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

Study Intervention Number:	PF-06866681
Study Intervention Name:	Nimenrix® (Meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine)
US IND Number:	N/A
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Phase:	3b

Short Title: A Phase 3b Open-Label Study of 2 Doses of Nimenrix in Infants

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	23 October 2020	N/A

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale

The purpose of this study is to evaluate the safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a booster dose at 12 months of age. Current posology allows for 2 doses of Nimenrix before 6 months of age, where the first dose is administered from 6 weeks onwards with a second dose at least 2 months later, with a booster at 12 months; and in infants from 6 months of age, a single dose at 6 months, with a booster dose at 12 months. This study will provide valuable immunogenicity and safety data for a single dose in healthy infants <6 months of age, followed by the booster at 12 months.

Objectives, Estimands, and Endpoints

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 *Neisseria 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	• rSBA titers for each of the MenA, MenC, MenW-135, and MenY serogroups.

Objectives	Estimands	Endpoints
	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.	
Secondary:	**Secondary:**	**Secondary:**

• 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.

• 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. • Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4, ≥1:8 for each	• 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.

Objectives	Estimands	Endpoints
	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.
CCI [redacted]		

Overall Design

This Phase 3b, multicenter, open-label study, with a single-arm design, will be conducted at investigator sites in Europe.

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).

Number of Participants

Approximately 150 participants will be enrolled into a single open-label vaccine group (receiving Nimenrix).

Intervention Groups and Duration

Each participant will participate in the study for approximately 10 months. Based on an estimated 4-month enrollment, the study duration will be approximately 14 months. Participants will receive Nimenrix via intramuscular injection. Details of sample size determination can be found in Section 9.2.

Data Monitoring Committee

A DMC will not be used for this study.

Statistical Methods

This is not a hypothesis-testing study; an estimation approach will be used to assess the immunogenicity and safety objectives in this study. All immunogenicity data will be summarized descriptively. For all binary endpoints (including primary endpoints), counts, percentages, and 2-sided 95% CIs using the Clopper-Pearson method will be calculated. For titer results, geometric means and 2-sided 95% CIs based on the t distribution will be computed.

The primary immunogenicity objectives will be evaluated by descriptive summary statistics

for the percentages of participants achieving rSBA titers ≥1:8 both at 1 month after the second dose of Nimenrix. Similarly GMTs will be summarized descriptively. In addition, hSBA titer results (both percentages and GMTs) will be summarized similarly to that of the rSBAs. Additionally, immune responses following 1 dose of Nimenrix will be summarized descriptively.

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs, including SAEs and NDCMCs.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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.

The investigator may schedule visits (unplanned visits), in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

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] (~5 mL)	X (~5 mL)	X[b] (~5 mL)	X (~5 mL)
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

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 AEs	X----------X		X----------X	
Record and report SAEs and NDCMCs[f]	X----------X		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.

2. INTRODUCTION

Nimenrix has been approved for:

- The prevention of invasive infections with *N meningitidis* serogroups A, C, W-135, and Y, using TT as the carrier.

2.1. Study Rationale

The purpose of this study is to evaluate the safety and immunogenicity of a single dose of Nimenrix in infants at 3 months of age, followed by a second dose at 12 months of age. Current posology allows for 2 doses of Nimenrix before 6 months of age, where the first dose is administered from 6 weeks onwards with a second dose at least 2 months later, with a booster at 12 months; and in infants from 6 months of age, a single dose at 6 months, with a booster dose at 12 months. This study will provide valuable immunogenicity and safety data for a single dose in healthy infants <6 months of age, followed by the booster at 12 months.

2.2. Background

2.2.1. Disease Overview

Invasive meningococcal disease, including meningitis and septicemia, often follows invasive infection by *Neisseria meningitidis* (*N meningitidis*; meningococcus) and is a major cause of death and morbidity throughout the world. The devastating disease caused by this bacteria is characterized by rapidly progressive sepsis, which can be fatal within a few hours of onset leaving antibiotic treatment ineffective. Severe permanent sequelae (eg, limb necrosis requiring amputation, hearing loss, chronic renal failure, and neurological damage) can result after infection and the mortality rate is 10% to 15%, even with appropriate therapy.[1] Morbidity and mortality rates are generally highest in infants and children less than 5 years of age and adolescents.[2] Meningococcal disease continues to be endemic in both industrialized (eg, Europe and the US) and developing countries. Epidemics occur worldwide, with the highest attack rates prevailing in the sub-Saharan countries.[1]

N meningitidis is a strictly human pathogen and is capable of generating epidemics and outbreaks of meningitis.[1,3] Asymptomatic nasopharyngeal colonization by meningococci is relatively common, though only a small percentage of those colonized develop invasive disease. Carriage prevalence varies with age, being lowest in young children and highest in adolescents and young adults.[4] Transmission occurs via droplets of respiratory secretions spread during close contact. Crowded conditions, therefore, considerably facilitate transmission and increase carriage.[5]

