Protocol C0921062

A PHASE 3B, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF NIMENRIX® IN HEALTHY INFANTS, GIVEN AT 3 AND 12 MONTHS OF AGE

Statistical Analysis Plan
(SAP)

Version: 1

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 24 Mar 2021	Original 23 Oct 2020	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C0921062. A brief description of the study design and the study objectives are given. Subsequent sections include definitions of the analysis populations and the immunogenicity and safety endpoints, followed by details regarding statistical analysis and reporting. A list of tables, listings, and figures; mock-up tables, listings, and figures; and programming rules are prepared separately based on the methods described in this document. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. Table 2 shows the study design. The impacts of COVID-19 will be assessed prior to the first planned analysis, and the SAP will be amended accordingly to account for these impacts, if needed.

Table 2. Study Design

	Vaccination 1	Follow-up Visit 1	Vaccination 2	Follow-up Visit 2
Visit Window (Days)	**Day 1**	**28 to 42 Days After Visit 1**	**270 to 300 Days After Visit 1**	**28 to 42 Days After Visit 3**
Visit Number	**1**	**2**	**3**	**4**
Group (n=150)	Nimenrix		Nimenrix	
Blood draw	5 mL[a]	5 mL	5 mL[a]	5 mL

a. The blood sample will be collected prior to vaccination.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in Table 3. The estimands to evaluate the immunogenicity objectives are based on evaluable populations (see Section 4 for definitions). These estimands estimate the vaccine effect in a hypothetical setting where participants follow the study schedules and protocol requirements, as directed.

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary (Safety):	Primary (Safety):	Primary (Safety):
• To describe the safety of 2 doses of Nimenrix when administered in healthy infants at 3 and 12 months of age.	In participants receiving Dose 1 and 2: • The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after Dose 2 (Visit 3, 12 months of age) of Nimenrix. • The percentage of participants reporting at least 1 AE, at least 1 SAE, and at least 1 NDCMC during the following time period: • Within 30 days after Dose 2 (Visit 3, 12 months of age) of Nimenrix. • The percentage of participants reporting at least 1 immediate AE after Dose 2 (Visit 3, 12 months of age) of Nimenrix.	• Local reactions (redness, swelling, and pain at the injection site). • Systemic events (fever, decreased appetite, drowsiness, and irritability). • AEs. • SAEs. • NDCMCs.
Primary (Immunogenicity):	Primary (Immunogenicity):	Primary (Immunogenicity):
• To describe the immune response for *N meningitidis* serogroups A, C, W-135, and Y induced by 2 doses of Nimenrix administered at 3 and 12 months of age.	In participants receiving both doses of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants): • Percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix. • rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY GMTs for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix.	• rSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups.

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Secondary (Safety):	Secondary (Safety):	Secondary (Safety):

• To describe the safety of 1 dose of Nimenrix when administered in healthy infants at 3 months of age.	In participants receiving at least 1 dose of study intervention:
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after Dose 1 (Visit 1, 3 months of age) of Nimenrix.
	• The percentage of participants reporting at least 1 AE, at least 1 SAE, and at least 1 NDCMC during the following time period:
	  • Within 30 days after Dose 1 (Visit 1, 3 months of age) of Nimenrix.
	• The percentage of participants reporting at least 1 SAE and at least 1 NDCMC during the following time periods:
	  • During the follow-up phase: From 1 month after Dose 1 (Visit 2, 4 months of age) through 9 months after Dose 1 (Visit 3, 12 months of age) of Nimenrix.
	  • 9 Months after the vaccination: From Dose 1 (Visit 1, 3 months of age) through 9 months after Dose 1 (Visit 3, 12 months of age) of Nimenrix.
	• The percentage of participants reporting at least 1 immediate AE after Dose 1 (Visit 1, 3 months of age) of Nimenrix.
		• Local reactions (redness, swelling, and pain at the injection site).
		• Systemic events (fever, decreased appetite, drowsiness, and irritability).
		• AEs.
		• SAEs.
		• NDCMCs.

Secondary (Immunogenicity):	Secondary (Immunogenicity):	Secondary (Immunogenicity):
• To describe the immune response for *N meningitidis* serogroups A, C, W-135, and Y induced by 1 dose of Nimenrix administered at 3 months of age.	In participants who have received the first dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants): • Percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix. • rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY GMTs for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix.	• rSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups. • hSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups.

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
	• Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4, ≥1:8 for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix. • hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY GMTs for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix. • Percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:128 for each serogroup at baseline (Visit 1, 3 months of age) and at 1 month after Dose 1 (Visit 2, 4 months of age) of Nimenrix.	
• To further describe the immune response for *N meningitidis* serogroups A, C, W-135, and Y induced by 2 doses of Nimenrix administered at 3 and 12 months of age.	In participants who have received the first and second dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants): • Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4, ≥1:8 for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix. • hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY GMTs for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix. • Percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:128 for each serogroup at baseline (Visit 1, 3 months of age), at 1 month after Dose 1 (Visit 2, 4 months of age), at Dose 2 (Visit 3, 12 months of age), and at 1 month after Dose 2 (Visit 4, 13 months of age) of Nimenrix.	• hSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups. • rSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups.

Table 3. List of Primary, Secondary, and Exploratory Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Exploratory:	Exploratory:	Exploratory:
• N/A	• N/A	• N/A

In addition to the primary and secondary safety endpoints, exploratory safety endpoints and estimands related to either after Dose 1 or Dose 2 are added in the SAP.

The estimands are:

In participants who have received at least 1 dose of investigational product:

- The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after any dose (Dose 1 [Visit 1, 3 months of age] or Dose 2 [Visit 3, 12 months of age]) of Nimenrix.

- The percentage of participants reporting at least 1 AE, at least 1 SAE, and at least 1 NDCMC during the following time period:

    - Within 30 days after any dose (Dose 1 [Visit 1, 3 months of age] or Dose 2 [Visit 3, 12 months of age]) of Nimenrix.

