A PHASE 2b, RANDOMIZED, OBSERVER-BLINDED TRIAL TO DESCRIBE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MenABCWY ADMINISTERED ON 2 DIFFERENT DOSING SCHEDULES IN HEALTHY PARTICIPANTS ≥11 TO <15 YEARS OF AGE

Study Intervention Number:	PF-06886992
Study Intervention Name:	*Neisseria meningitidis* Group A, B, C, W, and Y Vaccine (MenABCWY)
US IND Number:	17319
EudraCT Number:	2019-004923-19
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Phase:	2b

Short Title: A Trial to Describe the Safety and Immunogenicity of MenABCWY When Administered on 2 Schedules

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	07 January 2021	• Updated the study design to decrease intervals between MenABCWY doses from 24 and 48 months to 12 and 36 months in order to shorten the duration of the study. • Removed Visit 11 (36-month post-Dose 2 antibody persistence visit for Group 1 and 12-month post-Dose 2 antibody persistence visit for Group 2) and the associated immunogenicity objectives/estimands from the study design. Visit 11 is no longer applicable. • Updated the time period for collecting SAEs, MAEs, and NDCMCs from 6 months after each vaccination to 6 months after Vaccinations 1 and 2, and 1 month after Vaccination 3 as Visit 11 was removed from the study design. Removed associated estimands relating to descriptive summaries of SAEs, MAEs, and NDCMCs reported during the Vaccination 3 follow-up phase. • Added estimands for the immunogenicity analysis of the blood draw after the saline injection in Group 2 per CBER feedback. • Reduced the planned statistical analyses from 3 (after Visit 5, after Visit 10, and end of study) to 2 (after Visit 5 and end of study). Visit 10 is now the final visit in the study design. • Added instructions to schedule Visit 6 (12-month antibody persistence) in Group 1 and Visit 8 (Safety Telephone Contact 2) in Group 2 as in-person visits, with Visit 8 to be later converted to a telephone contact once study unblinding has occurred, in order to maximize scheduling efficiency. • Updated CT SAE Report Form to Vaccine SAE Reporting Form throughout, as per PACL dated 08 May 2020. • Corrected the description of the bivalent rLP2086 PFS from a 0.7 mL PFS to a high-fill volume PFS as the volume contained in the PFS is not precisely 0.7 mL. • Made a correction in Section 8.2.1 indicating that pregnancy tests will be performed in all female participants rather than WOCBP. • Replaced the term SRM with ISF throughout the protocol as the term SRM is no longer used. • Added Appendix 8: Alternative Measures During Public Emergencies as described in CT02-CT45-COVID19-SD-GL01. • Updated to the 15 May 2020 protocol template.
Original protocol	04 February 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

In Study B1971057, an FIH and POC study for MenABCWY, 543 participants received MenABCWY on a 0- and 6-month schedule. Results from B1971057 indicated MenABCWY, when given on a 0- and 6-month schedule, is well tolerated with an acceptable safety profile, and also provides a high degree of protective immune responses without interference among all 5 serogroup components tested. These results are comparable to Phase 2 and 3 bivalent rLP2086 (Trumenba®) studies, which demonstrate that by increasing the interval between 2 doses, immune responses are enhanced. Study B1971057 also demonstrated that 1 dose of MenACWY-TT (Nimenrix®) provides protective immune responses in a high proportion of those vaccinated, consistent with Phase 3 data supporting licensure of Nimenrix.

The aim of this Phase 2b descriptive study is to assess the potential utility of MenABCWY in the framework of current US meningococcal vaccination practices, which are based on the Centers for Disease Control and Prevention's ACIP recommendations. This study will describe the immune response following 1 and 2 doses of MenABCWY when administered at 12- and 36-month intervals in healthy participants ≥11 to <15 years of age at the time of their first dose. The persistence of the immune response will be described for 24 months after 2 doses of MenABCWY administered on a 0- and 12-month schedule.

Data obtained from prior studies supporting the licensure of the 2 vaccines comprising MenABCWY, MenACWY-TT (Nimenrix) and bivalent rLP2086 (Trumenba), support a favorable benefit-risk assessment for continued study of MenABCWY.

Objectives, Estimands, and Endpoints

Randomization group descriptions are shown in Section 1.2.

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 36-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule).	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
Primary Safety:	**Primary Safety:**	**Primary Safety:**

To describe the safety profile of MenABCWY when administered on a 0- and 12-month and a 0- and 36-month schedule.	In participants receiving at least 1 dose of study intervention:
	• The percentage of participants reporting at least 1 AE, at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods:
	  • 30 Days after each vaccination.
	  • 30 Days after any MenABCWY vaccination.
	  • During the Vaccination 1, 2, and 3 vaccination phases:
	  ○ From Vaccination 1 (Visit 1) through 1 month after Vaccination 1 (Visit 2) in Groups 1 and 2.
		• AEs, SAEs, MAEs, NDCMCs, and immediate AEs.
		• Days missing from school or work because of AEs.

