (N. meningitidis)*, a Gram-negative diplococcus found exclusively in humans. It is associated with high morbidity and mortality. Worldwide, most cases of IMD are caused by serogroups A, B, C, Y, and W (1-3). Some age groups are disproportionately affected by IMD, with major peaks of IMD incidence occurring in infants and in adolescents and young adults.

The epidemiology of *N. meningitidis* can be described as complex, unpredictable, geographically variable, and changing over time. IMD occurs worldwide in both endemic and epidemic forms with seasonal variation.

In Europe, the European Center for Disease Prevention and Control (ECDC) annually publishes an epidemiological report on IMD, based on data retrieved from the European Surveillance System (TESSy) which is used to collect, analyze, and disseminate data on communicable diseases. The last report has been published in April 2019, based on 2017 data. As per this report, in 2017, the overall notification rate of IMD in European Union (EU)/European Economic Area (EEA) countries was 0.6 per 100 000 population, similar to the notification rate for previous years. Four countries (France, Germany, Spain, and the United Kingdom) accounted for 58% of all confirmed cases. In Italy, the notification rate of IMD was 0.3 per 100 000 population, while in Spain it was 0.6 per 100 000 population (4).

In Europe the incidence rate of IMD has remained stable over the last 5 to 10 years, with the highest peak occurring in the population less than 4 years of age and a smaller peak in the 15 to 24-years age group. Overall, the highest incidence rate in Europe is caused by serogroup B, followed by serogroups W and C (4).

The incidence of IMD in Italy reported by the Istituto Superiore di Sanità showed a slight increase from 2008 to 2016 in the general population (0.30 to 0.38 per 100 000) and among young children below 4 years of age (1.64 to 1.83 per 100 000) (5). In 2017, age-specific serogroup distribution

showed a higher incidence of serogroup B in infants and highest incidence of serogroup Y in the 5 to 9-years age group, 15 to 24-years age group, and > 65 years age group (6).

The incidence of IMD in Spain showed nearly similar rate from 2013 to 2017 (0.3 to 0.6 per 100 000) in the general population (4). In 1999 and 2000, the incidence of IMD was 1.53 and 1.75 per 100 000, respectively, leading to the inclusion of MenC conjugate vaccine in the infant vaccination schedule in 2000 (7).

The incidence of IMD in Singapore from 2001 to 2018 was 0.1 to 0.3 per 100 000 population (8).

Meningococcal carriage is low in infants but increases during childhood and peaks in 12 to 19-years age group (9). Vaccination of adolescents not only provides direct protection against IMD, but also reduces carriage, thus maintaining a herd effect shown to be important even in other age groups (10-12). Therefore, adolescent vaccination against *N. meningitidis* is already recommended in several countries worldwide (13).

In Europe, increased incidence of IMD due to serogroup C in the late 1990s, and availability of meningococcal serogroup C conjugate vaccine (MenC), have led many countries to introduce MenC vaccination for toddlers (± infants) in the 2000's (14). By 2016, MenC was integrated into the national routine childhood immunization programs of 15 EU/EEA countries (4). Therefore, as of today, many European adolescents have been primed with monovalent MenC before 2 years of age. This is not the case in Singapore where meningococcal vaccination is not part of routine vaccination recommended for children and adolescents, hence, adolescents in Singapore are MenC naïve (8).

Bordetella pertussis and human papilloma virus (HPV) are also important disease-causing pathogens, with a high risk of transmission in adolescents and young adults. Periodic resurgences of pertussis were recorded every 3 to 5 years even in industrialized countries with high immunization rates, with increased incidence in adolescents and adults (15).

The HPV is a group of viruses, of which more than 100 types have been described. About 40 of them can infect the genitals. At least 14 HPV types classified as 'high risk' can cause cervical cancer in women and are associated with other anogenital cancers and head and neck cancers in both men and women.

Immunizations against diphtheria, tetanus, pertussis, and polio (as a booster dose) and against HPV (primarily in females, but also in males, as 2- or 3-dose schedules according to age) are also recommended by the World Health Organization (WHO) during adolescence (16) and most countries worldwide have implemented their use in vaccination programs.

However, adherence to current recommendations and vaccination schedules among adolescents is problematic (17), especially for the multi-dose schedules needed for HPV vaccination (18).

Therefore, vaccine co-administration resulting in a reduced number of clinic visits may improve the implementation and achievable coverage of adolescent vaccination programs.

The goal for MenACYW conjugate vaccine is to provide broad protection against IMD caused by serogroups A, C, W, and Y. Initial licensure in EU (planned Q1 2021) and other countries will be in individuals from 12 months of age, adolescents, and adults, including those 56 years of age and older. MenACYW conjugate vaccine is licensed in the US since April 2020 for individuals

24 month of age and older. Further, clinical studies are ongoing to support an extension of the licensure in individuals from 6 weeks of age and older.

Data regarding co-administration with other vaccines are available for 4vHPV and Tdap in meningococcal vaccine naïve adolescents (19), but not available to date with 9vHPV and Tdap-IPV.

This study (MEQ00071) will compare the immunogenicity and describe the safety of MenACYW conjugate vaccine versus Nimenrix®, and when administered alone or concomitantly with 9vHPV and Tdap-IPV vaccines in a healthy adolescent population who are MenC naïve or primed before 2 years of age.

MenACYW conjugate vaccine has been given to over 7000 participants (infants, toddlers, children, adolescents, and adults > 56 years of age) in completed Phase II and Phase III studies. In these studies, MenACYW conjugate vaccine was found to be well tolerated and did not reveal any apparent safety concerns. The relevant Phase II (MET50) and Phase III (MET43 and MET56) studies that concern the adolescents and adult populations (10 to 55 years of age) are discussed in the Investigator's Brochure Section 5.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events (AEs), the potential risks, and uncertainties of MenACYW conjugate vaccine may be found in the Investigator's Brochure.

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.1.

Table 2.1: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: MenACYW conjugate vaccine		
Anaphylaxis	Known important risk occurring at a low frequency (very rare) based on what would be common for any vaccine No cases with MenACYW conjugate vaccine in the completed studies	Observation period after vaccination for early detection and treatment Exclusion criteria: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances
Guillain-Barré syndrome (GBS)	Important potential risk-based on post-marketing experience for other quadrivalent meningococcal conjugate vaccines occurring with a low frequency (very rare) with no definite evidence of excess risk identified in population based study (20-22). A review by the Institute of Medicine found inadequate evidence to accept or reject a causal relationship between tetanus toxoid-containing vaccines and GBS (23) No cases with MenACYW Conjugate Vaccine in the completed studies	Exclusion criteria: Personal history of Guillain-Barré syndrome

Bell's palsy Refer to Investigator's Brochure Section 6 for more information regarding potential risks	Important potential risk-based on post-marketing experience for other quadrivalent meningococcal conjugate vaccines occurring at a low frequency (very rare). A post-marketing observational safety study conducted in a US health maintenance organization found a statistically significant association with Bell's palsy when a licensed quadrivalent meningococcal conjugate vaccine (MCV4-CRM [Menveo®]) was administered concomitantly with other vaccines (Tdap, HPV, and/or influenza vaccine), while no association was found when the vaccine was administered alone (24). This study used a longer risk interval than used in previous studies, beyond the biologically plausible and widely accepted risk interval of 42 days. No cases with MenACYW conjugate vaccine within 42 days of vaccination in the completed studies	No risk mitigation actions
Comparator: Nimenrix®		
For all countries in the European Union, including Italy and Spain: Refer to the European Medicines Agency (EMA) approved summary of product characteristics (SmPC) of Nimenrix® for more information regarding potential risks (25)	Identified and potential risks observed in clinical studies and/or post-marketing surveillance	Exclusion/inclusion criteria take in account contraindications, warnings and precautions as defined in product label

For all countries in Asia, including Singapore: Refer to the prescribing information.		
Study Procedures		
Vasovagal reactions (fainting)	Syncope can occur following, or even before, any vaccination or blood draw as a psychogenic response to the needle injection, most commonly in the adolescent age group (26) Cases of vasovagal-like response (eg, dizziness) or syncope have been observed infrequently in adolescent or young adult study participants within 30 minutes of vaccination with MenACYW conjugate vaccine	Observation period after vaccination for early detection and treatment. Procedures should be in place to prevent falling injury and manage syncopal reactions
Co-administered Vaccine - 9vHPV (Gardasil® 9):		
Refer to the SmPC or package insert for more information regarding potential risks (27)	Identified and potential risks observed in clinical studies and/or post-marketing surveillance	Exclusion/inclusion criteria take in account contraindications, warnings and precautions as defined in product label
Co-administered Vaccine - Tdap-IPV (Repevax®/Triaxis® Polio/Adacel® Polio):		
Refer to the SmPC or package insert for more information regarding potential risks (28) (29) (30)	Identified and potential risks observed in clinical studies and/or post-marketing surveillance	Exclusion/inclusion criteria take in account contraindications, warnings and precautions as defined in product label

Potential risks of the concomitant administration:

No additional risks are expected following the concomitant administration of MenACYW conjugate vaccine with 9vHPV and Tdap-IPV.