- The percentage of participants reporting at least 1 SAE and at least 1 NDCMC during the following time periods:

    - Throughout the study, from Dose 1 (Visit 2, 4 months of age) until 1 month after Dose 2 (Visit 3, 12 months of age) of Nimenrix.

2.2. Study Design

This Phase 3b, multicenter, open-label study, with a single arm design, will be conducted at investigator sites in Europe. Approximately 150 healthy infants 3 months of age will be enrolled to a single vaccine group to receive Nimenrix (MenACWY-TT).

On Day 1 (Visit 1), participants will be assessed for eligibility (including medical history and meningococcal vaccine history). If eligible, participants will have blood drawn for immunogenicity assessments and will receive the first dose of Nimenrix. Participants will receive a second dose of Nimenrix at 12 months of age (Visit 3).

Participants will have blood drawn prior to vaccination at Visit 1 and Visit 3 and 1 month after each vaccination at Visit 2 and Visit 4. E-diaries will be used to collect local reaction and systemic event data for 7 days after each vaccination. AEs will be collected through 1 month after each vaccination. In addition, SAEs and NDCMCs will be collected throughout the study from Visit 1 through Visit 4.

In the case of extreme circumstances, such as natural disasters or a pandemic, visits for follow-up or procedures may need to be conducted through other means (eg, telephone, home visits).

2.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the Study Assessments and Procedures section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Table 4. Schedule of Activities (SoA)

Visit Number	1	2	3	4
Visit Description	**Vaccination 1**	**Follow-up Visit 1**	**Vaccination 2**	**Follow-up Visit 2**
Visit Window (Days)	**Day 1**	**28 to 42 Days After Visit 1**	**270 to 300 Days After Visit 1**	**28 to 42 Days After Visit 3**
Obtain informed consent	X			
Assign a participant number	X			
Record demography, medical history, physical examination, vital signs	X			
Record nonstudy vaccine information	X	X	X	X
Record medication information[a]	X	X	X	X
Review inclusion and exclusion criteria	X			
Measure prevaccination temperature	X		X	
Review temporary delay criteria	X	X	X	X
Review continued eligibility		X	X	X
Obtain blood draw for immunogenicity assessment	X[b] (~5mL)	X (~5mL)	X[b] (~5mL)	X (~5mL)
Administer investigational product[c]	X		X	
Observe and record acute reactions for 30 minutes after investigational product administration	X		X	
Provide the parent(s)/legal guardian(s) with a contact card	X			
Provide parent(s)/legal guardian(s) with an e-diary, thermometer, and measuring device and instruct to collect local reactions and systemic events until 7 days after vaccination[d]	X		X	
Review and/or collect e-diary (if applicable)[e]		X		X
Record and report AEs	X----------X		X----------X	

Table 4. Schedule of Activities (SoA)

Visit Number	1	2	3	4
Visit Description	**Vaccination 1**	**Follow-up Visit 1**	**Vaccination 2**	**Follow-up Visit 2**
Visit Window (Days)	**Day 1**	**28 to 42 Days After Visit 1**	**270 to 300 Days After Visit 1**	**28 to 42 Days After Visit 3**
Record and report SAEs and NDCMCs[f]	X----------	----------	----------	----------X

a. Only concomitant medications used to treat SAEs and NDCMCs will be recorded.
b. Blood sample will be collected prior to vaccination.
c. Remind the participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
d. The participant's parent(s)/legal guardian(s) will record local reactions and systemic events in an e-diary for the 7 days following each dose of Nimenrix. Use of antipyretic/pain medications will also be collected daily in an e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling >14 caliper units, severe pain at the injection site, or a fever >40.0°C or has an emergency room visit or hospitalization.
e. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following each dose of Nimenrix to evaluate participant compliance and as part of the ongoing safety review.
f. An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

In participants receiving Dose 1 and Dose 2:

- Local reactions (redness, swelling, and pain at injection site) within 7 days after Dose 2.
- Systemic events (fever, decreased appetite, drowsiness, and irritability) within 7 days after Dose 2.
- Use of antipyretic medications within 7 days after Dose 2.
- AEs within 30 days after Dose 2.
- SAEs during the study within 30 days after Dose 2.
- NDCMCs during the study within 30 days after Dose 2.
- Immediate AEs after Dose 2.

3.1.2. Primary Immunogenicity Endpoints

In participants receiving both doses of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants):

- rSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2 of Nimenrix.
    - Classification of titer as ≥1:8 at each time point.

3.2. Secondary Endpoints

3.2.1. Secondary Safety Endpoints

In participants receiving at least 1 dose of study intervention:

- Local reactions (redness, swelling, and pain at injection site) within 7 days after Dose 1.
- Systemic events (fever, decreased appetite, drowsiness, and irritability) within 7 days after Dose 1.
- AEs within 30 days after Dose 1.
- SAEs during the study (within 30 days after Dose 1, from 1 month after Dose 1 through 9 months after Dose 1, and from Dose 1 through 9 months after Dose 1).

- NDCMCs during the study (within 30 days after Dose 1, from 1 month after Dose 1 through 9 months after Dose 1, and from Dose 1 through 9 months after Dose 1).

- Immediate AEs after Dose 1.

3.2.2. Secondary Immunogenicity Endpoints

In participants who have received the first dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants):

- rSBA titer for each of the MenA, MenC, MenW-135, and MenY serogroups at baseline and at 1 month after Dose 1.
    - Classification of titer as ≥1:8, ≥1:128 at each time point.

- hSBA titer for each of the MenA, MenC, MenW-135, and MenY serogroups at baseline and at 1 month after Dose 1.
    - Classification of titer as ≥1:4, ≥1:8 at each time point.

In participants who have received the first and second dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants):

- rSBA titer for each of the MenA, MenC, MenW-135, and MenY serogroups at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2.
    - Classification of titer as ≥1:128 at each time point.