Twelve meningococcal serogroups are currently recognized based on capsular polysaccharide gene analysis.[6] Serogroups A, B, C, W, Y, and, more recently, X are the most common causes of invasive meningococcal disease worldwide. Serogroup A is considered an important cause of disease in Asia, and prior to the introduction of MenAfriVac in 2010, it caused regular epidemics in sub-Saharan countries. In Europe and Latin America, serogroup B is the most prevalent serogroup, followed by serogroups W and

C to account for the large majority of cases.[2,3,7] However, both disease incidence and serogroup distribution vary geographically and temporally.[3]

A major advance in meningococcal disease prevention has been the development of meningococcal conjugate vaccines. In addition to monovalent serogroup C conjugate vaccines, quadrivalent conjugate vaccines against serogroups A, C, W-135, and Y are available, and recently serogroup B vaccines have been licensed in Europe and the US. Many countries are still using monovalent serogroup C conjugate vaccines in their vaccination schedules. Although some countries are starting to include quadrivalent meningococcal vaccine recommendations, the vast majority of countries have not adopted a routine program for infants in the first year of life with meningococcal polysaccharide groups A, C, W, and Y conjugate vaccine (MenACWY).

2.3. Benefit/Risk Assessment

Pfizer has developed a quadrivalent conjugate vaccine (MenACWY-TT) for the prevention of invasive infections with *N meningitidis* serogroups A, C, W-135, and Y using TT as the carrier. This vaccine has been shown to be immunogenic and well tolerated in individuals from 6 weeks of age.[8,9,10] This MenACWY-TT conjugate vaccine (Nimenrix) has been licensed for use in the EU since April 2012 for individuals 12 months of age and above and was licensed in December 2016 for use in a lowered age of indication to 6 weeks of age.[8,11] Nimenrix is approved for use in over 80 countries.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Nimenrix may be found in the SmPC, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) – Nimenrix		
The common risks associated with Nimenrix in infants categorized as very common or common adverse reactions include appetite loss, irritability, drowsiness, fever, swelling at injection site, tenderness at injection site, redness at injection site, diarrhea, vomiting, and rash; uncommon adverse reactions include crying, nausea, injection site hematoma, injection site induration, injection site pruritus, injection site warmth, and injection site anesthesia; and adverse reactions categorized with unknown frequency include extensive limb swelling at the injection site, frequently associated with erythema and sometimes involving the adjacent joint or swelling of the entire limb.	The risks are based on the known safety profile of Nimenrix in infants as presented in the Nimenrix SmPC.	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Individuals with significant reactions after vaccination or AEs considered by the investigator to present increased risk to the participant if rechallenged or who develop exclusionary conditions during the conduct of the study will be excluded from interventions but may be followed for safety.
Study Procedures – Venipuncture		
There is a risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Venipuncture is required to collect immunogenicity data from participants.	Only qualified nurses, physicians, nurse practitioners, physician's assistants, phlebotomists, or medical assistants certified or otherwise authorized to draw blood per the standards and procedures of the investigative site as allowed by institutional, local, and state guidance will be allowed to draw blood to minimize local complications. The volume and frequency of blood sample collection during the study has been minimized as much as possible.

2.3.2. Benefit Assessment

The potential benefits of participation in this study include potential protection against invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y, and W-135.

Other benefits to the individual participant may include physical examination by a medical provider at the start of the study, a thorough review of the participant's vaccination status, and evaluations and management of some illnesses (AEs) that occur during participation in the study as part of protocol-specified scheduled and unscheduled assessments.

2.3.3. Overall Benefit/Risk Conclusion

The anticipated benefit (protective immunity against invasive infections with *N meningitidis* serogroups A, C, Y, and W-135) that may be afforded to participants outweighs the potential risks in this study, including the possibility of transient local and systemic reactogenicity events of varying severity and possible complications from needlesticks (vaccination or venipuncture) for an overall favorable benefit/risk assessment.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

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.
Secondary:	**Secondary:**	**Secondary:**
• 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:	• Local reactions (redness, swelling, and pain at the injection site). • Systemic events (fever, decreased appetite, drowsiness, and irritability). • AEs. • SAEs.

Objectives	Estimands	Endpoints

	• 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.
		• NDCMCs.

• 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. • 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.	• 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.

Objectives	Estimands	Endpoints
• 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.
CCI [redacted]		

4. STUDY DESIGN

4.1. Overall 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).

4.2. Scientific Rationale for Study Design

Refer to Section 2.1.

4.3. Justification for Dose

Nimenrix is indicated for active immunization to prevent invasive disease caused by *N meningitidis* serogroups A, C, W-135, and Y and is approved for use in Europe, and in a number of ex-US countries, in individuals 6 weeks of age and older.

The safety, tolerability, and immunogenicity of Nimenrix are well established in individuals 6 weeks to 55 years of age.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all study visits.

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female infants born at >36 weeks of gestation and who are 3 months of age (≥76 to ≤104 days) at the time of consent (the day of birth is considered day of life 1).

Type of Participant and Disease Characteristics:

2. Participants whose parent(s)/legal guardian(s) is willing and able to comply with scheduled visits, treatment plan, and other study procedures.

3. Healthy infants determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study.

4. Participants who are available for the duration of the study and whose parent(s)/legal guardian(s) can be contacted by telephone during study participation.