The study MET50 of coadministration of MenACYW conjugate vaccine with the licensed 4vHPV and Tdap vaccines in adolescents revealed no apparent safety concerns. MenACYW conjugate vaccine was well tolerated when given concomitantly with 4vHPV and Tdap vaccines, and the safety profiles of the concomitant vaccines 4vHPV and Tdap were comparable when administered with or without MenACYW conjugate vaccine.

2.3.2 Benefits from Study Participation

MenACYW conjugate vaccine is undergoing active clinical investigation. Based on the data from previous studies, evaluation of the immunogenicity profile of MenACYW conjugate vaccine in different age groups shows that most participants developed seroprotective levels of antibodies after vaccination. The safety evaluation indicates that the vaccine is well tolerated, and no safety issues have been detected to date.

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

Since all participants will receive the adolescent dose of Tdap-IPV, they will likely gain immunological protection against tetanus, diphtheria, acellular pertussis (whooping cough), and poliomyelitis.

Participants who complete the 2- or 3-dose series of 9vHPV vaccine will likely gain immunological protection against genital cancers, precancers, and (genital) warts caused by human papillomavirus (types 6/11/16/18/31/33/45/52/58).

As with any vaccine, MenACYW conjugate vaccine, Nimenrix®, 9vHPV, and Tdap-IPV vaccines may not protect 100% of individuals against the diseases they are designed to prevent.

2.3.3 COVID-19 Risk Assessment

MenACYW conjugate vaccine, Nimenrix®, 9vHPV, and Tdap-IPV vaccines would not cause immune suppression. Therefore, the risk that a participant in this study will contract COVID-19 solely due to the administration of the study vaccine will be similar to the risk that a person not participating in this study will contract COVID-19.

However, the risk of exposure to infected people cannot be completely excluded as the participants may need to expose to public area (eg, commute to the site and at the site).

Risk Mitigation:

- Not start the study until the local confinement measures or other safety restrictions linked to the Covid-19 pandemic are lifted by the local Authorities.
- Continued risk assessment by the Investigator and Sponsor before deciding to start the study.
- Reduce the public exposure while ambulatory when possible.

2.3.4 Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to participants enrolled in this study, the potential risks that may result from study participation are balanced by the anticipated benefits that may be afforded to participants.

3 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 3.1.

Table 3.1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the non-inferiority of the seroprotection rate (serum bactericidal assay using human complement [hSBA] titer ≥ 1:8) to meningococcal serogroups A, C, W, and Y following the administration of a single dose of MenACYW conjugate vaccine (Group 1) compared to a single dose of Nimenrix® (Group 2)	• Seroprotection against meningococcal serogroups A, C, W, and Y measured by hSBA titer ≥ 1:8 in Groups 1 and 2, on Day (D)31 (+14 days)
Secondary	

Immunogenicity
• To describe the antibody response of meningococcal serogroups A, C, W, and Y measured by hSBA, before and 1 month following meningococcal vaccination administered alone (Groups 1 and 2) or concomitantly with 9vHPV and Tdap-IPV vaccines (Group 3)
	• Antibody titers against meningococcal serogroups A, C, W, and Y measured by hSBA in each group assessed before vaccination (D01) and 1 month later (D31 [+14 days]):
	  • ≥ 1:4 and ≥ 1:8
	  • ≥ 4-fold rise from pre-vaccination to post-vaccination
	  • Vaccine seroresponse defined as follows:
	  • For a participant with a pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:16
	  • For a participant with a pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer

• To describe the antibody response of meningococcal serogroup C measured by hSBA and rSBA, before vaccination and at D31 after vaccination with MenACYW conjugate vaccine or Nimenrix® (Groups 1 and 2) according to MenC primed status	• Antibody titer against meningococcal serogroup C measured by hSBA in Groups 1 and 2 according to MenC primed status assessed before vaccination (D01) and at D31 (+14 days) The specific endpoints will be similar to those defined for the first secondary objective. • Antibody titers against meningococcal serogroup C measured by rSBA in a subset

Objectives	Endpoints
	of Groups 1 and 2 according to MenC primed status assessed before vaccination (D01) and at D31 (+14 days) The specific endpoints will be similar to those defined for the first observational objective.

• To describe the antibody response against antigens of 9vHPV and Tdap-IPV vaccines, before and 1 month following vaccination	• Antibody titers or concentrations against antigens contained in Tdap-IPV measured on D31 (+14 days) and D61 (+14 days) in Groups 1 and 2, and on D01 and D31 (+14 days) in Group 3:
	  • Anti-tetanus and anti-diphtheria antibody concentrations
	  • Anti-tetanus and anti-diphtheria antibody concentrations ratio
	  • Anti-tetanus and anti-diphtheria antibody concentrations ≥ 0.1 international units/milliliter (IU/mL) and ≥ 1.0 IU/mL
	  • Anti-polio 1, 2, and 3 antibody titers
	  • Anti-polio 1, 2, and 3 antibody titers ratio
	  • Anti-polio 1, 2, and 3 antibody titers ≥ 1:8
	  • Anti-pertussis antibody concentration (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae types 2 and 3 [FIM])
	  • Anti-pertussis antibody concentrations ratio (PT, FHA, PRN, FIM)
	  • Anti-pertussis vaccine seroresponse (PT, FHA, PRN, FIM), defined as follows:
	  • ≥ 4 × baseline concentration, if the anti-pertussis antibody concentration at baseline (D01) is < 4 × lower limit of quantification (LLOQ)

Objectives	Endpoints

	• or ≥ 2 × baseline concentration, if the anti-pertussis antibody concentration at baseline (D01) is ≥ 4 × LLOQ
	• Antibody titers against antigens contained in HPV vaccine measured on D31 (+14 days) and D61 (+14 days) in Groups 1 and 2, and on D01 and D31 (+14 days) in Group 3:
	  • Anti-HPV antibody titers for each of the HPV types (types 6, 11, 16, 18, 31, 33, 45, 52, and 58)
	  • Anti-HPV antibody titer ratio for each of the HPV types
	  • Vaccine seroconversion for each of the HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58) by D31 (+14 days) after vaccination, with seroconversion defined as follows:
	  • Changing serostatus from seronegative at baseline (D01) to seropositive by D31 (+14 days) after vaccination. A participant with a titer at or above the serostatus cut-off for a given HPV type is considered seropositive for that type. The serostatus cut-offs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 are 30, 16, 20, 24, 10, 8, 8, 8, and 8 milli-Merck units (mMU)/mL, respectively

Safety • To describe the safety profile in each group after each and any vaccination	The safety profile will be evaluated for each vaccine within 30 days (+14 days) after each vaccination. The following endpoints will be used for the evaluation of safety: • Unsolicited systemic AEs reported in the 30 minutes after each vaccination • Solicited (pre-listed in the participant's diary card and [electronic] Case Report Form [CRF]) injection site and systemic reactions

Objectives	Endpoints
	starting any time from the day of vaccination through 7 days after each vaccination • Unsolicited (recorded in a diary card) non-serious AEs reported up to 30 days after each vaccination • Serious adverse events (SAEs) (including adverse events of special interest [AESI]) reported throughout the study, ie, from D01 (first vaccination) to the last study day (D61 for Groups 1 and 2 and D31 for Group 3) Depending on the items, the endpoints recorded or derived could include: • Nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration/number of days of occurrence, intensity, relationship to the vaccine, whether the AE led to early termination from the study, outcome, and seriousness criterion
Observational	
Immunogenicity • To describe the antibody response of meningococcal serogroups A, C, W, and Y measured by serum bactericidal assay using baby rabbit complement (rSBA), before and on D31 following meningococcal vaccination, in a subset of the first 50 participants from each group	Antibody titers against meningococcal serogroups A, C, W, and Y measured by rSBA in a subset of the first 50 participants in each group assessed before vaccination (D01), and at D31 (+14 days): • ≥ 1:8 and ≥ 1:128 • ≥ 4-fold rise from pre-vaccination to post-vaccination • Vaccine seroresponse measured by rSBA in each group, with seroresponse defined as follows: • For a participant with pre-vaccination titer < 1:8, a post-vaccination titer ≥ 1:32