- hSBA titer for each of the MenA, MenC, MenW-135, and MenY serogroups strains at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2.
    - Classification of titer as ≥1:4, ≥1:8 at each time point.

At each visit where assay titers are available (Visits 1, 2, 3, and 4), participants with rSBA (or hSBA) titers ≥ LLOQ will be derived as follows:

= . , if the assay result is missing, indeterminate, or otherwise unavailable;

= 1, if the assay result meets the specific LLOQ value;

= 0, if the assay result does not meet the specific LLOQ value.

The threshold values for MenA, MenC, MenW-135, and MenY serogroups are:

- ≥1:8 and ≥1:128 for rSBA titers

- ≥1:4 and ≥1:8 for hSBA titers

3.3. Other Endpoint

3.3.1. Exploratory Safety Endpoints

In participants receiving any dose of study intervention:

- Local reactions (redness, swelling, and pain at injection site) within 7 days after any dose.
- Systemic events (fever, decreased appetite, drowsiness, and irritability) within 7 days after any dose.
- AEs within 30 days after any dose.
- SAEs within 30 days after any dose and throughout study (from Dose 1 through 1 month after Dose 2).
- NDCMCs within 30 days after any dose and throughout study (from Dose 1 through 1 month after Dose 2).

3.4. Baseline Variables

3.4.1. Demographic, Medical History, and Baseline Characteristic Variables

Demographic variables collected at each dose include sex (male or female), race, ethnicity, and date of birth. Race collected includes:

- Black or African American
- Asian
- White
- Not reported

Ethnicity collected includes:

- Hispanic or Latino
- Non-Hispanic/non-Latino
- Not reported

Age at each dose (in days) will be derived as (dose date – date of birth +1). For participants who were enrolled but not vaccinated, the consent date will be used in place of the date of Dose 1 for the Dose 1 age calculation.

In cases where more than 1 category is selected for race, the participant would be counted under the category “multiracial” for analysis.

Medical history will be assessed at Visit 1 and categorized according to the current version of MedDRA (at the time of reporting).

The physical examination will be assessed prior to vaccination at Visit 1 and each body system examined will be recorded in the CRF as normal, abnormal, or not done.

3.5. Safety Endpoints

3.5.1. Adverse Events

The relationship between (S)AEs and the investigational products will be characterized as related or not related as determined by investigators and as described in the protocol. The severity of AEs will be characterized as mild, moderate, and severe.

The time period for actively eliciting and collecting (S)AEs and NDCMCs for each participant is outlined in Table 5.

Table 5. Summary of Adverse Event Collection

Visit Window (Days)	Visits 1-2	Visit 3-4
	Day 1 Through 28 to 42 Days After Visit 1	270 to 300 Days After Visit 1 Through 28 to 42 Days After Visit 3
Nonserious AEs	ICD through and including Visit 2 (1 month after Dose 1)	From Visit 3 through and including Visit 4 (1 month after Dose 2)
SAEs	ICD through the end of study	
NDCMCs	ICD through the end of study	
Immediate AEs	Within the first 30 minutes of each dose	

Abbreviations: ICD = informed consent document; NDCMC = newly diagnosed chronic medical condition.

An NDCMC is defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects.

The time period for actively eliciting and collecting AEs ("active collection period") for each participant/parent(s)/legal guardian begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 2, and from Visit 3 through including Visit 4. SAEs and NDCMCs will be categorized according to MedDRA terms. NDCMCs and SAEs will be collected from the signing of the ICD through the end of the study. For participants who are screen failures, the active collection period ends when screen failure status is determined.

Medical occurrences that begin before consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

All events collected on the CRF will be categorized according to the current version of MedDRA (at the time of reporting).

3.5.1.1. Analysis Intervals

There will be 6 analysis intervals for the AE data collected via the CRF (Table 6). The analysis populations used for these intervals are described in detail in Section 4.

Table 6. Analysis Intervals for AEs, SAEs, and NDCMCs

#	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)	Safety Data
1	Within 30 days after Dose 1	Dose 1 safety	Vax 1 date	Vax 1 date + 30 days	AEs, SAEs, NDCMCs
2	Within 30 days after Dose 2	Dose 2 safety	Vax 2 date	Vax 2 date + 30 days	AEs, SAEs, NDCMCs
3	Within 30 days after any dose	Safety	Vax 1 date or Vax 2 date	Vax 1 date + 30 days or Vax 2 date + 30 days	AEs, SAEs, NDCMCs
4	From 1 month after Dose 1 through 9 months after Dose 1	Dose 1 safety	Visit 2 date	Visit 3 date	SAEs, NDCMCs
5	From Dose 1 through 9 months after Dose 1	Dose 1 safety	Vax 1 date	Visit 3 date	SAEs, NDCMCs
6	Throughout study	Safety	Vax 1 date	Visit 4 date	SAEs, NDCMCs

Abbreviations: NDCMC – newly diagnosed chronic medical condition.

Two analysis intervals will be applied to immediate AEs (Table 7).

Table 7. Analysis Intervals for Immediate AEs

#	Analysis Interval	Analysis Population	Interval Start Date/Time (Inclusive)	Interval Stop Date/Time (Inclusive)
1	Dose 1	Dose 1 safety	Vax 1 time	Vax 1 time + 30 minutes
2	Dose 2	Dose 2 safety	Vax 2 time	Vax 2 time + 30 minutes

3.5.2. Reactogenicity Data

Reactogenicity data are solicited AEs. The reactogenicity data collected from the study e-diary will include: local reactions (redness, swelling, and pain at the injection site), systemic events (fever, decreased appetite, drowsiness, and irritability), and use of antipyretic medication.

The e-diary will record reactogenicity data from Day 1 to Day 7 following investigational product administration (Day 1 is the day of vaccination). Local reactions at the site of

investigational product administration will be recorded (sites will be asked to administer Nimenrix into the left thigh of participants).

Three analysis intervals will be applied to reactogenicity data (Table 8).