Informed Consent:

5. Participants whose parent(s)/legal guardian(s) is capable of giving signed informed consent, as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. A previous anaphylactic reaction to any vaccine or vaccine-related component.

2. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection.

3. History of microbiologically proven disease caused by *N meningitidis* or *Neisseria gonorrhoeae*.

4. Significant neurological disorder or history of seizure (including simple febrile seizure).

5. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).

6. Family history of congenital or hereditary immunodeficiency.

7. Other medical or psychiatric condition, including recent or active suicidal ideation/behavior, or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

8. Major known congenital malformation or serious chronic disorder.

Prior/Concomitant Therapy:

9. Previous vaccination with any meningococcal vaccine containing groups A, C, W, or Y. Written vaccination history must be obtained prior to enrollment.

10. Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

11. Current use of systemic antibiotics with no foreseeable date of discontinuation prior to anticipated date on enrollment (first vaccination).

12. Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day or equivalent. Inhaled and topical steroids are allowed.

Prior/Concurrent Clinical Study Experience:

13. Participation in other studies involving investigational drug(s) or investigational vaccine(s) within 28 days prior to study entry and/or during study participation.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

14. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants whose parent(s)/legal guardian(s) has consented to participate in the clinical study but are not randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

5.5.1. Temporary Delay Criteria

The following conditions are temporary or self-limiting and a participant may be vaccinated and/or have blood drawn in the study once the condition(s) has/have resolved and no other exclusion criteria are met. The prevaccination immunogenicity blood draw and vaccination should take place on the same day (Visit 1 and Visit 3).

5.5.1.1. Criteria for Temporarily Delaying Vaccine Administration

- Current febrile illness (temperature ≥38.0ºC) or other acute illness within 48 hours before investigational product administration.
- Participant has received antipyretic medication or other pain medication on the planned day of vaccination.
- Participant has received any nonlive vaccine (or intramuscular/sublingual allergen immunotherapy) within 14 days, or any live vaccine within 28 days, before investigational product administration.
- Participant has received tetanus-containing vaccines within 30 days before investigational product administration.
- Participant is less than 5 days into a course of systemic antibiotic therapy.
- Participant has received systemic (oral, intravenous, or intramuscular) corticosteroid therapy within the previous 28 days.

5.5.1.2. Criteria for Temporarily Delaying Blood Draw

- Participant has received systemic antibiotic therapy within the last 5 days (must have full 5-day interval between date of last dose and date of blood collection).

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

For this study, the investigational product is Nimenrix.

6.1.1. Nimenrix (MenACWY-TT)

The lyophilized white powder of MenACWY-TT vaccine will be reconstituted with the supplied diluent to obtain 0.5 mL for administration. The entire contents of the supplied container of diluent must be added to the vial containing the powder. The sterile diluent is clear and colorless and presented in a prefilled syringe (PFS). After addition of the diluent to the powder, the mixture should be well shaken until the powder is completely dissolved in the diluent. The vaccine will appear as a clear colorless solution. The vaccine should be administered immediately after reconstitution.

Intervention Name	**Nimenrix**
Dose Formulation	Nimenrix is supplied as a lyophilized powder in a single-dose vial and a solvent in a PFS to be reconstituted for injection.
Dosage Level(s)	0.5-mL dose
Route of Administration	Intramuscular
IMP or NIMP	IMP
Sourcing	Pfizer
Packaging and Labeling	Study intervention will be provided as a lyophilized powder in a single-dose vial and a solvent in a PFS. The vial and PFS will be packaged in a carton and labeled as required per country requirement.

6.1.2. Medical Devices

1. In this study, the medical device being used will be the PFS for Nimenrix.

2. Instructions for medical device use are provided in the IP manual.

3. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9 and appropriately managed by the sponsor.

6.1.3. Administration

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

At Visit 1 and Visit 3, a 0.5-mL dose of Nimenrix will be administered intramuscularly in the infant's anterolateral region of the left thigh by a qualified site staff member.

Any routine immunizations required per local practice will be permitted and should be administered in the right thigh.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Study intervention will be shipped at +2°C to +8°C to each study site after required regulatory and legal documents have been received by the sponsor. Upon receipt at the study site, the study intervention should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study

intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

5. Receipt of materials, door opening and closing, and other routine handling operations, where the products are briefly out of the temperature range described in the labeling, are not considered excursions.

6. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

7. Study interventions should be stored in their original containers.

8. See the IP manual for storage conditions of the study intervention.

9. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. Empty outer study intervention containers must be retained until reviewed by the sponsor's representative and then may be destroyed after the sponsor's representative has performed accountability. Study intervention return/destruction must be documented on the accountability log.

10. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified, GCP-trained, and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label study with 1 vaccine group. The specific study intervention dispensed to the participant will be assigned using an IRT. The site will refer to the IRT prior to the

start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately qualified and designated study staff at the investigator site.

6.5. Concomitant Therapy

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.