Objectives	Endpoints
	• For participants with pre-vaccination titer ≥ 1:8, a post-vaccination titer at least 4-fold greater that the pre-vaccination titer
• To describe the kinetics of antibody titers against meningococcal serogroups A, C, W, and Y in a subset of the first 60 participants in Group 3, measured by hSBA before, on D07, and on D31 following vaccination	• Antibody titers against meningococcal serogroups A, C, W, and Y measured by hSBA in a subset of the first 60 participants in Group 3 before vaccination (D01), at D07, and at D31 (+14 days) The specific endpoints will be similar to those defined for the first secondary objective at the time points applicable for the subset of Group 3

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Parallel, multi-center, multinational
Phase	IIIb
Control method	Active-controlled (control = licensed quadrivalent meningococcal polysaccharide conjugate vaccine [Nimenrix®])
Study population	Healthy adolescents aged 10 to 17 years
Level and method of blinding	Partially observer-blind (open-label for one of the study groups)
Study intervention assignment method	Randomization

Number of participants	464 participants
Intervention groups	Randomization in a 3:3:2 ratio in the following study groups: • Group 1 (investigational group – sequential administration): MenACYW conjugate vaccine on Day (D) 01 and 9vHPV* + Tdap-IPV vaccines on D31: n=174 • Group 2 (control group – sequential administration): Nimenrix® on D01 and 9vHPV* + Tdap-IPV vaccines on D31: n=174 • Group 3 (investigational group – concomitant administration): MenACYW conjugate vaccine + 9vHPV* + Tdap-IPV vaccines on D01: n=116 ***Note**: This is the first dose of 9vHPV, of the 2-dose or 3-dose series according to the national recommendations and age of the participant. These additional vaccinations for the completion of 9vHPV schedule will take place outside of the objectives and scope of this study and thus will not be described in this protocol
Total duration of study participation	Approximately 60 days for participants in Groups 1 and 2; approximately 30 days for participants in Group 3
Countries	Countries in Europe (Spain, Italy and Hungary) and Countries in Asia (Singapore, potential other countries to be determined)
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

4.2 Scientific Rationale for Study Design

The primary objective of this study is to demonstrate the non-inferiority of the seroprotection rate (using hSBA titer ≥ 1:8) to meningococcal serogroups A, C, W, and Y following the administration of a single dose of MenACYW conjugate vaccine (Group 1) compared to a single dose of Nimenrix® (Group 2). An hSBA titer ≥ 1:8 is a well-recognized surrogate of protection against IMD caused by serogroups A, C, W, and Y. Seroprotection is preferred over seroresponse by the EMA.

In this study, we will be comparing the immunogenicity of MenACYW conjugate vaccine versus Nimenrix® in the adolescent population. To date, comparison data of MenACYW conjugate vaccine versus Nimenrix® has only been generated in toddlers. Nimenrix® is the standard of care in several countries, hence, it will be used as the active comparator in this study to generate data in adolescents. Both, toddlers and adolescents are the age groups that are targeted by national immunization program in Europe and other regions.

Other vaccines which will be co-administered in this study along with MenACYW conjugate vaccine include 9vHPV (first dose of the 2-dose or 3-dose series according to the National recommendations and age of the participant) and Tdap-IPV. The 9vHPV has been recently licensed in Europe and is becoming the standard of care. Generating co-administration data of MenACYW conjugate vaccine with 9vHPV and Tdap-IPV may help obtain high vaccine coverage rates.

In other studies, included in the MenACYW conjugate vaccine Common Technical Dossier for initial licensure, titers were measured by hSBA for the primary endpoint. The same assay will therefore be used in this study for the comparison of MenACYW conjugate vaccine to Nimenrix®. Titers measured by rSBA will also be described in a subset of the first 50 participants from each group.

According to the country and vaccination strategies, adolescents are either the only age group targeted for meningococcal vaccination (and therefore are meningococcal vaccination naïve before that age) or have been primed before 2 years of age (mainly with MenC as MenACYW vaccines have only been implemented more recently). Many European countries have MenC recommendations for infants/toddlers since the 2000's, hence, an important part of the current adolescent population in Europe are MenC primed. Therefore, this study plans to enroll both MenC naïve and MenC primed adolescents. Currently available data generated for MenACYW conjugate vaccine is only in meningococcal vaccine naïve adolescents or in adolescents primed with quadrivalent meningococcal conjugate vaccine at 10 years or above. The aim of this study is to generate data in the 'real life' situation with adolescents who are MenC primed before 2 years of age and unprimed adolescents.

This study will be conducted in European countries (Spain, Italy and Hungary) and Asian countries (Singapore, potential other countries to be determined). In Italy's and Spain's national vaccination plan for infants, MenC vaccination was introduced in 2005 and 2000, respectively (31-33). Thus, in Italy and Spain, an important part of the adolescent population will be MenC primed (MenC CRM or MenC-TT conjugate vaccines). In Singapore, adolescents will be MenC naïve. Nimenrix®, 9vHPV, and Tdap-IPV vaccines are available in all these countries.

An additional blood sample will be taken at D07 in a subset of the first 60 participants in Group 3 for evaluation of antibody kinetics. Kinetics will be described in order to have a better knowledge on the immune response in the week following vaccination. This could be of interest for travelers and adolescents studying abroad who are being vaccinated only a few days before departure.

Since the vaccines for the study groups have different appearances, this study will be partially observer-blind. This means that Groups 1 and 2 will be observer-blind (ie, everyone in the study other than the staff member who will administer the vaccine will be blinded) and Group 3 will be open-label. This open-label design for Group 3 is due to the different vaccination schedule for this group than for Groups 1 and 2. The primary objective of this study will include Groups 1 and 2 (both groups being observer-blind), while Group 3 (open-label) will be a part of secondary and observational objectives.

4.3 Justification for Dose

All participants will receive a single dose of either MenACYW conjugate vaccine or Nimenrix® as per the current/intended indication in this age group for quadrivalent meningococcal conjugate vaccines.

One dose of Tdap-IPV vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria, acellular pertussis (whooping cough), and poliomyelitis.

Depending on National recommendations and age of the participant, the schedule for 9vHPV vaccination can be 2 or 3 doses. The first dose will be administered during this study. All participants should then receive a second dose (and third dose) of 9vHPV vaccine several months after the first dose. These vaccinations for the completion of 9vHPV schedule will take place outside of the objectives and scope of this study and thus will not be described in this protocol.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed the last visit planned in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the clinical study report is finalized.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

There is no screening period nor screening criteria other than the inclusion and exclusion criteria.

5.1 Inclusion Criteria

Participants are eligible for the study only if all of the following criteria are met:

I01: Aged 10 to 17 years on the day of inclusion[a]

I02: Meningococcal serogroup C conjugate vaccine (MenC) naïve participants or participants having received monovalent MenC priming in infancy (< 2 years of age)[b]

I03: Assent form has been signed and dated by the participant as per local regulation, and Informed Consent Form has been signed and dated by the parent/legally acceptable representative and by the participant if she/he turns 18 years old during the study

I04: Participant and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all study procedures

I05: Covered by health insurance, if required by local regulations

5.2 Exclusion Criteria

Participants are not eligible for the study if any of the following criteria are met:

E01: Participant is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after last vaccination. To be considered of non-childbearing potential, a female must be pre-menarche[c]

E02: Previous vaccination against meningococcal disease with either the study vaccine or another vaccine (ie, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, or Y; or meningococcal B serogroup-containing vaccine), except licensed monovalent MenC vaccination received before 2 years of age

E03: Participation at the time of study enrollment (or in the 4 weeks preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

E04: Receipt of any vaccine in the 4 weeks preceding any study vaccination or planned receipt of any vaccine in the 4 weeks following any study vaccination except for influenza vaccination, which may be received at least 2 weeks before study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines

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[a] "10 to 17 years" means from the day of the 10th birthday to the day before the 18th birthday

[b] Irrespective of the number of doses of MenC received in infancy

[c] Pre-menarche females will declare by themselves that they have not yet started menstruation. If a young female participant reaches menarche during the study, then she is to be considered as a female of childbearing potential from that time forward

E05: History of vaccination with any tetanus, diphtheria, pertussis, or inactivated polio virus vaccine within the previous 3 years

E06: Previous human papilloma virus (HPV) vaccination

E07: Receipt of immune globulins, blood or blood-derived products in the past 3 months

E08: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E09: History of meningococcal infection, confirmed either clinically, serologically, or microbiologically

E10: Known history of diphtheria, tetanus, pertussis, poliomyelitis, and/or HPV infection or disease.