Table 8. Analysis Interval for Reactogenicity Data

#	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)
1	Dose 1	Dose 1 safety	Vax 1 date	Vax 1 date + 6 days (or until resolved day)
2	Dose 2	Dose 2 safety	Vax 2 date	Vax 2 date + 6 days (or until resolved day)
3	Any dose	Safety	Vax 1 or Vax 2 date	Vax 1 or Vax 2 date + 6 days (or until resolved day)

3.5.2.1. Local Reactions Endpoints

For each local reaction, the derivation of whether or not the specific reaction occurred on each day and "any day (Days 1 through 7, where Day 1 is the day of vaccination)" will be made. The variable will be calculated for each vaccination as well as overall reactions for any vaccination. The derivation of this variable is given in Table 9**.**

Table 9. Derived Variables for Local Reactions

Variable	Yes (1)[a]	No (0)	Missing (.)
Each day (Days 1-7)	Participant/parent/legal guardian reports the reaction as "mild," "moderate," or "severe" on each individual day.	Participant/parent/legal guardian reports the reaction as "none" on the individual day.	Participant did not report on the reaction on the individual day.
Any day (Days 1-7)	Participant/parent/legal guardian reports the reaction as "mild," "moderate," or "severe" on any day (Days 1-7).	Participant/parent legal guardian reports the reaction as "none" on all 7 days or as a combination of "none" and missing on all 7 days.	Participant did not report on the reaction on any of the 7 days.

a. For redness and swelling, "mild," "moderate, and "severe" categories are based on the caliper size reported from the e-diary and defined in Table 10.

A caliper (measuring device) is used to measure the redness or swelling of the injection site area. Caliper units (range: 1-14+) are converted to centimeters according to 1 caliper unit = 0.5 centimeters and then categorized as none, mild, moderate, or severe based on the grading scale of local reactions in Table 10. Pain at the injection site will be assessed by the participant's parent(s)/legal guardian(s) according to the grading scale in Table 10.

Only an investigator is able to classify a participant's local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

Table 10. Local Reaction Grading Scale

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Grade 4[b]
Pain at injection site (tenderness)	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe pain (tenderness) at injection site
Redness	1 to 4 measuring device units = >0 to 2.0 cm	5 to 14 measuring device units = >2.0 to 7.0 cm	>14 measuring device units = >7.0 cm	Necrosis or exfoliative dermatitis
Swelling	1 to 4 measuring device units = >0 to 2.0 cm	5 to 14 measuring device units = >2.0 to 7.0 cm	>14 measuring device units = >7.0 cm	Necrosis

Abbreviations: CRF = case report form; e-diary = electronic diary.
Note: If the size of the redness and/or swelling falls between 2 measuring device units, the higher measuring device unit number will be recorded in the e-diary.

a. Parent(s)/legal guardian(s) of the participants experiencing local reactions >14 measuring device units (>7.0 cm) are to be contacted by the study site. An unscheduled visit may be required.
b. A Grade 4 assessment should be made by the investigator. A Grade 4 reaction will not be collected in the e-diary but will be recorded as an AE on the CRF. The severity of the local reaction should be graded using the AE grading scale.

The maximum severity (highest grading) of each local reaction within 7 days after vaccination will be derived for each vaccination as well as any vaccination. The maximum severity will be derived as follows:

- = ., if values are missing for all days (Days 1 to 7);
- = 0, if the participant's parent(s)/legal guardian(s) reports all reactions as "none" or a combination of "missing" and "none" for all days (Days 1 to 7);
- = *highest grade* (maximum severity) within 7 days after vaccination, if the answer is not "none" for at least 1 day.

For participants experiencing any local reactions (or those with derived reaction presence in Table 9), the maximum duration (last day of reaction – first day of reaction + 1) will be derived for the study vaccination. Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the participant

diary-recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing.

For reactions that continue into the next vaccination visit, the duration will be calculated in a segmented fashion. The reaction end date will be set to the day prior to the next vaccination and will have a new start date as the day of next vaccination. The duration will be calculated separately from the new start date to the date of resolution. Participants with reactions spanning multiple vaccination visits will be included in a footnote.

Participants with no reported reaction have no duration.

The onset day of each local reaction will be derived. The onset day is defined as the first day of reporting the reaction with any severity after vaccination.

In summary, the following variables will be derived for local reactions:

1. Each local reaction on each day (Days 1 to 7) after each vaccination.
2. Each local reaction on any day (Days 1 to 7) after each vaccination and any vaccination.
3. Any local reaction on any day (Days 1 to 7) after each vaccination and after any vaccination.
4. Maximum severity of each local reaction on any day (Days 1 to 7) after each vaccination and any vaccination.
5. Maximum duration of each local reaction after each vaccination.

3.5.2.2. Systemic Events Endpoints

For the first 7 days following each study vaccination (Days 1 through 7, where Day 1 is the day of vaccination), the participant's parent(s)/legal guardian(s) will be asked to assess the severity of each event according to Table 11.

Only an investigator is able to classify a participant's systemic event as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant's parent(s)/legal guardian(s). Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

Table 11. Systemic Event Grading Scale

Systemic Event	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Grade 4[a]
Decreased appetite (loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to feed	Emergency room visit or hospitalization for severe decreased appetite (loss of appetite)
Drowsiness (increased sleep)	Increased or prolonged sleeping bouts	Slightly subdued interfering with daily activity	Disabling not interested in usual daily activity	Emergency room visit or hospitalization for severe drowsiness (increased sleep)
Irritability (fussiness) (synonymous with restless sleep; decreased sleep)	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted	Emergency room visit or hospitalization for severe irritability (fussiness)

Abbreviations: CRF = case report form; e-diary = electronic diary.

a. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF. The severity of the systemic event should be graded using the AE severity grading scale.

Temperature will be collected in the e-diary, daily, for 7 days after each vaccination (Days 1 through 7, where Day 1 is the day of vaccination) and at any time during the 7 days when fever is suspected. The highest temperature for each day will be recorded in the e-diary. The protocol defines fever as a temperature ≥38.0°C. Fever will be scaled as shown in Table 12.