6.5.1. Prohibited During the Study

- Prophylactic antipyretics and other pain medications to prevent symptoms associated with the investigational product are not permitted.
- On the day of planned vaccination, if the participant has received antipyretics or other pain medications prior to a planned administration of the investigational product, vaccination should be temporarily delayed as specified in Section 5.5.1.
- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during study participation.
- Receipt of any blood products, including immunoglobulin.
- Nonstudy meningococcal vaccine groups A, C, W, or Y.
- Nonlive or live nonstudy vaccines are not permitted 14 and 28 days, respectively, before or after any study vaccination.

- Tetanus-containing vaccines are not permitted 30 days before any study vaccination.
- Intramuscular/sublingual allergen therapy is not permitted within 14 days of any study vaccination.
- Systemic (oral, intravenous, or intramuscular) corticosteroid therapy within 28 days of any study vaccination.

6.5.2. Permitted During the Study

- 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) prior to study vaccine administration, as specified below.
- Nonstudy vaccines (other than 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 study vaccine administration. Tetanus-containing vaccines are allowed any time during the study (and can be given at the same time as study vaccine) but should not be administered within 30 days before study vaccine administration.
- Antipyretics and other pain medications to treat symptoms associated with the investigational product 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.

6.5.3. Prohibited Prior Treatments

Receipt of any blood products, including immunoglobulin, prior to the first study vaccine administration is prohibited.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: AEs, parent(s)/legal guardian(s) request, and protocol violation.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for collection of safety information. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Withdrawn consent (refused further follow-up);
- Lost to follow-up;
- Medication error without associated AE;
- Death;
- Study terminated by sponsor;
- AEs;
- Protocol violation;
- No longer meets eligibility criteria.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant's parent(s)/legal guardian(s). All attempts to contact the parent(s)/legal guardian(s) and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The parent(s)/legal guardian(s) should be questioned regarding the reason for the participant's withdrawal. The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, the parent(s)/legal guardian(s) may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

The parent(s)/legal guardian(s) should be requested to have the participant return for a final visit, if applicable, and the investigator will perform the procedures indicated for the next visit. Any AEs or SAEs that are continuing at the time of withdrawal from the study should be followed until resolution or, in case of permanent impairment, until the condition stabilizes.

If the participant withdraws from the study and his/her parent(s)/legal guardian(s) also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Vaccine SAE Reporting Form.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Participants who have received the investigational product will not be replaced regardless of the reason for withdrawal.

7.2.1. Withdrawal of Consent

Participants whose parent(s)/legal guardian(s) requests the participant discontinues receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant's parent(s)/legal guardian(s) specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant's parent(s)/legal guardian(s) to provide this information. The participant's parent(s)/legal guardian(s) should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and the participant's parent(s)/legal guardian(s) is unable to be contacted by the study site.

The following actions must be taken if a participant's parent(s)/legal guardian(s) fails to return to the clinic for a required study visit or cannot be reached by telephone:

- The site must attempt to contact the participant's parent(s)/legal guardian(s) and reschedule the missed visit as soon as possible and counsel the participant's parent(s)/legal guardian(s) on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant's parent(s)/legal guardian(s) wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant's parent(s)/legal guardian(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant's parent(s)/legal guardian(s) continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy and/or Immunogenicity Assessments

Blood samples (approximately 5 mL per sample) for immunogenicity assessments will be collected from all participants prior to Dose 1 (Day 1), at 1 month after Dose 1 (Visit 2), prior to Dose 2 (Visit 3) and 1 month after Dose 2 (Visit 4).

Sample collection, processing, storage, and shipping information can be found in the ISF or equivalent manual. Sera will be used for immunogenicity assessments, assay development, and routine assay maintenance.

8.1.1. Antibodies Against *N meningitidis* Serogroups A, C, W-135, and Y

8.1.1.1. Bactericidal Assay (rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY)

Bactericidal antibodies are recognized as surrogate markers of protection. An rSBA cutoff of 1:8 was shown to be the most consistent with observed efficacy at 4 weeks after vaccination with the meningococcal serogroup C conjugate vaccine in postlicensure efficacy estimates in the UK.[12] The threshold for protection for other serogroups is still to be defined, although it is common practice to extend the 1:8 cutoff for rSBA-MenA, rSBA-MenW-135, and rSBA-MenY.[13] The percentage of participants achieving rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers ≥1:8, ≥1:128 will be reported, along with GMTs.

8.1.1.2. Bactericidal Assay (hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY)

The established correlate of protection for the hSBA-MenC assay using human sera as the exogenous complement source is 1:4.[14] The same cut-off will be used for serogroups A, W-135, and Y. The percentage of participants achieving hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY antibody titers ≥1:4, ≥1:8 will be reported, along with GMTs.

8.1.2. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed.

The participant's parent(s)/legal guardian(s) may request that the participant's samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed.

8.2. Safety Assessments

A clinical assessment, including medical history and measurement of temperature as appropriate for the age of the child, according to routine local practice, will be performed on all participants prior to vaccination to determine participant eligibility and to establish a clinical baseline. Significant medical history and significant findings observed during physical examination (if performed) will be recorded in the medical history CRF. Temperature measurement prior to vaccination will be documented and recorded in the CRF.