E11: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances[a]

E12: Personal history of Guillain-Barré syndrome

E13: Personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within at least 10 years of the proposed study vaccination

E14: Personal history of new or past encephalopathy, progressive or unstable neurological disorder, or unstable epilepsy

E15: Verbal report of thrombocytopenia, contraindicating intramuscular vaccination

E16: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination

E17: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E18: Current alcohol abuse or drug addiction

E19: Chronic illness[b] that, in the opinion of the Investigator, is at a stage where it may interfere with study conduct or completion

E20: Moderate or severe acute illness/infection (according to Investigator's judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective participant

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[a] The components of MenACYW conjugate vaccine are listed under Section 6.1 of this protocol and in the Investigator's Brochure Section 3. The components of Nimenrix®, 9vHPV, and Tdap-IPV are listed under Section 6.1 of this protocol

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

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

E21: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw

E22: Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

E23: Participant at high risk for meningococcal infection during the study (specifically but not limited to participants with persistent complement deficiency, with anatomic or functional asplenia, or participants traveling to countries with high endemic or epidemic disease)

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

5.3 Lifestyle Considerations

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. Screening information is recorded in the source documents.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened when the condition excluding them from participation is resolved (eg, fever, antibiotics received within 72 hours, etc).

6 Study Intervention

Study intervention is defined as any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

6.1 Note: routine vaccines administered outside of study protocol are not considered as study interventions. Study Intervention Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study intervention

Intervention Name	MenACYW conjugate vaccine Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)	Nimenrix®: Meningococcal group A, C, W-135, and Y conjugate vaccine (Pfizer Limited, Sandwich, United Kingdom)	9vHPV (Gardasil® 9): Human Papillomavirus 9-valent Vaccine (Recombinant, adsorbed) (Merck Sharp & Dohme Limited, Kenilworth, NJ, USA)	Tdap-IPV (Repevax®/Triaxis® Polio/Adacel® Polio): Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine (Sanofi Pasteur Limited, Toronto, Ontario, Canada)
Use	Experimental	Active comparator	Co-administered vaccine	Co-administered vaccine
IMP and NIMP	IMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	Liquid solution	Powder and solvent for solution for injection	Suspension for injection	Suspension for injection

Unit Dose Strength	Meningococcal capsular polysaccharides:
	• Serogroup A 10 µg
	• Serogroup C 10 µg
	• Serogroup Y 10 µg
	• Serogroup W 10 µg
		• *N. meningitidis* group A polysaccharide * 5 µg
		• *N. meningitidis* group C polysaccharide * 5 µg
		• *N. meningitidis* group W-135 polysaccharide * 5 µg
			• 30 µg of HPV 6 L1 protein
			• 40 µg of HPV 11 L1 protein
			• 60 µg of HPV 16 L1 protein
			• 40 µg of HPV 18 L1 protein
				• Tetanus toxoid 5 Lf
				• Diphtheria toxoid 2 Lf
				• Acellular pertussis:
				  • PT 2.5 µg
				  • FHA 5 µg
				  • PRN 3 µg
				  • FIM 5 µg

	Tetanus toxoid protein carrier approximately 55 µg*
	**Tetanus toxoid protein quantity is approximate and dependent on the polysaccharide-to-protein ratio for the conjugates used in each formulation*
		• *N. meningitidis* group Y polysaccharide * 5 µg
		**Conjugated to tetanus toxoid protein carrier 44 µg*
			• 20 µg of HPV 31 L1 protein
			• 20 µg of HPV 33 L1 protein
			• 20 µg of HPV 45 L1 protein
			• 20 µg of HPV 52 L1 protein
			• 20 µg of HPV 58 L1 protein
			L1 protein in the form of virus-like particles produced in yeast cells (*Saccharomyces cerevisiae* CANA DE 3C-5 [Strain 1895]) by recombinant DNA technology.
			Adsorbed on amorphous aluminum hydroxyphosphate sulphate adjuvant (0.5 mg aluminum).
				• Inactivated Poliomyelitis Vaccine
				  • Type 1 (Mahoney) 40 D-antigen units*
				  • Type 2 (MEF-1) 8 D-antigen units*
				  • Type 3 (Saukett) 32 D-antigen units*
				** Or the equivalent antigen quantity, determined by suitable immunochemical method*
				• Aluminum phosphate (adjuvant) 1.5 mg (0.33 mg aluminum)

Excipients/ Diluent	Sodium acetate buffered saline	Sucrose, trometamol, sodium chloride, and water for injections	Sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injections	• 2-phenoxyethanol 0.6% v/v • Polysorbate 80 < 5 µg (< 10 ppm) • Also contains traces of water

				for injection q.s. 0.5 mL Manufacturing Process Residuals Bovine serum albumin, formaldehyde, glutaraldehyde, polymyxin B, neomycin, and streptomycin are present in trace amounts.
Dosage Level	0.5 mL per dose	0.5 mL per dose	0.5 mL per dose	0.5 mL per dose
Number of Doses/Dosing Interval	1 dose	1 dose	1 dose	1 dose
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Site of Administration	Deltoid muscle	Deltoid muscle	Deltoid muscle	Deltoid muscle
Sourcing	Provided by Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	The study interventions, MenACYW conjugate vaccine (single-dose vial), Nimenrix®, and other products will be supplied with investigational labeling and packaging according to national regulations. Each single dose of study interventions will be identified by a unique number on the detachable label and on the outer carton label. The detachable label is for the sites to attach to the source documents. See the Operating Guidelines for additional label detail.			
Current/Former Name or Alias	NA	NA	NA	NA
Batch Number	C1100201	C1100426	C1099228	C1100891

DNA: deoxyribo nucleic acid; FHA: filamentous hemagglutinin; FIM: fimbriae types 2 and 3; IMP: investigational medicinal product; Lf: limits of flocculation; NA: not applicable; NIMP: non-investigational medicinal product; ppm: part per million; PRN: pertactin; PT: pertussis toxoid; q.s.: quantity sufficient; v/v: volume/volume

6.2 Preparation/Handling/Storage/Accountability

MenACYW conjugate vaccine is supplied in single-dose (0.5 mL) vials. Nimenrix® is supplied as a white powder or cake in a single dose glass vial and a clear and colorless solvent in a pre-filled syringe. The other products (9vHPV vaccine and Tdap-IPV vaccine) are supplied as a suspension in a pre-filled syringe.

All study interventions will be administered intramuscularly in the deltoid muscle of arm. Also see Nimenrix®, 9vHPV, Tdap-IPV vaccine package inserts for more details on administration.

In all 3 groups, 9vHPV and Tdap-IPV vaccines will be administered in the contralateral arm (ie, arm opposite to the one where MenACYW conjugate vaccine or Nimenrix® is given) with the 9vHPV and Tdap-IPV vaccine injections separated by minimum 2.5 cm distance.

The site of injection for each vaccine should be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle will be disposed of in accordance with currently established guidelines.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content, and extraneous particulate matter and/or discoloration, whenever solution and container permit. If any of these conditions exist, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor. The rubber stopper should not be removed from any of the vaccine vials.

Detailed guidance and information are provided in the Operating Guidelines.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Operating Guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

On the day of enrollment, participants who meet the inclusion/exclusion criteria, and who sign the Assent Form (AF) and whose parents/legally acceptable representatives sign the Informed Consent Form (ICF) will be randomly assigned to Groups 1, 2, or 3 in a 3:3:2 ratio.

The site staff will connect to the interactive response technology (IRT) system, enter the identification and security information, and confirm a minimal amount of data in response to IRT system prompts. The IRT system will then provide at least the participant number and vaccine group assignment. The IRT will also state whether the participant has been assigned to the D07 blood draw subset (first 60 participants of Group 3 only), and whether the participant will be in the rSBA testing subset (first 50 participants of each group). The full detailed procedures for group allocation are described in the Operating Guidelines. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

Participant numbers that are assigned by the IRT system will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). For example:

Participant 380000100005 is the fifth participant enrolled in Center Number 1 in Italy (380 being the Italy country code).