Table 12. Severity Scale for Fever

Temperature 38.0-38.4°C
Temperature >38.4-38.9°C
Temperature >38.9-40.0°C
Temperature >40.0°C

Note: Fever is defined as temperature ≥38.0°C.

For each systemic event, the following variables will be available, similar to local reactions:

1. Each systemic event on each day (Days 1 to 7) after each vaccination.
2. Each systemic event on any day (Days 1 to 7) after each vaccination and any vaccination.
3. Any systemic event on any day (Days 1 to 7) after each vaccination and after any vaccination.

4. Maximum severity of each systemic event on any day (Days 1 to 7) after each vaccination and any vaccination.

5. Maximum duration of each systemic event after each vaccination.

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 3.5.2.1).

3.5.2.3. Use of Antipyretic Medication

The use of antipyretic medication (Yes/No) will be recorded in the e-diary for 7 days (Day 1 to Day 7) after each vaccination.

The following variables will be derived:

1. Use of antipyretic medication on each day (Days 1 to 7) after each vaccination.

2. Use of antipyretic medication on any day (Days 1 to 7) after each vaccination and any vaccination.

3. Maximum duration of use of antipyretic medication after each vaccination.

3.5.3. Laboratory Data

Laboratory assessments will not be collected for this study.

3.5.4. Medical Device Errors

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used. If a medical device error involves an AE, it will be summarized according to AE reporting conventions.

3.6. Study Conduct

3.6.1. E-Diary Completion

For any given day, an e-diary will be transmitted and considered complete if all expected data (the 3 local reactions, the 5 systemic events including fever, and the use of antipyretic medications) are available. If all data are missing for all items on the e-diary, for all days following vaccination, the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all days are available (ie, not missing) and data are valid. Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

The following e-diary compliance variables will be provided for each vaccination:

- Compliance per day: the numerator is the number of participants who completed (transmitted) the e-diary on a given day (Day 1 to Day 7) and the denominator is the total number of participants who received the vaccination.

- At least X days: the numerator is the number of participants who completed (transmitted) the e-diary on X days and the denominator is the total number of participants who received a vaccination (X = 1 through 7; compliance will be computed for each value of X).

- All 7 days: the numerator is the number of participants who completed (transmitted) the e-diary on all 7 days and the denominator is the total number of participants who received a vaccination.

3.6.2. Nonstudy Vaccines and Concomitant Medications

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD up to Visit 4 will be recorded on the CRF.

Permitted during the study include:

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed. However, while prioritizing standard clinical care, efforts should be made not to administer nonstudy vaccines within 14 days (for nonlive vaccines) or 28 days (for live vaccines) as specified below.

- Nonstudy vaccines (other than any meningococcal vaccine groups A, C, W, or Y) that are part of recommended immunization schedules are allowed any time during the study but should not be administered within 14 days (for nonlive vaccines) and 28 days (for live vaccines) of investigational product administration. Tetanus-containing vaccines are allowed any time during the study (and can be given at the same time as the investigational product) but should not be administered within 30 days before investigational product administration.

- Antipyretics and other pain medication used to treat symptoms associated with investigational product administration are permitted.

- A local anesthetic may be used at the site of the blood draw.

- Topical antibiotics are permitted.

- Topical and inhaled corticosteroids are permitted.

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD up to Visit 4 (approximately 1 month after Dose 2) will be recorded in the CRF.

The name, start and stop dates, and route of administration for concomitant medications (prescription and nonprescription) used to treat NDCMCs and SAEs (excluding events recorded only in the e-diary) from the signing of the ICD through Visit 4 will be recorded in the CRF.

Treatments will be categorized according to the current version of the WHO Drug Dictionary (at the time of reporting).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database. Classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants, or participant's parent(s)/legal guardian(s), who sign the ICD.
Evaluable	Defined according to post–Dose 1 evaluable and post–Dose 2 evaluable criteria.
mITT	Defined according to post–Dose 1 and post–Dose 2 criteria.
Safety	All enrolled participants who receive at least 1 dose of the investigational product and have safety data reported after vaccination.

Defined Population for Analysis	Description
Post–Dose 1 evaluable immunogenicity population	1. Were enrolled and eligible through Visit 2. 2. Received the investigational product at Visit 1. 3. Had blood drawn for assay testing within the required time frames at Month 0 (Visit 1; before Dose 1) and Month 1 (Visit 2; 1 month after the Dose 1: window 28-42 days). 4. Had at least 1 valid and determinate MenA, MenC, MenW- 135, and MenY assay result at Visit 2 (1 month after Dose 1). 5. Had received no prohibited vaccines or medications through Visit 2. 6. Had no major protocol deviations through Visit 2.
Post–Dose 2 evaluable immunogenicity population	1. Were enrolled and eligible through 1 month after Dose 2 of Nimenrix. 2. Received the investigational products at Visit 1 and Visit 3. 3. Had blood drawn for assay testing within the required time frames at Month 0 (Visit 1; before Dose 1) and at 1 month after Dose 2 (Visit 4; 1 month after Dose 2: window 28-42 days). 4. Had at least 1 valid and determinate MenA, MenC, MenW-135, and MenY assay result at Visit 4 (1 month after Dose 2). 5. Had received no prohibited vaccines or medications through Visit 4. 6. Had no major protocol deviations through Visit 4.
Post–Dose 1 mITT	All participants who received at least 1 dose of Nimenrix and had at least 1 valid and determinate MenA, MenC, MenW-135, and MenY assay result available at Visit 2.
Post–Dose 2 mITT	All participants who received 2 doses of Nimenrix and had at least 1 valid and determinate MenA, MenC, MenW-135, and MenY assay result available at Visit 4.

Defined Population for Analysis	Description
Dose 1 safety population	This population will include participants who received the first dose of investigational product at Visit 1 and for whom safety information is available from Visit 1 to prior to Visit 3.
Dose 2 safety population	This population will include participants who received the first and second dose of investigational product at Visit 1 and Visit 3 and for whom safety information is available from Visit 3.