The participant will be observed for 30 minutes after each vaccination and any reactions during the visit will be assessed and recorded as AEs. AEs occurring within the first 30 minutes after investigational product administration will be defined as immediate AEs. The time of onset will be recorded for any AE that occurs on the same day as investigational product administration.

E-diary events, including local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) that occur within the 7 days following investigational product administration (Days 1 to 7, where Day 1 is the day of vaccination) are graded as described in Section 8.2.2. Furthermore, AEs, SAEs, and NDCMCs will be collected as defined in Section 10.3.

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Participant E-Diary

The parent(s)/legal guardian(s) will be asked to monitor and record local reactions, specific systemic events, and antipyretic/pain medication taken for 7 days, each evening, following each study vaccination using an e-diary (in a provisioned device application on a personal device). This system, hereafter referred to as the e-diary, allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions, specific systemic events, and antipyretic/pain medication reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting.

The daily e-diary data will not be captured in the CRF. However, if a participant is withdrawn because of events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

The investigator (or appropriately qualified designee) must obtain stop dates for any local reactions or specific systemic events on the last day that the e-diary was completed. The stop dates should be entered in the CRF.

The investigator (or appropriately qualified designee) is required to review the e-diary data online to evaluate participant compliance and as part of the ongoing safety review.

8.2.2. Grading Scale for E-Diary Events

The grading scales used in this study to assess e-diary events as described below are based on concepts outlined in the FDA CBER guidelines on toxicity grading scales for adults and adolescent volunteers enrolled in preventive vaccine clinical trials but have been adapted for applicability to healthy infants.[15]

8.2.2.1. Local Reactions

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 redness, swelling, and pain at the Nimenrix injection site and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device units (range: 1 to >14) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scale in Table 1. The participant's parent(s)/legal guardian(s) will be prompted to contact the investigator if the participant

experiences a severe (Grade 3 or above) local reaction to assess the reaction and perform an unscheduled visit as appropriate.

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). If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the participant's parent(s)/legal guardian(s) regarding signs and symptoms that would prompt site contact.

The procedure for notification of the sponsor is provided in the ISF or equivalent.

Table 1. Local Reaction Grading Scale

	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. Grade 4 assessment should be made by the investigator. Grade 4 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 in Section 10.3.5.

8.2.2.2. Systemic Events (Systemic Symptoms and Fever)

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 decreased appetite, drowsiness/increased sleep, and irritability and to record the symptoms in the e-diary (in a provisioned device or application on a personal device) in the evening. The symptoms will be assessed by the participant's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scale in Table 2. The participant's parent(s)/legal guardian(s) will also be instructed to contact site staff if the participant experiences any possible Grade 4 systemic event (ie, emergency room visit or hospitalization for severe

decreased appetite, severe drowsiness/increased sleep, or severe irritability) within 7 days after vaccination. Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

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). If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor.

The procedure for notification of the sponsor is provided in the ISF or equivalent.

Table 2. Systemic Event Grading Scale

	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 in Section 10.3.5.

8.2.2.2.1. Fever

In order to record information on fever, a digital thermometer will be given to the participant's parent(s)/legal guardian(s) with instructions on how to measure temperature at home. Temperature will be collected in the evening, daily, for 7 days following each study vaccination (Days 1 through 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as a temperature of ≥38.0°C. The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 38.0°C in order to collect a stop date in the CRF). A participant's parent(s)/legal guardian(s)

will be prompted to contact the investigator if the participant experiences a fever >40.0°C within the 7 days following vaccination to assess the fever and perform an unscheduled visit as appropriate (see Section 8.11.5). Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information if a temperature >38.9°C is entered into the e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 3.

Table 3. Ranges for Fever

38.0°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C

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

8.2.2.3. Use of Antipyretic/Pain Medication

The participant's parent(s)/legal guardian(s) will be asked to record the use of antipyretic/pain medication (Yes/No) in the e-diary (in a provisioned device or application on a personal device) in the evening, daily, for 7 days after each investigational product.

8.2.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments are not required by this protocol.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant's parent(s)/legal guardian(s). Events that, in the clinical judgment of the investigator, are 1) consistent with normal growth and development and 2) do not differ significantly in frequency or severity from expected are not generally to be considered AEs. Examples may include, but are not limited to, teething, contact diaper rash, spitting up, colic, or typical fussiness/crying in infants and children.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant's parent(s)/legal guardian(s) will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant's parent(s)/legal guardian(s) provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2 and from Visit 3 through Visit 4 for AEs and through and including Visit 4 for SAEs and NDCMCs. Between Visit 2 and Visit 3, only SAEs and NDCMCs will be reported.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate, according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding via Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding via occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Reporting Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety.

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study for the purposes of administering and preparing study intervention. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 5.

Note: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 5.

8.3.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP manual. The Medical Device Complaint CRF will also be completed.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Section 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE.**

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 1 dose within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Please refer to Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

8.11.1. Visit 1 – Vaccination 1 (Day 1)

- Obtain a personally signed and dated ICD indicating that the participant's parent(s)/legal guardian(s) has been informed of all pertinent aspects of the study before performing any study-specific procedures.

- Assign a participant number.