Participant 724001100006 is the sixth participant enrolled in Center Number 11 in Spain (724 being the Spain country code).

Participant 702000800004 is the fourth participant enrolled in Center Number 8 in Singapore (702 being the Singapore country code).

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

6.3.2 Blinding and Code-breaking Procedures

The study will be performed in a partially observer-blind fashion:

In Groups 1 and 2

- Investigators and study staff who conduct the safety assessment, participants, parents/legally acceptable representatives, the Sponsor, and laboratory personnel performing the serology testing will be kept blinded to the vaccine received
- Only the study staff who prepare and administer the vaccine and are not involved with the safety evaluation will know which vaccine is administered

In Group 3

- Everyone involved in the study (ie, Investigator, study staff, the Sponsor, participants, parents/legally acceptable representatives) will know which vaccine is administered. This open-label design for Group 3 is due to the different vaccination schedule for this group than for Groups 1 and 2.

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

The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has

been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur Responsible Medical Officer if a participant's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking Case Report Form (CRF) is to be completed.

The Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) must be notified of the code-breaking, in accordance with local regulations. All documentation pertaining to the event must be retained in the site's study records and, in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

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

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

The code-breaking procedures are described in the Operating Guidelines.

6.4 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 6.1), and that any noncompliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified and trained study personnel
- The person in charge of study intervention management at the site will maintain accountability records of study intervention delivery to the study site, study intervention inventory at the site, dose given to each participant, and unused or wasted doses

6.5 Concomitant Therapy

At the time of enrollment, ongoing medications and other therapies (eg, blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions/AEs during study participation.

Documentation in the CRF of ongoing concomitant medication will be limited to specific categories of medication of interest beginning on the day of first vaccination. This may include medications of interest that were started prior to the day of vaccination.

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

Reportable medications (Category 1, 2, and 3) will be collected in the source document from the day of first vaccination to the end of the study[a] and in the CRF as per the instructions given below for each category.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Three standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids [therapy duration less than 2 weeks], and other immune-modulators) Category 1 medication do not define the Per-Protocol Analysis Set (PPAS).

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

- Category 1 medications will be reported in the CRF from the day of each vaccination to the end of the solicited and unsolicited follow-up period after each vaccination.

- Category 2: medications impacting or that may have an impact on the immune response and used to define the PPAS; for example:
  - Flu vaccines administered within 14 days pre or post each trial vaccination, including the day of the study vaccination visit
  - Any vaccine (including COVID-19 vaccine) other than study vaccines (vaccines not described in the Protocol) within the 28 days (4 weeks) preceding or after the trial vaccination, including the day of the study vaccination visit
  - Immune globulins, blood or blood-derived products: used in the 3 months preceding the first blood draw and up to the last blood draw
  - Immunosuppressive therapy such as immune-suppressors, immune-modulators with immunosuppressive properties, long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks) used in the past 3 months preceding the study vaccination and up to the last blood draw, anti-cancer chemotherapy, anti-proliferative drugs such as deoxyribonucleic acid (DNA) synthesis inhibitors, or radiation therapy: used in the 6 months preceding the first study vaccination, and up to the last blood draw

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

- Category 3: systemic (oral or injectable) antibiotics received within 72 hours preceding each visit for blood draw related to IMP assessment (meningococcal vaccines) and used to define

[a] Participant's parents/legally acceptable representatives will be required to document all medications received in the diary cards. The sites will focus on only recording the medications belonging to the 3 categories in the other source documents.

the PPAS, as they may interfere with bioassays used for antibody testing when taken before a blood draw

Category 3 medications will be reported in the CRF for the period of 3 days (72 hours) before each blood draw.

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

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

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

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance.

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

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication received belongs to one of the pre-listed categories. Medications will not be coded.

6.5.1 Rescue Medicine

Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on-site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.6 Dose Modification

Not applicable.

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

6.7 Intervention After the End of the Study

Depending on the age of the participant at the time of first dose administration during this study, and according to national recommendation, all participants should receive a second dose (and third dose) of 9vHPV vaccine several months after the first dose. These additional vaccinations for the completion of 9vHPV schedule will take place outside of the objectives and scope of this study and thus will not be described in this protocol. Also, these additional 9vHPV vaccinations will not be provided by the Sponsor.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Temporary Contraindications

Should a participant experience one of the conditions listed below, the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the SoA.

- Febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) or moderate or severe acute illness/infection on the day of vaccination, according to Investigator's judgment.
- Receipt of any vaccine (other than the study vaccines) in the 4 weeks preceding any study vaccination or planned receipt of any vaccine in the 4 weeks following any study vaccination except for influenza vaccination, which may be received at least 2 weeks before study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.
- Receipt of immune globulins, blood, or blood-derived products in the past 3 months.
- Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 6 months, or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).

7.1.2 Temporary Contraindications for Blood Sample

Should a participant receive oral or injectable antibiotic therapy within 3 days (72 hours) prior to a blood draw, the Investigator will postpone that blood draw until it has been 3 days since the participant 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 the appropriate timeframe, the blood sample should be collected without postponement, and it should be documented appropriately that the sample was taken less than 3 days after stopping antibiotic treatment.

7.1.3 Definitive Contraindications

Participants will permanently discontinue (definitive discontinuation) study intervention for the reasons listed below. These participants must not receive any additional dose of study intervention but should continue to be followed for safety and immunogenicity. Additional unscheduled visits may be performed for safety reasons and information will be reported in the source documents.

Should a participant experience 1 of the conditions listed below, the Investigator will discontinue vaccination:

DCI01: Pregnancy, as indicated by a positive urine test

In the event of a local or national immunization program with a pandemic influenza vaccine,COVID-19 vaccine or any other vaccine as needed, participants who receive the vaccine mentioned above at any time during the study will not be withdrawn from the study.

7.2 Participant Discontinuation/Withdrawal from the Study

- Participants and their parents/legally acceptable representatives will be informed that they have the right to withdraw their child from the study at any time.
- A participant may withdraw from the study at any time at his/her own request, or at the request of the participant's parent/legally acceptable representative, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons without the permission of the participant or their parent/legally acceptable representative. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF: AE, Lost to Follow-up, Protocol Deviation, or Withdrawal by participant or parent/legally acceptable representative.
- The withdrawn participants will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- Withdrawn participants may be replaced.

Follow-up of Discontinuations

For participants who have prematurely terminated the study, the site should attempt to contact them and complete all scheduled safety follow-ups, except if they specified that they do not want to be contacted again and it is documented in the source document.

For participants where the reason for early termination is lost to follow-up, the site will not attempt to obtain further safety information. See Section 7.3 for definition of "lost to follow-up".

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit or cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods), or at least to determine his/her health status while fully respecting his/her rights. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- There is no screening period nor screening criteria for this study other than the inclusion and exclusion criteria (see Section 5). The initial evaluations will include collection of medical history, recent or ongoing treatments, physical examination as per standard of care (see Section 8.2.2), and urinary pregnancy test (for female participant sexually active and that have reached puberty) will be performed for all groups at Visit 1 and also at Visit 2 (Groups 1 and 2) to check that all the inclusion and exclusion criteria are fulfilled before enrolment of the participant and the vaccine(s) administration.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Blood samples will be collected as described in the SoA table (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 21 mL, see Table 8.1 and Table 8.2. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 8.1: Blood sampling volume (mL) per visit- Groups 1 and 2

Visit Number **Study Timelines (Days/Months)** **Time Windows (Days)**	**Visit 1** **D01**		**Visit 2** **D31 (Visit 1 + 30 days)** **+ 14**		**Visit 3** **Day 61 (Visit 2 + 30 days)** **+ 14**
	Immunogenicity assessments				
	BL01AA (5 mL)*†	BL01AR (5mL)†	BL02AA (8 mL)*†	BL02AR (8mL)†	BL03AA (8 mL)
Meningococcal serogroups (A, C, W, Y) - human	x	x	x	x	
Meningococcal serogroups (A, C, W, Y) - rabbit		x		x	
Tetanus			x	x	x
Diphtheria			x	x	x
Polio (types 1, 2, 3)			x	x	x
Pertussis (PT, FHA, PRN, FIM)			x	x	x
HPV			x	x	x
TOTAL	5 mL		8 mL		8 mL

FHA: filamentous hemagglutinin; FIM: fimbriae types 2 and 3; HPV: human papillomavirus; PRN: pertactin; PT: pertussis toxoid.
* Blood samples at D01 and D31 will be drawn before administration of the vaccines.
† Blood sample volume indicated for BL01AA, BL01AR, BL02AA and BL02AR will be taken from all participants including those participants in the rSBA subset. In the rSBA subset, the antibody response to meningococcal serogroups (A, C, W, and Y) will be measured by rSBA assay in addition to hSBA assay (refer to Section 6.3.1 for more details on rSBA subset).