For determination of the evaluable immunogenicity population(s), Items 1 through 4 will be computerized checks of the data, while Items 5 and 6 will be determined by clinical review. A major protocol violation is a protocol violation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity (eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine). The sponsor's global medical monitor will identify those participants with a protocol violation prior to the immunogenicity analysis performed for the study.

4.1. Vaccine/Stratum Misallocation

- Vaccinated but no randomization number assigned: These participants will be included in the safety population for safety analysis, but will be excluded from immunogenicity analyses.

- Enrolled with randomized number assigned but not vaccinated: These participants will be excluded from any safety analyses. They may be included in the mITT population if any assay results are available and will be reported under their randomized group for immunogenicity analyses.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No specific hypotheses will be tested in this study.

5.2. General Methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the proportion (%) and the n (the numerator) and N (the denominator) used in the calculation of the proportion.

5.2.1. Analyses for Binary Endpoints

The number and percentage of participants in each category will be summarized. The exact 2-sided 95% CIs for percentages, and for difference in percentages, will also be presented, where appropriate. The exact 2-sided 95% CIs for the proportion will be constructed by the Clopper-Pearson method described by Agresti.[1] The exact 2-sided 95% CIs will be presented in terms of percentages.

5.2.1.1. Immunogenicity Data

Each MenACWY serogroup has a qualified LLOQ value defined in Table 13.

Table 13. Qualified rSBA and hSBA LLOQ for MenACWY Serogroups

Serogroup	LLOQ
MenA	1:4
MenC	1:4
MenW-135	1:4
MenY	1:4

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenACWY = *Neisseria meningitidis* group A, C, W, and Y; rSBA = serum bactericidal assay using rabbit complement.

The SAP may be updated when the validated LLOQs for the MenA, MenC, MenW-135, and MenY serogroups are available.

5.2.1.2. Safety Data

All safety endpoints (including reactogenicity data recorded from the e-diary and AE data recorded from the CRF) will be summarized with percentages and exact 2-sided 95% CIs (Clopper-Pearson method).

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Geometric Mean Titers

GMTs will be computed for each rSBA and hSBA titer MenA, MenC, MenW-135, and MenY serogroups. If the rSBA and hSBA result is below LLOQ, it will be set to 0.5 × LLOQ for the GMT calculation. The assay results at each blood sampling time point will be (natural-log) logarithmically transformed for analysis. GMTs are obtained by calculating log transformations of indicated values, averaging the log values, then exponentiating the result. The associated exact 2-sided 95% CIs are obtained by exponentiating the limits of CIs for the mean logarithm of the rSBA (or hSBA) titers (based on the Student t distribution).

5.2.2.2. Reverse Cumulative Distribution Curves

RCDCs for MenA, MenC, MenW-135, and MenY serogroups for available time points may be generated.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms on handling missing AE start dates will be applied according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

5.3.1.1. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 7-day e-diary data is available, the "any day (Days 1 to 7)" data will be considered nonmissing. Participants are excluded from the analysis if they do not receive the particular dose or the safety data are missing on all days within the interval.

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are nonmissing. The e-diary transmission and completion status will be summarized per Section 6.5.4. The e-diary completion summary will provide the missing data information on the reactogenicity data.

Based on data from available studies, the missing data on reactogenicity are minimal, which is consistent with Li et al (2011).[2] No sensitivity analysis is planned for reactogenicity data.

5.3.2. Immunogenicity Data

As assay data are expected to be missing completely at random, the primary analysis for the primary objectives will be based upon the observed, determinate observations. No imputation will be performed. The proportion of participants with missing immunogenicity data may be summarized at each blood sampling visit for the MenA, MenC, MenW-135, and MenY serogroups. The denominator will be the as-randomized population. The category of missing reasons (QNS, indeterminate, not done, dropout) may also be summarized.

If there is less than a 10% difference in the total number of participants included between the mITT and evaluable populations, only the evaluable population will be used in the analysis of immunogenicity results. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis. For the rSBA and hSBA assay results, the following values will be set to missing: QNS (insufficient sera), indeterminate results, and not done. Participants without blood draw (ie, dropout) will also have missing data for immunogenicity.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions Within 7 Days After Dose 2

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Intercurrent events and missing data: Missing e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analysis.

- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of each local reaction on any day (Days 1 to 7) after vaccination.
  - Presence or absence of any local reaction on any day (Days 1 to 7) after vaccination.
  - Maximum severity of each local reaction on any day (Days 1 to 7) after vaccination.

6.1.1.2. Systemic Events Within 7 Days After Dose 2

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of each systemic event on any day (Days 1 to 7) after vaccination.
  - Presence or absence of any systemic event on any day (Days 1 to 7) after vaccination.
  - Maximum severity of each systemic event on any day (Days 1 to 7) after vaccination.

6.1.1.3. Use of Antipyretic Medications Within 7 Days After Dose 2

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing e-diary data will not be imputed.
- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Use of antipyretic medication on any day (Days 1 to 7) after vaccination.

6.1.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Intercurrent events and missing data: Missing AE dates will be handled according to the Pfizer safety rules.

- For the group, the numbers and percentage of participants with SAEs and NDCMCs for the analysis interval of within 30 days after Dose 2, defined in Table 6, will be summarized. The (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.1.1.5. Adverse Events

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs will be provided for all events.

- Intercurrent events and missing data: Missing AE dates will be handled according to the Pfizer safety rules.

- For the group, the numbers of participants with AEs for the analysis interval of within 30 days after Dose 2, defined in Table 6, will be summarized. The (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.1.1.6. Immediate Adverse Events

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Intercurrent events and missing data: Missing AE dates will be handled according to the Pfizer safety rules.

- The number and percentage of participants reporting AEs occurring within the 30-minute observation period immediately after vaccination will be summarized according to the analysis interval defined in Table 7. These summaries will include exact 2-sided Clopper-Pearson 95% CIs.

