NCT04490018

SAP SMT Core Body

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

Study Phase: Phase IIIb

SAP Core Body Version: 1.0

SAP Core Body Date: 24-June-2021

Protocol Version Number: 5.0

The SAP Code Body should be used in conjunction of the study protocol and the SAP TLF.

Version History

Not applicable as this is the first version of the SAP Core Body.

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Table of Contents

[redacted]

[redacted]

List of Tables

[redacted]

List of Figures

[redacted]

1 Overall Design

The design of the study is summarized in Table 1.1.

Table 1.1: 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

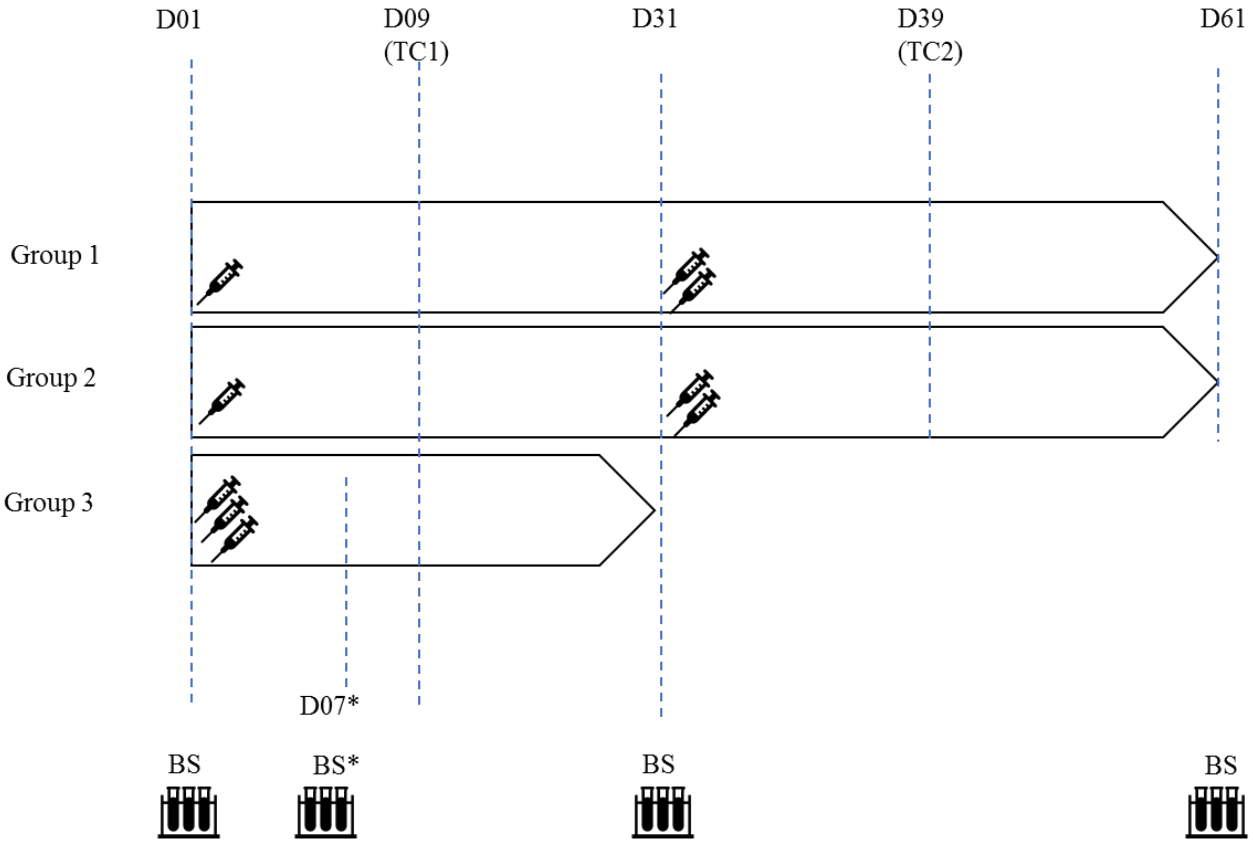
[redacted]

	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

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

[redacted]

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

The schedule of activities for Group 1 and Group 2 are given in Table 1.2 and for Group 3 are given in Table 1.3.

[redacted]

Table 1.2: 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
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		

[redacted]

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:						
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				
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

[redacted]

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 1.3: 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			

[redacted]

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:					
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**			
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			

[redacted]

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:					
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.

[redacted]

‡‡ 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 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 2.1.

Table 2.1: 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	• 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

[redacted]

Objectives	Endpoints
conjugate vaccine or Nimenrix® (Groups 1 and 2) according to MenC primed status	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

[redacted]

Objectives	Endpoints
	(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 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

[redacted]

Objectives	Endpoints
	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 presence, 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

[redacted]

Objectives	Endpoints
	titer < 1:8, a post-vaccination titer ≥ 1:32 • 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

[redacted]

3 Statistical Considerations

3.1 Statistical Hypotheses

Primary Objective

See Section 9.1 of the protocol.