Table 8.2: Blood sampling volume (mL) per visit- Group 3

Visit Number Study Timelines (Days/Months) Time Windows (Days)	Visit 1 D01		Visit 2 D07 (Visit 1 + 6 days)* + 2	Visit 3 Day 31 (Visit 1 + 30 days) + 14	
	Immunogenicity assessments				
	BL01BB (8 mL)†§	BL01BR (8mL) §	BL02D7 (5 mL) §	BL03BB (8 mL)	BL03BR (8 mL)
Meningococcal serogroups (A, C, W, Y) - human	x	x	x	x	x
Meningococcal serogroups (A, C, W, Y) - rabbit		x			x
Tetanus	x	x		x	x
Diphtheria	x	x		x	x
Polio (types 1, 2, 3)	x	x		x	x
Pertussis (PT, FHA, PRN, FIM)	x	x		x	x
HPV	x	x		x	x
TOTAL	8 mL		5 mL	8 mL	

FHA: filamentous hemagglutinin; FIM: fimbriae types 2 and 3; HPV: human papillomavirus; PRN: pertactin; PT: pertussis toxoid.
* Blood sample at D07 will be taken only in subset of the first 60 participants.
† Blood sample at D01 will be drawn before administration of the vaccines.
§ Blood sample volume indicated for BL01BB, BL01BR and BL02D7 will be taken from all participants including those participants in the rSBA subset. In the rSBA subset, the antibody response to meningococcal serogroups (A, C, W, and Y) will be measured by rSBA assay in addition to hSBA assay (refer to Section 6.3.1 for more details on rSBA subset).

Guidance and information for the sample collection, preparation, storage, and shipment are provided in the Operating Guidelines.

8.1 Efficacy and Immunogenicity Assessments

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

The hSBA, 9vHPV, and Tdap-IPV testing will be performed at Global Clinical Immunology (GCI), Swiftwater, Pennsylvania or at qualified contract laboratories for GCI. The rSBA testing will be performed at Vaccine Evaluation Unit, Public Health Laboratory, Manchester (Pr Ray Borrow), United Kingdom.

Antibodies to Meningococcal Antigens (hSBA Method)

Functional meningococcal antibody activity against serogroups A, C, W, and Y will be measured by hSBA. [redacted]

[redacted] 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.

Anti-Diphtheria, Tetanus, and Pertussis Antibodies

The diphtheria, tetanus, and pertussis electrochemiluminescent is a multiplexed serological assay which allows for the simultaneous quantification of human antibodies to 6 specific antigens including diphtheria toxoid, tetanus toxoid, and 4 pertussis antigens: PT, FHA, FIM, and PRN. [redacted]

Anti-Poliovirus (Types 1, 2, and 3) Antibodies

Anti-poliovirus types 1, 2, and 3 will be measured by neutralization assay. [redacted]

Anti-HPV Antibodies

Anti-HPV antibodies will be measured by the direct virus-like particle (VLP) electrochemiluminescence multi-plex immunoassay for detection of antibodies towards HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. [redacted]

[redacted]

Antibodies to Meningococcal Antigens (rSBA Method)

Functional meningococcal antibody activity against serogroups A, C, W, and Y will be measured in an SBA utilizing baby rabbit complement. Two-fold dilutions of test sera are prepared in sterile 96-well microtiter plates. [redacted] This method will be performed on blood samples (refer to Table 8.1 and Table 8.2) in a subset. In the event of insufficient serum sample volume, the conduct of the hSBA assay is of higher priority than the assays for antigens of concomitant vaccines and the conduct of the assays for antigens of concomitant vaccines is of higher priority than the rSBA assay.

8.2 Safety Assessments

This section presents safety assessments other than AEs which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Medical History

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

8.2.2 Physical Examinations

At Visit 1 and Visit 3 (all groups) and at Visit 2 (Groups 1 and 2 only), the Investigator or a delegate will perform a clinical or medically driven physical examination. Information will be recorded in the source document.

Physical examination should be performed as per standard of care including, but not limited to, a general examination of the main body systems of interest (ie, heart, lung, skin, neurologic, muscular-skeletal, lymphatic system, etc). Temperature to be measured by oral (preferred route), rectal, or axillary route using a digital thermometer before vaccination and daily during the 7 days after vaccination and recorded in the diary card. 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.

8.2.3 Vital Signs

Pre-vaccination temperature will be systematically collected by the Investigator on the source document by oral (preferred route), rectal, or axillary route using a digital thermometer. Tympanic scan, infrared skin scan, and temporal artery scan thermometers must not be used.

8.2.4 Clinical Safety Laboratory Assessments

A urine human chorionic gonadotropin pregnancy test will be performed in sexually active female participants of childbearing potential before each vaccination visit.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.3.

AEs will be reported by the participants/parents/legally acceptable representatives to the Investigator, then by the Investigator to the Sponsor.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

Participants 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.

Reactogenicity

Solicited injection site reactions will be collected from D01 to D08 after each vaccination.

Solicited systemic reactions will be collected from D01 to D08 after each vaccination.

The solicited injection site reactions and systemic reactions that are pre-listed in the diary cards and CRF, together with the intensity scales, are presented in Appendix 10.3.5.1.1.

Unsolicited Non-serious Adverse Events

Unsolicited non-serious AEs will be collected from D01 to D31 after each vaccination.

The intensity grading scale for unsolicited non-serious AEs are presented in Appendix 10.3.5.1.2.

Adverse Events of Special Interest

AESI will be collected throughout the study.

See Section 8.3.6 for the list of AESI.

Serious Adverse Events

Information on SAEs will be collected and assessed throughout the study, from D01 (first vaccination) until 30 days after the last vaccination. However, before the first study intervention administration, only SAEs related to study procedures are to be collected (eg, SAE related to the blood sampling before the vaccination).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will not be recorded on the AE section of the CRF.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting AEs and SAEs

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information. These diary cards will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants/parents/legally acceptable representatives will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct participants/parents/legally acceptable representatives on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the participants/parents/legally acceptable representatives to collect the information recorded in the diary card and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

The method of recording, evaluating, and assessing causal relationship of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

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

- The AE is considered by the Investigator to be related to the study intervention administered
- The AE caused the discontinuation of the participant from the study or from vaccination

The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IEC/IRB, and Investigators.
- For all studies except those investigating medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IEC/IRB, if appropriate according to local requirements.

8.3.5 Pregnancy

Pregnancy and/or the absence of the use of effective contraceptive methods are exclusion criteria for enrollment in this study, but a participant could potentially become pregnant during her participation.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until delivery, by the Investigator, and recorded in the Pregnancy CRF. Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 1 month of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

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

- Generalized seizures (febrile and non-febrile) (34)
- Kawasaki disease (35-37)
- Guillain-Barré syndrome (38)
- Idiopathic thrombocytopenic purpura (39)

These events have been listed as AESI based on the feedback received from the EU regulators for the MenACYW conjugate vaccine.

No safety concerns relating to these AESI have been identified with the use of MenACYW conjugate vaccine in the completed clinical studies. Due to their medical importance and to ensure expedited communication to the Sponsor, these AESI are to be considered and collected as SAEs and reported to the Sponsor according to the procedure described in Appendix 10.3.4. Further instructions on the data collection for these events and the relevant definitions will be provided in the Operating Guidelines.

8.4 Treatment of Overdose

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately
- Closely monitor the participant for any AE/SAE
- Document the quantity of the excess of the overdose in the source documents

8.5 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) are evaluated in this study.

8.9 Immunogenicity Assessments

See Section 8.1.2.

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 Statistical Considerations

Clinical data will be analyzed under the responsibility of the Biostatistics Platform of the Sponsor. A Statistical Analysis Plan (SAP) will be written and peer-reviewed before any analyses. In accordance with the protocol, the SAP will describe all analyses to be performed by the Sponsor and all the conventions to be taken.

9.1 Statistical Hypotheses

Primary Objective

A non-inferiority approach will be used to compare post-vaccination (ie, 30 days after the vaccination) seroprotection rates of MenACYW conjugate vaccine (Group 1) to that of Nimenrix® (Group 2).