Objectives	Estimands	Endpoints
	○ From Vaccination 2 (Visit 4) through 1 month after Vaccination 2 (Visit 5) in Groups 1 and 2. ○ From Vaccination 3 (Visit 9) through 1 month after Vaccination 3 (Visit 10) in Group 2. • The percentage of participants reporting at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods: • During the follow-up phases: ○ From 1 month after Vaccination 1 (Visit 2) through 6 months after Vaccination 1 (Visit 3) in Groups 1 and 2. ○ From 1 month after Vaccination 2 (Visit 5) through 6 months after Vaccination 2 in Groups 1 and 2. • 6 Months after Vaccinations 1 and 2: ○ From Vaccination 1 (Visit 1) through 6 months after Vaccination 1 (Visit 3) in Groups 1 and 2. ○ From Vaccination 2 (Visit 4) through 6 months after Vaccination 2 in Groups 1 and 2. • The percentage of participants reporting at least 1 immediate AE after each vaccination. • The percentage of participants who missed days of school or work because of AEs occurring within 6 months after Vaccinations 1 and 2, and within 1 month after Vaccination 3.	
Secondary Immunogenicity:	**Secondary Immunogenicity:**	**Secondary Immunogenicity:**
To describe the immune response for MenA, MenC, MenW, and MenY induced by 1 and 2 doses of MenABCWY administered on a 0- and 12-month schedule.	In participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (ie, hSBA titer of ≥1:8) for each ACWY test strain at baseline and 1 month after the first dose of MenABCWY in Group 1 (0- and 12-month schedule).	• hSBA titer for each of the MenACWY test strains.

Objectives	Estimands	Endpoints
	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each ACWY test strain at baseline and 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	
To describe the immune response for MenA, MenC, MenW, and MenY induced by 1 and 2 doses of MenABCWY administered on a 0- and 36-month schedule.	In participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (ie, hSBA titer of ≥1:8) for each ACWY test strain at baseline and 1 month after the first dose of MenABCWY Group 2 (0- and 36-month schedule), In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each ACWY test strain at baseline and 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule).	• hSBA titer for each of the MenACWY test strains.
To describe the persistence of the MenB response following 2 doses of MenABCWY administered on a 0- and 12-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the 4 primary MenB test strains at 12 months and 24 months after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

Objectives	Estimands	Endpoints
To describe the persistence of the MenA, MenC, MenW, and MenY response following 2 doses of MenABCWY when administered on a 0- and 12-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each ACWY test strain at 12 months and 24 months after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	• hSBA titer for each of the MenACWY test strains.

Overall Design

This is a Phase 2b, randomized, observer-blinded, multicenter trial in which approximately 300 US participants ≥11 to <15 years of age will be randomly assigned at a 1:1 ratio to receive MenABCWY either on a 0- and 12-month schedule (Group 1) or on a 0- and 36-month schedule (Group 2) as shown in Section 1.2. All participants will be naïve to any meningococcal vaccine prior to enrollment.

Participants will have blood drawn prior to Vaccination 1 and 1 month after each vaccination. Additionally, to facilitate the description of antibody persistence after 2 doses of MenABCWY, participants in Group 1 (0- and 12-month schedule) will have blood drawn at 12 and 24 months after the second dose of MenABCWY. The sponsor will be blinded to dosing schedule assignment through Month 13 (1 month after the second dose of MenABCWY in Group 1 [0- and 12-month schedule]), after which the dosing schedule assignment for all participants will be unblinded. The second dose of MenABCWY in Group 2 (0- and 36-month schedule) will be administered in an open-label manner.

A total of approximately 300 participants will be enrolled, and each participant will participate in the study for approximately 37 months.

Statistical Methods

This is not a hypothesis-testing study; an estimation approach will be used to assess the descriptive immunogenicity and safety objectives. All immunogenicity data will be summarized descriptively within each vaccination group. All of the binary endpoints (including primary endpoints) will be summarized with 2-sided 95% CIs using the Clopper-Pearson method. GMTs for hSBA results will also be summarized with 95% CIs. The study team will remain blinded until all participants have completed Visit 5, after which select data will be reported, including immunogenicity data for Group 1. A final analysis will be done after all available data have been collected.