- Obtain and record the participant's demographic information (including date of birth, sex, race, and ethnicity). The complete date of birth (ie, DD-MMM-YYYY) will be collected to critically evaluate the immune response and safety profile by age.

- Record medical history of significance (including significant birth history); record any findings on the medical history CRF.

- Perform a physical examination, including body length and weight, evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, neurological, musculoskeletal, and lymph nodes, including worsening of medical history conditions. Results must be recorded on source documents and the CRF. Findings from a physical examination conducted as part of standard routine care and before informed consent may be used for the purposes of the study only if the examination was performed no more than 2 days before vaccination. A brief examination must be performed on the day of vaccination to document that no change in health has occurred in the interim.

- Record vaccine history.

- Prior to vaccination, measure and record the participant's temperature (°C), as per local clinical practice.

- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.

- Prior to vaccination, collect a blood sample of approximately 5 mL for immunogenicity assessments (a topical anesthetic is permitted).

- A site staff member will prepare the investigational product according to the IP manual.

- Administer a single 0.5-mL injection of Nimenrix into the left anterolateral thigh.

- Site staff must observe the participant for 30 minutes after vaccination for any reactions. Record any AEs in the participant's source documents and on the AE page of the CRF, and any SAEs on an SAE form as applicable. Record concomitant medications as described in Section 6.5.

- Issue the participant's parent(s)/legal guardian(s) a measuring device to measure any injection site reactions and a digital thermometer and provide instructions on their use.

- Issue the participant's parent(s)/legal guardian(s) an e-diary (device or application). Provide instructions on use and completion of the e-diary. Ask the participant's

parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian(s) to contact the site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C, redness and/or swelling at the injection site measuring >14 measuring device units (>7 cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Ask the participant's parent(s)/legal guardian(s) to contact the site staff or investigator as soon as possible if any significant illness or medical event (eg, emergency room or hospitalization) occurs.

- Provide the participant's parent(s)/legal guardian(s) with the participant contact card containing the study and investigator information (see Section 10.1.10).

- Inform 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).

- The investigator or an authorized designee completes the CRF and the source documents and updates the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.2. Visit 2 – 1-Month Follow-up Visit 1 (28 to 42 Days After Visit 1)

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5.1).

- Record nonstudy vaccinations administered since Visit 1, as described in Section 6.5.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Collect the e-diary (if device provided).

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit, follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing),

record as described in Section 10.3, and record concomitant medications as described in Section 6.5.

- Collect a blood sample of approximately 5 mL for immunogenicity assessments (a topical anesthetic is permitted).

- The investigator or an authorized designee completes the CRF and the source documents.

8.11.3. Visit 3 – Vaccination 2 (270 to 300 Days After Visit 1)

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5.1).

- Record nonstudy vaccinations administered since Visit 2, as described in Section 6.5.

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit, follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing), record as described in Section 10.3, and record concomitant medications used to treat NDCMCs and AEs/SAEs.

- Prior to vaccination, measure and record the participant's temperature (°C), as per local clinical practice.

- Prior to vaccination, collect a blood sample of approximately 5 mL for immunogenicity assessments (a topical anesthetic is permitted).

- Administer a single 0.5-mL injection of Nimenrix into the left anterolateral thigh.

- Site staff must observe the participant for 30 minutes after vaccination for any reactions. Record any AEs in the participant's source documents and on the AE page of the CRF, and any SAEs on an SAE form as applicable. Record concomitant medications as described in Section 6.5.

- Issue the participant's parent(s)/legal guardian(s) a measuring device to measure any injection site reactions and a digital thermometer and provide instructions on their use.

- Issue the participant's parent(s)/legal guardian(s) an e-diary (device or application). Provide instructions on use and completion of the e-diary. Ask the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian(s) to contact the site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever

>40.0°C, redness and/or swelling at the injection site measuring >14 measuring device units (>7 cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Remind the participant's parent(s)/legal guardian(s) to contact the site staff or investigator as soon as possible if any significant illness or medical event (eg, emergency room or hospitalization) occurs.

- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card. Provide a participant contact card if needed.

- 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).

- The investigator or an authorized designee completes the CRF and the source documents and updates the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.4. Visit 4 – 1-Month Follow-up Visit 2 (28 to 42 Days After Visit 3)

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5.1).

- Record nonstudy vaccinations administered since Visit 3, as described in Section 6.5.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Collect the e-diary (if device provided).

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3, and record concomitant medications as described in Section 6.5.

- Collect a blood sample of approximately 5 mL for immunogenicity assessments (a topical anesthetic is permitted).

- The investigator or an authorized designee completes the CRF and the source documents.

8.11.5. Unscheduled Visits

If the participant's parent(s)/legal guardian(s) reports redness or swelling at the injection site measuring >14 measuring device units (>7 cm), severe injection site pain, or a fever >40.0°C during the 7-day postvaccination period, a telephone contact must occur as soon as possible between the investigator or medically qualified designee and the participant's parent(s)/legal guardian(s) to assess if an unscheduled visit is required. A visit must be scheduled as soon as possible to assess the extent of the reaction unless:

- The participant's parent(s)/legal guardian(s) is unable to bring the participant to the unscheduled visit.
- The reaction is no longer present at the time of the telephone contact.
- The participant's parent(s)/legal guardian(s) recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the CRF and in the participant's source documentation.