The primary objective is to demonstrate that 30 days after the administration of MenACYW conjugate vaccine or Nimenrix®, the percentage of participants who achieve an hSBA titer ≥ 1:8 for meningococcal serogroups A, C, W, Y in participants who received MenACYW conjugate vaccine (Group 1) is non-inferior to the corresponding percentage in participants who received Nimenrix® (Group 2).

Details on statistical methods are provided in Section 9.4.

Secondary and Observational Objectives

No hypotheses will be tested. The analyses will be descriptive.

9.2 Sample Size Determination

Approximately 464 participants are expected to be enrolled.

For the Primary Objective

With 174 enrolled participants in Group 1 and Group 2 each, 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, and Y hSBA antibody titers ≥ 1:8 (difference in the percentage of seroprotected participants in the 2 groups) after a single dose of MenACYW conjugate vaccine or Nimenrix®, assuming:

- A 10% dropout rate from the PPAS (155 participants evaluable per Group 1 and Group 2)
- A 1-sided alpha level of 2.5%
- A non-inferiority margin of 10% (percentage difference)

See Table 9.1 below for power of the study for primary objective.

Table 9.1: Power of the study for the primary objective

Antigen	Estimated percentage of hSBA titer ≥ 1:8 MenACYW*	Non-inferiority margin†	Power
A	93.5%	10%	90.7%
C	98.5%	10%	> 99.9%
Y	97.2%	10%	99.3%
W	99.1%	10%	> 99.9%
Overall			≥ 90%

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

* Percentages of participants with an hSBA titer ≥ 1:8 are based on the MET50 MenACYW (Group 1) post-dose result. The power is calculated with the assumption that the estimates from Group 1 equal that of Group 2 corresponding to the estimated percentages in Group 2 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, considering the level of the reference rate taken in Group 2, it is reasonable to use 10%.

For the Secondary and Observational Objectives

The sample size has been arbitrarily set to 116 participants in Group 3, as well as the sample size of the subsets, as these data are not intended to be used for any hypothesis testing. No formal sample size calculations were performed.

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

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Safety Analysis Set (SafAS)	Participants who have received at least one dose of the study vaccines[a] and have any safety data available. Three SafAS will be defined. ***Overall SafAS for any dose:*** Participants who have received at least one dose of the study vaccines[b] and have any safety data available. ***SafAS for vaccination at Visit 1 (SafAS1):*** Participants who have received at least one dose of the study vaccines[a] at Visit 1 (all groups) and have any safety data available. ***SafAS for vaccination at Visit 2 (SafAS2):*** Participants who have received at least one dose of the study vaccines[a] at Visit 2 (Group 1 and 2) and have any safety data available. For each SafAS, all participants will have their safety analyzed according to the study vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Two FAS will be defined: one for hSBA measurement and one for rSBA measurement. ***hSBA FAS:***

[a] For which safety data are scheduled to be collected.

[b] For which safety data are scheduled to be collected.

Population	Description
	Subset of randomized participants who received at least one dose of the study vaccines and had a valid post-vaccination serology result. ***rSBA FAS:*** Subset of randomized participants who received at least one dose of the study vaccines and had a valid post-vaccination serology rSBA result. Participants will be analyzed according to the intervention to which they were randomized.
Per-protocol analysis sets (PPAS)	Subset of hSBA FAS and rSBA FAS. Three PPAS will be defined: two for meningococcal vaccines (hSBA PPASM and rSBA PPASM) and one for concomitant vaccines (PPASC). ***hSBA and rSBA PPASM:*** Participants presenting with at least 1 of the following relevant protocol deviations will be excluded from the hSBA and rSBA PPASM: • Participant did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria • Participant did not receive the meningococcal vaccine • Participant 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 • Participant 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 (BL02AA or BL02AR) in Group 1 and 2: • Visit 2: Visit 1 + 30 days [+14 days] • Blood sampling 3 (BL03BB or BL03BR) in Group 3: • Visit 3: Visit 1 + 30 days [+14 days]

Population	Description
	• Participant received a protocol-prohibited therapy/medication /vaccine (Category 2 or Category 3) • Participant had other protocol violations that affected the participant's immune response, as determined by the clinical team before locking the database In addition, to the reasons listed above, participant will also be excluded from the ***hSBA PPASM*** if: • Participant serology samples did not produce a valid test result (ie, hSBA result for all meningococcal antigens are missing) And from ***rSBA PPASM*** if: • Participant serology samples did not produce a valid test result (ie, rSBA result for all meningococcal antigens are missing) ***PPASC:*** Participants presenting with at least 1 of the following relevant protocol deviations will be excluded from the PPASC: • Participant did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria • Participant did not complete the vaccination schedule • Participant 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 • Participants did not receive the vaccine in the proper time window: • Visit 2: Visit 1 + 30 days [+14 days] (Group 1 and 2) • Participant did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn: • Blood sampling 3 (BL03AA) in Group 1 and 2: • Visit 3: Visit 2 + 30 days [+14 days] • Blood sampling 3 (BL03BB or BL03BR) in Group 3:

Population	Description
	• Visit 3: Visit 1 + 30 days [+14 days] • Participant received a protocol-prohibited therapy/medication /vaccine (Category 2 or Category 3) • Participants with their serology samples that did not produce a valid test result (ie, results for all antigens contained in 9vHPV and Tdap-IPV vaccines are missing) • Participant had other protocol violations that affected the participant's immune response, as determined by the clinical team before locking the database In the event of a local or national immunization program (eg, with a pandemic influenza vaccine or COVID-19 vaccine), participants who receive 1 or more doses of pandemic influenza vaccine or COVID-19 vaccine at any time during the study will not be withdrawn from the study. If the participant receives the COVID-19 vaccine within this period of 28 days pre or post IMP vaccination (including the day of the study visit for IMP vaccine), she/he will be excluded from the PPAS population but will not be excluded from the study.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of all the endpoints including primary, secondary, and observational endpoints.

9.4.1 General Considerations

Immunogenicity analyses will be performed on the appropriate PPAS and FAS. Safety analysis will be performed on the SafAS.

9.4.2 Primary Hypotheses and Methods

For primary endpoint, refer to Section 3.

The primary objective will be met if the following null hypothesis is rejected for each of the 4 serogroup A, C, W, Y:

$$H_0: p_{\text{MenACYW}} - p_{Nimenrix} \leq -0.1$$
$$H_1: p_{\text{MenACYW}} - p_{Nimenrix} > -0.1$$

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

The 95% confidence interval (CI) of the difference in proportion will be computed using the Wilson Score method without continuity correction (Newcombe method) (40).

If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages is > -0.1, the non-inferiority will be demonstrated.

Non-inferiority will be demonstrated if all 4 individual null hypotheses (4 serogroups) are rejected.

9.4.3 Secondary Hypotheses and Methods

Immunogenicity

For secondary immunogenicity endpoints, refer to Section 3.

The statistical analysis for secondary objectives will be descriptive.

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

Safety

For secondary safety endpoints, refer to Section 3.

Safety results will be described for participants in all study groups. The main parameters for the safety endpoints will be described by frequency counts and 95% CIs (based on the Clopper-Pearson method).

9.4.4 Observational Endpoints

For observational endpoints, refer to Section 3.

The statistical analysis for observational objectives will be descriptive and will be carried out similar to the secondary immunogenicity analysis described in Section 9.4.3. More details about statistical analyses of observational objectives will be given in the SAP.

9.4.5 Sensitivity analysis due to COVID-19 pandemic

The impact of COVID-19 pandemic situation on study conduction will be summarized through impact on visit procedures, study completion and major/critical protocol deviations due to COVID-19. The participants impacted by COVID-19 pandemic situation will be defined as the participants 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 participants are impacted as per this

definition, the main immunogenicity and safety endpoints will also be summarized in these participants to assess the impact of COVID-19 situation on the study outcome.

9.5 Interim Analyses

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study.

No analyses are planned to be performed prior to the formal completion of the study.

9.6 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term "participant" is used throughout this protocol. However, the term "participant" will be used in the CRF in order to comply with the Clinical Data Interchange Standards Consortium requirements.

10.2 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IEC/IRB by the Investigator or the Sponsor (according to local regulations) and reviewed and approved by the IEC/IRB before the study is initiated
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and

- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IEC/IRB of SAEs or other significant safety findings as required by IEC/IRB procedures.

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IEC/IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.2.1 Financial Disclosure

Information related to financial disclosure is described in the Investigator's contract.