6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. rSBA Titer for Each of the MenA, MenC, MenW-135, and MenY Serogroups

6.1.2.1.1. Main Analysis

- Analysis set: Post–Dose 2 evaluable population.

- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.

- Intercurrent events and missing data: Missing serology results will not be imputed.

- The following analysis will be described:
  - The percentage of participants achieving a rSBA titer ≥1:8 for each of MenA, MenC, MenW-135, and MenY serogroups, at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2.
  - rSBA GMTs for each of the MenA, MenC, MenW-135, and MenY serogroups, at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2.

6.1.2.1.2. Sensitivity/Supplementary Analyses

The main analysis will also be performed on the mITT population if there is a difference of more than 10% between the evaluable immunogenicity and corresponding mITT populations.

6.2. Secondary Endpoints

6.2.1. Secondary Safety Endpoints

6.2.1.1. Local Reactions Within 7 Days After Dose 1

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of each local reaction on any day (Days 1 to 7) after vaccination.
  - Presence or absence of any local reaction on any day (Days 1 to 7) after vaccination.
  - Maximum severity of each local reaction on any day (Days 1 to 7) after vaccination.

6.2.1.2. Systemic Events Within 7 Days After Dose 1

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:

- Presence or absence of each systemic event on any day (Days 1 to 7) after vaccination.
- Presence or absence of any systemic event on any day (Days 1 to 7) after vaccination.
- Maximum severity of each systemic event on any day (Days 1 to 7) after vaccination.

6.2.1.3. Use of Antipyretic Medications Within 7 Days After Dose 1

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Use of antipyretic medication on any day (Days 1 to 7) after vaccination.

6.2.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing AE dates will be handled according to the Pfizer safety rules.
- For the group, the numbers and percentage of participants with SAEs and NDCMCs for the analysis interval of within 30 days after Dose 1, from 1 month after Dose 1 through 9 months after Dose 1, and from Dose 1 through 9 months after Dose 1 defined in Table 6 will be summarized. The (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.2.1.5. Adverse Events

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs will be provided for all events.
- Intercurrent events and missing data: Missing AE dates will be handled according to the Pfizer safety rules.

- For the group, the numbers of participants with AEs for the analysis interval of within 30 days after Dose 1, defined in Table 6, will be summarized. The (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.2.1.6. Immediate Adverse Events

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing AE dates will be handled according to the Pfizer safety rules.
- The number and percentage of participants reporting AEs occurring within the 30-minute observation period immediately after vaccination will be summarized according to the analysis interval defined in Table 7. These summaries will include Clopper-Pearson 95% CIs.

6.2.2. Secondary Immunogenicity Endpoints

6.2.2.1. rSBA Titer for Each of MenA, MenC, MenW-135, and MenY Serogroups

6.2.2.1.1. Main Analysis for Post–Dose 1

In participants who have received the first dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants):

- Analysis set: Post–Dose 1 evaluable population.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing serology results will not be imputed.
- For participants who have received the first dose, the following analysis will be described:
  - The percentage of participants achieving an rSBA titer ≥1:8 or ≥1:128 for each of the MenA, MenC, MenW-135, and MenY serogroups, at baseline and at 1 month after Dose 1.
  - rSBA GMTs for each of the MenA, MenC, MenW-135, and MenY serogroups, at baseline and at 1 month after Dose 1.

6.2.2.1.2. Sensitivity/Supplementary Analysis for Post–Dose 1

The main analysis will also be performed on the mITT population if there is a difference of more than 10% between the evaluable immunogenicity and corresponding mITT populations.

6.2.2.1.3. Main Analysis for Post–Dose 2

In participants who have received the first and second dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants):

- Analysis set: Post–Dose 2 evaluable population.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing serology results will not be imputed.
- For participants who have received the first and second dose, the following analysis will be described:
    - The percentage of participants achieving an rSBA titer ≥1:128 for each the MenA, MenC, MenW-135, and MenY serogroups, at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2.

6.2.2.1.4. Sensitivity/Supplementary Analysis for Post–Dose 2

The main analysis will also be performed on the mITT population if there is a difference of more than 10% between the evaluable immunogenicity and corresponding mITT populations.

6.2.2.2. hSBA Titer for Each of the MenA, MenC, MenW-135, and MenY Serogroups

6.2.2.2.1. Main Analysis Post–Dose 1

In participants who have received the first dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants):

- Analysis set: Post–Dose 1 evaluable populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing serology results will not be imputed.
- For participants who have received the first dose, the following analysis will be described:
    - The percentage of participants achieving an hSBA titer ≥1:4 or ≥1:8 for each of the MenA, MenC, MenW-135, and MenY serogroups, at baseline and at 1 month after Dose 1.
    - hSBA GMTs for each of the of the MenA, MenC, MenW-135, and MenY serogroups, at baseline and at 1 month after Dose 1.

6.2.2.2.2. Sensitivity/Supplementary Analysis for Post–Dose 1

The main analysis will also be performed on the mITT population if there is a difference of more than 10% between the evaluable immunogenicity and corresponding mITT populations.

6.2.2.2.3. Main Analysis Post–Dose 2

In participants who have received the first and second dose of Nimenrix and who are in compliance with the key protocol criteria (evaluable participants):

- Analysis set: Post–Dose 2 evaluable populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing serology results will not be imputed.
- For participants who have received the first dose, the following analysis will be described:
  - The percentage of participants achieving an hSBA titer ≥1:4 or ≥1:8 for each of the MenA, MenC, MenW-135, and MenY serogroups, at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2.
  - hSBA GMTs for each of the of the MenA, MenC, MenW-135, and MenY serogroups, at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2.

6.2.2.2.4. Sensitivity/Supplementary Analysis for Post–Dose 2

The main analysis will also be performed on the mITT population if there is a difference of more than 10% between the evaluable immunogenicity and corresponding mITT populations.