If the participant's parent(s)/legal guardian(s) is unable to bring the participant to an unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing reactions must be assessed at the next scheduled visit.

During the scheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff, such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure temperature (°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess any injection site pain that is present in accordance with the grading scale provided in Section 8.2.2.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

The participant's parent(s)/legal guardian(s) will also be instructed to contact the study site staff if the participant experiences any emergency room visit or hospitalization for decreased appetite, drowsiness/increased sleep, irritability, or local reaction within 7 days of vaccination.

The participant's parent(s)/legal guardian(s) will also be instructed to contact the study site to report any significant illness, medical event, or hospitalization that occurs during the study period. The study site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

Additionally, study site staff may contact the participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

No specific hypotheses will be tested in this study.

9.1.1. Estimands

The estimand(s) corresponding to each primary, secondary, CCI [redacted] objective are described in Section 3. The estimands to evaluate the immunogenicity objectives are based on the evaluable population (see Section 9.3 for the definition). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed.

In the primary safety objective evaluations, missing AE dates will be imputed according to Pfizer Safety rules.

9.2. Sample Size Determination

The study sample size is not based on any hypothesis testing criteria. All statistical analyses of immunogenicity and safety will be descriptive. The study will enroll approximately 150 participants. Assuming up to approximately 15% exclusion rate from the applicable evaluable population, there will be approximately 130 evaluable participants.

Table 4 shows the expected width of the 95% CI by percentage of evaluable participants achieving an rSBA titer ≥1:8 for each serogroup.

Table 4. Expected Width of 95% CIs by Percentage of Participants Achieving an rSBA Titer ≥1:8 for Each Serogroup

Percentage of Participants	Number of Evaluable Participants	Expected Width of 95% CI (%)
60	130	17.4
70	130	16.4
80	130	14.4
90	130	11.1

Abbreviation: rSBA = serum bactericidal assay using rabbit complement.

The probability of observing at least 1 occurrence of any AE for true event percentages between 0.1% and 2.0%, when Nimenrix is administered to 150 participants, is displayed in Table 5.

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates

Assumed True Event Percentage	Probability (N=150)
0.1%	0.14
0.5%	0.53
1.0%	0.78
2.0%	0.95

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

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 study intervention and have safety data reported after vaccination.

Defined Population for Analysis	Description
Post–Dose 1 evaluable	All enrolled participants who were eligible throughout Visit 2, received the investigational product at Visit 1, 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), had at least 1 valid and determinate MenA, MenC, MenW-135, and MenY assay result at Visit 2, had received no prohibited vaccines or treatment through Visit 2, and had no major protocol deviations through Visit 2. A major protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity (eg, participant's receipt of a prohibited vaccine or a medication that might affect immune response or a medication error with a suspected decrease in potency of the vaccine).
Post–Dose 2 evaluable	All enrolled participants who were eligible throughout 1 month after Dose 2 of Nimenrix, received the investigational product at Visit 1 and Visit 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 (window 28-42 days), had at least 1 valid and determinate MenA, MenC, MenW-135, and MenY assay result at 1 month after Dose 2, had received no prohibited vaccines or treatment through Visit 4 and had no major protocol deviations through Visit 4. A major protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity (eg, participant's receipt of a prohibited vaccine or medication that might affect immune response or a medication error with a suspected decrease in potency of the vaccine).
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.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Immunogenicity Analyses

Primary	For each of the MenA, MenC, MenW-135, and MenY serogroups, the percentage of participants with an rSBA titer ≥1:8 at baseline, at 1 month after Dose 1 of Nimenrix, at Dose 2, and at 1 month after Dose 2 will be calculated. The rSBA GMTs for each of the MenA, MenC, MenW-135, and MenY serogroups at baseline, at 1 month after Dose 1 of Nimenrix, at Dose 2, and at 1 month after Dose 2 will be summarized. These analyses will be based on the post–Dose 2 evaluable population. Exact 2-sided 95% CIs for the percentages will be provided using the Clopper-Pearson method. GMTs and their 2-sided 95% CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, then exponentiating the results. Titers below LLOQ will be set to 0.5 × LLOQ for analysis. Supportive analyses will be performed based on the applicable mITT population. Missing serology data will not be imputed.
Secondary	For each of the MenA, MenC, MenW-135, and MenY serogroups, the percentage of participants with an rSBA titer ≥1:8 at baseline and at 1 month after Dose 1 of Nimenrix will be calculated. The rSBA GMTs for each of the MenA, MenC, MenW-135, and MenY serogroups at baseline and at 1 month after Dose 1 of Nimenrix will be summarized. These analyses will be based on the post–Dose 1 evaluable population. For each of the MenA, MenC, MenW-135, and MenY serogroups, the percentage of participants with an hSBA titer ≥1:4, and separately for ≥1:8, at baseline and at 1 month after Dose 1 of Nimenrix will be calculated. The hSBA GMTs for each of the MenA, MenC, MenW-135, and MenY serogroups at baseline and at 1 month after Dose 1 of Nimenrix will be summarized. For each of the MenA, MenC, MenW-135, and MenY serogroups, the percentage of participants with an rSBA titer ≥1:128, at baseline and at 1 month after Dose 1 of Nimenrix will be calculated. These analyses will be based on the post-Dose 1 evaluable population.