Secondary and Observational Objectives

Immunogenicity:

See Section 9.1 of the protocol.

Safety:

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

3.2 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 3.1 below for power of the study for primary objective.

Table 3.1: 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%

[redacted]

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.

3.3 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[1] 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[2] 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

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

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

[redacted]

Population	Description
	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)	Not applicable for SMT analysis
Per-protocol analysis sets (PPAS)	Not applicable for SMT analysis

The safety analysis will be performed on the Safety Analysis Set (SafAS, SafAS1 and SafAS2).

3.4 Statistical Analyses

This section is a summary of the planned statistical analyses of all safety endpoints.

3.4.1 General Considerations

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 or later.

For descriptive purposes, the following statistics will be presented:

Table 3.2: Descriptive statistics produced

Disposition and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Baseline characteristics	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs for main endpoints) of subjects. Unsolicited: Number and percentage (95% CIs for main endpoints) of subjects and number of events.

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

[redacted]

3.4.2 Primary Endpoint

Not applicable for SMT analysis.

3.4.3 Secondary Endpoints

Immunogenicity

Not applicable for SMT analysis.

Safety

Safety results will be described for participants in all study groups. Group 1 and Group 2 will be pooled in order to maintain the blind. The main parameters for the safety endpoints will be described by frequency counts and 95% CIs (based on the Clopper-Pearson method).

Safety analyses will include but are not limited to the following descriptions listed in Table 3.3

Table 3.3: Statistical analyses for safety secondary objectives

Item	Time and Group	Description
All and related Immediate unsolicited systemic AEs	Within 30 minutes after each vaccination; Within 30 minutes after any vaccine injection	Summary Frequency Table presenting the number and percentage of subjects experiencing the endpoint of interest as well as the number of AEs/ARs by MedDRA SOC and PT.
All and related AEs leading to study discontinuation	D0 to D30 after each vaccination; During the entire study period after any vaccination (i.e. from Day 0 to last phone call)	Summary Frequency Table presenting the number and percentage of subjects experiencing the endpoint of interest as well as the number of AEs/ARs by MedDRA SOC and PT.
Solicited reactions	D0 to D7 after each vaccination D0 to D7 after any vaccination.	Summary Frequency Table presenting the number and percentage of subjects experiencing the endpoint of interest for solicited injection site reaction and solicited systemic reaction during the solicited time period.
All and related Unsolicited	D0 to D30 after each vaccination;	Summary Frequency Table presenting the number and percentage of subjects

[redacted]

Item	Time and Group	Description
non-serious AEs	D0 to D30 after any vaccination	experiencing the endpoint of interest as well as the number of all AEs/ARs by MedDRA SOC and PT.
AEs ongoing	At D30 after each vaccination; At D30 after any vaccination	Summary Frequency Table presenting in a blinded manner the number and percentage of subjects experiencing the endpoint of interest as well as the number of AEs/ARs by MedDRA SOC and PT
All and related SAEs	Day 0 to Day 30 after each vaccination; During the entire study period after any vaccination	Summary Frequency Table the number of subjects experiencing the endpoint of interest as well as the number of SAEs by MedDRA SOC and PT
All and related AESIs		Summary Frequency Table the number of subjects experiencing the endpoint of interest as well as the number of AESIs by MedDRA SOC and PT

3.4.4 Observational Endpoint[s]

Not applicable for SMT analysis

3.4.5 Sensitivity analysis due to COVID-19 pandemic

Not applicable for SMT analysis

3.4.6 Handling of Missing Data and Outliers

3.4.6.1 Safety

3.4.6.1.1 Immediate

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

3.4.6.1.2 Causal Relationship

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

[redacted]

- For unsolicited systemic AE, missing relationship to IMP will be considered as related to study vaccines[3] at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

3.4.6.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

3.4.6.1.4 Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the last vaccination (computed according to the section 4.2.1.2.3). If either the start date or end date is missing or partially missing, the duration will be considered missing.

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

3.4.6.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.6.2 Immunogenicity

Not applicable.

3.5 Interim Analysis

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.

3.6 Data Monitoring Committee (DMC)

Not applicable.

[3] A study vaccine is any vaccine that is administered as part of the study, including the meningococcal vaccines (MenACYW conjugate vaccine and Nimenrix), and the concomitant vaccines (Tdap-IPV and 9vHPV).

[redacted]

4 Complementary Information on Assessment Methods

Study assessments and procedures are detailed in Section 8 of the protocol. This section focusses on complementary/additional information not detailed in the protocol.

4.1 Complementary Information for Endpoints Assessment Methods

Not applicable.

4.2 Complementary Information on Derived Endpoints: Calculation Methods

4.2.1 Safety

4.2.1.1 Solicited Reactions

4.2.1.1.1 Daily Intensity

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

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

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as "No" and with all daily records missing (Unknown) then all daily intensities will be derived as None.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

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

Table 4.1: 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

[redacted]

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.

[redacted]

Table 4.2: 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	**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.	**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.	**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.

[redacted]

CRF term (MedDRA LLT)	Fever	Headache	Malaise	Myalgia
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	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 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 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.