10.2.2 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and his/her parent/legally acceptable representative and answer all questions regarding the study.
- Participants and their parents/legally acceptable representatives must be informed that their participation is voluntary. Participants and their parents/legally acceptable representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IEC/IRB or study center.
- As this study is conducted in adolescent participants, a separate AF has to be signed by the participants (as per local regulation). The AF is in addition to, not in place of an ICF that is signed by the parent/legally acceptable representative (and by an independent witness if required) and by the participant if he/she turns18 years old during the study.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF and AF.
- The actual ICF and AF used at each center may differ, depending on local regulations and IEC/IRB requirements. However, all versions must contain the standard information found in the sample ICF and AF provided by the Sponsor. Any change to the content of the ICF and AF must be approved by the Sponsor and the IEC/IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant's or parent's/legally acceptable representative's willingness to continue participation in the study,

this will be communicated to him/her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF and via a revised AF or an addendum to the original AF.

- Participants and their parents/legally acceptable representatives must be re-consented to the most current version of the ICF and AF during their participation in the study.
- A copy of the ICF and AF must be provided to the participants and their parents/legally acceptable representatives.
- A participant who is rescreened is not required to sign another AF and his/her parent/legally acceptable representative is not required to sign another ICF.
- The ICF will contain a specific section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant and their parent/legally acceptable representative the objectives of the exploratory research. Participants and their parents/legally acceptable representatives will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Recruitment Procedures

As this is a multi-center study with recruitment procedures differing between sites, the procedures will be described in a separate "Recruitment and Consent Process Form" in each site. In such a case, the form will be archived on-site.

10.2.3 Data Protection and Future Use of Stored Samples

- All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR. Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.
- Participants' race and ethnicity will be collected in this study because these characteristics may influence the immune response to the vaccines.
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant name or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data will be used for this study and in support of the whole drug development program for the Investigational Product, including negotiations with payers and publication of results.
- Any unused part of the serum samples (blood samples) will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for up to 25 years after the end of the study. These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

  The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health are dedicated for immediate use. In case they are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

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

10.2.4 Committees Structure

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study.

10.2.5 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in individuals are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.2.6 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs and AFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.2.7 Source Documents

“Source data” are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, ICFs/AFs, telephone contact logs, and worksheets.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Detailed guidance and information are provided in the Operating Guidelines.

10.2.8 Study and Site Start and Closure

Details on which clinical supplies are provided by the Sponsor or the site are described in the Operating Guidelines.

The study start date is considered as the date of the first visit planned in the SoA of the first participant. The study end date is considered as the date of the last visit of the last participant.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been either destroyed or returned to the Sponsor, all samples are shipped to the appropriate laboratories, the center study-site has all the documents necessary for archiving and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any Contract Research Organization used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.2.9 Publication Policy

Information related to publication policy is described in the Investigator's contract.

10.3 Appendix: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease or condition present or detected at the start of the study that do not worsen.

Other Definitions

Adverse Reaction:

All noxious and unintended responses to a study intervention related to any dose should be considered adverse reactions (AR).

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

Immediate Event/Reaction:

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

Injection Site Reaction/Administration Site Reactions:

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

Systemic Adverse Event/Adverse Reaction:

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).

Systemic AEs assessed as related to study intervention are referred as systemic ARs.

Adverse Event of Special Interest:

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. 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.

Reactogenicity/Solicited Reactions:

A solicited reaction is an "expected" AR (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF (eg, injection site pain or headache occurring between the day of vaccination and the next 7 days).

By definition, solicited reactions are considered as being related to the study intervention administered.

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

Unsolicited Adverse Event/Adverse Reaction:

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and/or onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to study intervention. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

Results in death

a. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

b. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

c. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

d. Is a congenital anomaly/birth defect

e. Other important medical event

- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious. These include generalized seizures (febrile and non-febrile), Kawasaki disease, Idiopathic thrombocytopenic purpura, and Guillain-Barré syndrome (see Section 8.3.6).
- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, new-onset diabetes or autoimmune disease.

Note: *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 participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

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 study intervention (see definition in Section 6) and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

- Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic AEs (except for non-serious AESI), relationship to study intervention will usually be assessed by the Investigator only.
  - For SAEs and non-serious AESI, relationship to study intervention will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
  - For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
- The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered[a] 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 study intervention administered, meaning that there is evidence or arguments to suggest a causal relationship
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.

[a] Study intervention administered can correspond to either the investigational product or other products when no investigational product is administered at the visit

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always makes an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causal relationship in light of follow-up information and send an SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, when available the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- Adverse events likely to be related to the study intervention, 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 participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Details regarding SAE reporting can be found in the Operating Guidelines.

SAE Reporting to the Sponsor via Paper CRF

The SAE paper CRF can be sent to the Sponsor by one of the following means:

- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com (see the Operating Guidelines for directions on how to send a password-protected e-mail).
- By express mail, to the following address:

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

Safety Emergency Call

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

This process does not replace the need to report an SAE. The Investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department.

10.3.5 Assessment of Intensity

The Investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.1.1 Solicited AR Intensity Grading Scale

Table 10.1: Solicited injection site reactions: terminology, definitions, and intensity scales – Adolescents aged ≥ 10 to <17 years

CRF term (MedDRA LLT)	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is 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*	**CRF:** 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. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

LLT: lowest level term; MedDRA: Medical Dictionary for Regulatory Activities.
* For the subjective reaction of pain, participants or 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 10.2: Solicited systemic reactions: terminology, definitions, and intensity scales –Adolescents aged ≥ 10 to < 17 years

CRF term (MedDRA LLT)	**Fever**	**Headache**	**Malaise**	**Myalgia**
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	**CRF:** 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.	**CRF:** 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.	**CRF:** 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: ≥ 39.0°C **or** ≥ 102.1°F	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. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities

LLT: lowest level term; MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions but fever, participants or 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:

Participants or 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 CRF. The preferred route for this study is oral.

10.3.5.1.2 Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.3.5.1.1).

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

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

10.4 Appendix: Collection of Pregnancy Information

DEFINITIONS:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the Following Categories Are Not Considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

COLLECTION OF PREGNANCY INFORMATION

Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information together with the contraceptive method if any will be recorded on the appropriate form and submitted to the Sponsor within 1 month of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 8 weeks beyond the estimated delivery date but will be in accordance with local regulations. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- In case of pregnancy during the primary series and if at least 1 dose of the study vaccine has been administered, the participant will not be discontinued from the study, but no further vaccination will be administered until after delivery (if applicable and still within the study vaccination window). However, the participant will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

10.4.1 Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
• **Effective Methods[d] That Are Not Considered Highly Effective** *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. d) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. e) Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix: Risk-based Approach

ICH E6-R2 guideline for GCP is introducing the « risk-based approach » concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.6 Appendix: Abbreviations

4vHPV	4-valent human papilloma virus
9vHPV	9-valent human papilloma virus
AE	adverse events
AESI	adverse events of special interest
AR	adverse reaction
CI	confidence interval
CO_2	carbon dioxide
CRF	Case Report Form
D	day
DNA	deoxyribonucleic acid
ECDC	European Center for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
FSH	follicle stimulating hormone
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
HPV	human papillomavirus
HRT	hormonal replacement therapy
hSBA	serum bactericidal assay using human complement
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IRB	Institutional Review Board

IRT	interactive response technology
IU	international units
LLOQ	lower limit of quantification
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MenC	meningococcal serogroup C conjugate vaccine
NIMP	non-investigational medicinal product
PPAS	Per-Protocol Analysis Sets
PPASC	Per-Protocol Analysis Set for concomitant vaccines
PPASM	Per-Protocol Analysis Set for meningococcal vaccines
PRN	pertactin
PT	pertussis toxoid
RMO	Responsible Medical Officer
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse events
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SmPC	summary of product characteristics
TBD	to be determined
Tdap	tetanus, diphtheria, and acellular pertussis
Tdap-IPV	tetanus, diphtheria, and acellular pertussis - inactivated polio vaccine [adsorbed, reduced antigen(s) content]
VLP	virus-like particle
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

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12 Sponsor Signature Page

Sponsor Signature

I confirm that this protocol (version 5.0 dated 19 May 2021) is in accordance with applicable regulations and Good Clinical Practice.

Function	Name	Date	Signature
Sponsor's Responsible Medical Officer	[redacted]	[redacted]	[redacted]
Project Manager and Study Leader	[redacted]	[redacted]	[redacted]