	For each of the MenA, MenC, MenW-135, and MenY serogroups, the percentage of participants with an hSBA titer ≥1:4, and separately for ≥1:8, at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2 of Nimenrix will be calculated. The hSBA 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 of Nimenrix will be summarized. For each of the MenA, MenC, MenW-135, and MenY serogroups, the percentage of participants with an rSBA titer ≥1:128 at baseline, at 1 month after Dose 1, at Dose 2, and at 1 month after Dose 2 of Nimenrix will be calculated. These analyses will be based on the post–Dose 2 evaluable population. Exact 2-sided 95% CIs for the percentages will be provided using the Clopper-Pearson method. Geometric means and their 2-sided 95% CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, then exponentiating the results. Titers below LLOQ will be set to 0.5 × LLOQ for analysis. Supportive analyses will be performed based on the applicable mITT population. Missing serology data will not be imputed.

CCI [redacted]

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population. Separate safety populations may be defined for each vaccination and detailed in the SAP.

Endpoint	Statistical Analysis Methods
Primary	The proportion of participants reporting local reactions at the investigational product administration site and systemic events within the 7-day period after Dose 2 will be described. Two (2)-sided 95% CIs based on the Clopper-Pearson method will be presented with the proportions. Severities of local reactions and systemic events reported after Dose 2 will also be described. The proportion of participants reporting the use of antipyretic medication for Days 1 to 7 will be compiled for after Dose 2. The percentage of participants reporting at least 1 AE, at least 1 SAE, and at least 1 NDCMC will be descriptively summarized (percentages

Endpoint	Statistical Analysis Methods
	and associated Clopper-Pearson 95% CIs) for each time period in Section 3, specifically following Dose 2. All AEs and SAEs will be categorized according to the latest version of MedDRA. Missing AE dates will be handled according to the Pfizer Safety rules. Detailed analyses for each safety endpoint will be addressed in the SAP.
Secondary	Similar summaries to those for the primary safety objectives will be performed, however specifically for safety summaries after the first dose of Nimenrix.

9.5. Interim Analyses

No interim analysis is planned in this study.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant's parent(s)/legal guardian(s) and answer all questions regarding the study. The participant's parent(s)/legal guardian(s) should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

The participant's parent(s)/legal guardian(s) must be informed that their participation is voluntary. The participant's parent(s)/legal guardian(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian(s) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant's parent(s)/legal guardian(s) must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian(s).

The participant's parent(s)/legal guardian(s) must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian(s) is fully informed about his or her right to access and correct the participant's personal data and to withdraw consent for the processing of the participant's personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

The participant's parent(s)/legal guardian(s) must be reconsented to the most current version of the ICD(s) during the participant's participation in the study.

A copy of the ICD(s) must be provided to the participant's parent(s)/legal guardian(s).

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the ISF.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention–related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the ISF.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant’s participation in the study. The contact number can also be used

by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible

suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Definition of Immediate Adverse Event

AEs occurring within the first 30 minutes after study intervention administration.

10.3.4. Definition of an NDCMC

A significant disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

10.3.5. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All

Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is**

very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.6. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

- Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.5. Appendix 5: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.5.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator for study participants, users, and other persons. This definition also includes events considered related to procedures for study participants only. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.5.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

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

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.5.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.5.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP manual and completing the Medical Device Complaint CRF.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.5.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

- Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.5.6. Reporting of SADEs

SADE Reporting to Pfizer Safety

Note: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DILI	drug-induced liver injury
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMT	geometric mean titer
HIPAA	Health Insurance Portability and Accountability Act
hSBA	serum bactericidal assay using human complement
hSBA-MenA	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A
hSBA-MenC	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group C
hSBA-MenW-135	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group W-135

Abbreviation	Term
hSBA-MenY	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group Y
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
ISO	International Organization for Standardization
LFT	liver function test
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* group A
MenACWY	meningococcal polysaccharide groups A, C, W, and Y conjugate vaccine
MenACWY-TT	meningococcal polysaccharide groups A, C, W, and Y tetanus toxoid conjugate vaccine
MenC	*Neisseria meningitidis* group C
MenW-135	*Neisseria meningitidis* group W-135
MenY	*Neisseria meningitidis* group Y
mITT	modified intent-to-treat
NDCMC	newly diagnosed chronic medical condition
N/A	not applicable
NIMP	noninvestigational medicinal product
PFS	prefilled syringe
PI	principal investigator
PT	prothrombin time
rSBA	serum bactericidal assay using rabbit complement
rSBA-MenA	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A
rSBA-MenC	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group C
rSBA-MenW-135	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group W-135

Abbreviation	Term
rSBA-MenY	serum bactericidal assay using rabbit complement
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	summary of product characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TT	tetanus toxoid
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect

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