4.2.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.2.1.1.3 Presence

Presence is derived from the maximum overall intensity over the time period considered:

- None: No presence

[redacted]

- Grade 1, Grade 2, or Grade 3: Presence
- Missing or Unknown: Missing presence

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

The time period is displayed as D1-D4, D5-D8, D9 and later.

4.2.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

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

Time of onset period is displayed as, D1-D4, D5-D8.

4.2.1.1.5 Number of Days of Presence During the Solicited Period

Number of days of presence over the period considered is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3.

4.2.1.1.6 Overall Number of Days of Presence

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

- (End date - last vaccination date) + (number of days of presence within the solicited period [8]) - length of the solicited period + 1

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

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.

[redacted]

- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables).

4.2.1.2 Unsolicited AEs

4.2.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event.

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

4.2.1.2.2 Intensity

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

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in Table 4.1 and Table 4.2 for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but < 25 mm in adults).

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

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

4.2.1.2.3 Last Vaccination

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

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

4.2.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of last vaccination as described in Section 4.2.1.2.3:

Time of Onset = start date of the unsolicited AE - date of last vaccination before the unsolicited AE + 1.

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

[redacted]

The unsolicited AEs will be analyzed "Within 30 days" after each vaccination, which corresponds to AEs with a time of onset between 1 and 31 days or missing. An AE with missing time of onset will be considered to have occurred just after the last vaccination (computed according to the Section 4.2.1.2.3), so will be included in these tables.

Time of onset period is computed as D1-D4, D5-D8, D9-D15, D16 or later, and Missing.

Note: Unsolicited AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis but will be listed separately.

4.2.1.2.5 Duration

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

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

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

4.2.1.2.6 Medically-Attended Adverse Event

Not applicable.

4.2.1.2.7 Serious Adverse Events

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

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

- Within 30 days
- During post-Dose 1 period (i.e., after Visit 01 and within 30 days after the injection performed at Visit 01 for all groups)
- During post-Dose 2 period (i.e., after Visit 02 and within 30 days after the injection performed at Visit 02 for Group 1 or Group 2)
- During the study (i.e., all SAEs occurred during the study)

4.2.1.2.8 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF.

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

- Within 30 days
- During post-Dose 1 period (i.e., after Visit 01 and within 30 days after the injection performed at Visit 01 for all groups)
- During post-Dose 2 period (i.e., after Visit 02 and within 30 days after the injection performed at Visit 02 for Group 1 or Group 2)

[redacted]

- During the study (i.e., all AESIs occurred during the study)

4.2.2 Other Safety Endpoints

4.2.2.1 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.2.2.2 Action Taken

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

4.2.2.3 Seriousness

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

4.2.2.4 Outcome

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

4.2.2.5 Causal Relationship

This information will be summarized as collected in the field “Relationship to IMP”. Missing causal relationship will be handled as described in Section 3.4.6.1.2. Relationship to study procedure is only presented in the listing.

4.2.2.6 Adverse Events Leading to Study Discontinuation

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

In general, the items that are counted are:

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

[redacted]

4.2.3 Immunogenicity

Not applicable for SMT analysis.

4.2.4 Efficacy

Not applicable for SMT analysis.

4.2.5 Derived Other Variables

4.2.5.1 Age for Demographics

The age of a subject in the study is the calendar age in years at the time of inclusion. It is displayed as an integer.

4.2.5.2 Duration of a Subject in the Trial

The duration of a subject in the study until last visit is computed in days as follows:

Maximum (Visit dates, Termination date) –V01 date +1

4.2.5.3 Duration of the Study

The duration of the study until last visit is computed as follows:

Maximum of all subjects (Visit dates, Termination date) – minimum for all subjects (V01 date) + 1

4.2.5.4 Time Interval

The time interval between 2 study timepoints (visits/vaccination/blood samples) is computed as follows:

Later date – earlier date.

[redacted]

5 Changes in the Conduct of the Trial or Planned Analyses

Not applicable.

[redacted]

6 Supporting Documentation

6.1 Appendix 1 List of 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
D	day
DMC	Data Monitoring Committee
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
GM	Geometric mean
GMT	Geometric mean of titer
GMC	Geometric mean of concentration
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

[redacted]

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
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MenC	meningococcal serogroup C conjugate vaccine
NA	Not applicable
NC	Not computed
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
RCDC	Reverse cumulative distribution curve
rSBA	serum bactericidal assay using baby rabbit complement
SAE	Serious adverse events
SafAS	Safety analysis set
SAP	Statistical analysis plan
SmPC	summary of product characteristics
SOC	(Primary) System organ class
PT	Preferred term
Tdap	tetanus, diphtheria, and acellular pertussis
Tdap-IPV	tetanus, diphtheria, and acellular pertussis - inactivated polio vaccine [adsorbed, reduced antigen(s) content]
TLF	Tables, listings and figures
VLP	virus-like particle

[redacted]

ULOQ	Upper level of quantitation
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

7 References

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in medicine. 1998;17(8):857-72.

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

[redacted]