6.3. Other Endpoints

6.3.1. Exploratory Safety Endpoints

6.3.1.1. Local Reaction Within 7 Days After Any Dose

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:

- Presence or absence of any local reaction on any day (Days 1 to 7) after any vaccination.
- Maximum severity of each local reaction on any day (Days 1 to 7) after any vaccination.

6.3.1.2. Systemic Events Within 7 Days After Any Dose

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of any systemic event on any day (Days 1 to 7) after any vaccination.
  - Maximum severity of each systemic event on any day (Days 1 to 7) after any vaccination.

6.3.1.3. Use of Antipyretic Medications Within 7 Days After Any Dose

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing e-diary data will not be imputed. Confirmed e-diary errors will be excluded from the analysis.
- For the group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Use of antipyretic medication on any day (Days 1 to 7) after any vaccination.

6.3.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing AE dates will be handled according to the Pfizer safety rules.

- For the group, the numbers and percentage of participants with SAEs and NDCMCs for the analysis interval of within 30 days after any vaccination and throughout the study defined in Table 6 will be summarized. The (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.3.1.5. Adverse Event

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics including associated Clopper-Pearson 95% CIs.
- Intercurrent events and missing data: Missing AE dates will be handled according to the Pfizer safety rules.
- For the group, the numbers of participants with AEs for the analysis interval of within 30 days after any dose and throughout the study defined in Table 6 will be summarized. The (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.4. Subset Analyses

Subgroup analyses may be performed on the important primary and secondary immunogenicity and safety endpoints described in Section 6.1 and Section 6.2. No subgroup analysis is planned for rare events (endpoints with less than 1% of participants in any group). Subgroups include sex, race, and geographic location.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct and Participant Disposition

All participants in the population will be included in the disposition summaries.

Disposition summaries include:

- N and % of participants included in each study population (mITT, post-Dose 1 evaluable immunogenicity, and post–Dose 2 evaluable immunogenicity).
- N and % of participants receiving each vaccination.
- N and % of participants completing all the vaccination visits (Dose 1 and Dose 2) and follow-up visits (1 month after Dose 1 and 1 month after Dose 2).
- N and % of participants who withdrew during the study (Visits 1 to 4) and the reason for withdrawal.

For each blood draw, the number and percentage of participants, vaccinated at each visit (Visits 1 and 3), and providing blood samples within the protocol-specified time frame, as well as before and after the specified time frame.

Participant data listings for participants who are included and excluded from each of the analysis populations and reason for exclusion may be provided. A listing of protocol deviations may also be provided.

6.5.2. Vaccine Exposure

Study vaccination data, temporary delays and reasons for vaccination delays, and noncompliant vaccine administration and reasons for noncompliance may be listed by vaccine group as administered. Participants not receiving vaccination may be listed.

6.5.3. Demographic, Medical History, and Baseline Characteristics

The safety and evaluable populations will be used to generate these tables. All summaries will be presented for the total population.

Variables defined in Section 3.4.1 will be reported according to Pfizer standard summary reporting.

Medical history and baseline physical examination will be summarized descriptively.

6.5.4. E-Diary Completion

E-diary compliance as defined in Section 3.6.1 will be summarized for each dose (Dose 1 and Dose 2) using descriptive statistics. The safety population will be used to generate the summary reports. The denominator for the e-diary compliance rates will be the total number of participants who received the specific vaccination.

6.5.5. Concomitant Medications and Nondrug Treatments

Nonstudy vaccines and concomitant medications will be categorized according to the WHO Drug Dictionary and will be descriptively summarized for participants in the safety population.

Antipyretic and other pain medication reported the day prior to vaccine administration will be summarized separately from the concomitant medications and for each vaccination separately.

6.6. Safety Summaries and Analyses

All safety data will be summarized according to the vaccine received. The safety population will be used for the analysis.

6.6.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered an exploratory analysis and its purpose is to generate hypotheses for further investigation.

6.6.1.1. Related Events

AEs and SAEs deemed by the investigator to be related to an investigational product will be summarized separately. The denominator for the percentages will be the safety population.

The number and percentage of participants reporting at least 1 related (S)AE and the total number of related events may be summarized by SOC and PT. Associated 95% exact CIs will also be displayed.

6.6.1.2. Severe Events

AEs deemed severe by the investigator may be summarized separately. The denominator for the percentages will be the safety population. The number and percentage of participants reporting at least 1 severe AE and the total number of severe AEs will be reported and will be summarized by SOC and PT. Associated 95% exact CIs will also be displayed.

6.6.1.3. AEs Leading to Study Withdrawal

Any AEs leading to withdrawal from the study may be included in a participant data listing.

6.6.1.4. Death

Any death data will be included in a participant data listing.

6.6.2. Reactogenicity Data

Local reactions and systemic events will be summarized according to Section 6.1.1, Section 6.2.1, and Section 6.3.1.

6.6.3. Physical Examination

Descriptive summaries (counts and percentages) and listings based on the safety population may be provided.

7. INTERIM ANALYSES

7.1. Introduction

No interim analysis is planned for the study. Only 1 analysis will be performed at the completion of the study.

This study will not use a DMC.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1. Agresti A. Exact small-sample inference. In: Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc; 2002:18-20.

2. Li X, Wang WWB, Liu GF, et al. Handling missing data in vaccine clinical trials for immunogenicity and safety evaluation. J Biopharm Stat. 2011;21(2):294-310.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
ACWY	meningococcal group A, C, W, and Y
AE	adverse event
CI	confidence interval
CRF	case report form
e-diary	electronic diary
DMC	data monitoring committee
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
ID	identification
LLOQ	lower limit of quantitation
LOD	limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* group A
MenACWY	*Neisseria meningitidis* group A, C, W, and Y
MenC	*Neisseria meningitidis* group C
MenW	*Neisseria meningitidis* group W
MenY	*Neisseria meningitidis* group Y
mITT	modified intent-to-treat
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
PT	preferred term
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
rSBA	serum bactericidal assay using rabbit complement
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	system organ class
US	United States
WHO	World Health Organization