The primary safety objectives will be assessed by descriptive summaries of AEs, SAEs, NDCMCs, MAEs, and immediate AEs in Groups 1 and 2 as described in Section 9.

1.2. Schema

Group 1 (0- and 12-Month Schedule)							
	Vaccination 1	**1 Month Post–Vaccination 1 Blood Draw**	**Safety Telephone Contact 1**	**Vaccination 2**	**1 Month Post–Vaccination 2 Blood Draw**	**12-Month Antibody Persistence Visit**	**24-Month Antibody Persistence Visit**
Approximate Month	**0**	**1**	**6**	**12**	**13**	**24**	**36**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[a]**
Group 1 (n=150)	MenABCWY			MenABCWY			
Blood draw	25 mL	25 mL			25 mL	25 mL	25 mL

a. Visits 8, 9, and 10 will not be conducted for Group 1 participants.

Group 2 (0- and 36-Month Schedule)								
	Vaccination 1	**1 Month Post–Vaccination 1 Blood Draw**	**Safety Telephone Contact 1**	**Vaccination 2**	**1 Month Post–Vaccination 2 Blood Draw**	**Safety Telephone Contact 2**	**Vaccination 3**	**1 Month Post–Vaccination 3 Blood Draw**
Approximate Month	**0**	**1**	**6**	**12**	**13**	**24**	**36**	**37**
Visit Number	**1**	**2**	**3**	**4**	**5[a]**	**8[b]**	**9**	**10**
Group 2 (n=150)	MenABCWY			Saline			MenABCWY	
Blood draw	25 mL	25 mL			25 mL			25 mL

a. Visits 6 and 7 will not be conducted for Group 2 participants.
b. Visit 8 will be scheduled as an in-person visit to maintain the blind and converted to a telephone visit once unblinding has occurred.

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.

Group 1 (0- and 12-Month Schedule)							
Visit Identifier Abbreviations used in this table may be found in Appendix 7	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7[a]**
Visit Description	**Vaccination 1**	**1 Month Post–Vaccination 1 Blood Draw**	**Safety Telephone Contact 1**	**Vaccination 2**	**1 Month Post–Vaccination 2 Blood Draw**	**12-Month Antibody Persistence Visit**	**24-Month Antibody Persistence Visit**
Approximate Month	**0**	**1**	**6**	**12**	**13**	**24**	**36**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**168 to 196 Days After Visit 1**	**336 to 394 Days After Visit 1**	**28 to 42 Days After Visit 4**	**336 to 394 Days After Visit 4**	**700 to 756 Days After Visit 4**
Informed consent	X						
Review eligibility criteria	X						
Demography	X						
Confirm continued eligibility[b]		X	X	X	X	X	X
Medical history	X						
Physical examination	X			X			
Record previous PRP-OMP vaccinations	X						
Urine pregnancy test for female participants (obtain results prior to vaccination)	X			X			
Oral temperature (prior to vaccination)	X			X			
Randomization	X						
Obtain blood sample (~25 mL)	X	X			X	X	X

Group 1 (0- and 12-Month Schedule)							
Visit Identifier Abbreviations used in this table may be found in Appendix 7	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7[a]**
Visit Description	**Vaccination 1**	**1 Month Post–Vaccination 1 Blood Draw**	**Safety Telephone Contact 1**	**Vaccination 2**	**1 Month Post–Vaccination 2 Blood Draw**	**12-Month Antibody Persistence Visit**	**24-Month Antibody Persistence Visit**
Approximate Month	**0**	**1**	**6**	**12**	**13**	**24**	**36**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**168 to 196 Days After Visit 1**	**336 to 394 Days After Visit 1**	**28 to 42 Days After Visit 4**	**336 to 394 Days After Visit 4**	**700 to 756 Days After Visit 4**
Study intervention administration and observation[c]	X			X			
Record nonstudy vaccinations[d]		X	X	X	X	X	
Provide the participant with a contact card	X						
Provide the participant with a memory aid		X			X		
Complete Study Visit/Telephone Contact AE Checklist[e]		X	X	X	X	X	X
Record concomitant medications used to treat AEs	X	X	X	X	X	X	X
(S)AE collection appropriate for the visit[f]	X	X	X	X	X	X	X

Note: A safety follow-up telephone contact should occur for all participants who withdraw from the study within 6 months after any vaccination. Refer to Section 8.11.3.

a. Visits 8, 9, and 10 will not be conducted for participants in Group 1.
b. Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements, as appropriate.
c. Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions.
d. Record nonstudy vaccinations as described in Section 6.5.
e. Checklist includes questions regarding NDCMCs, MAEs, and missed days of school or work, as well as neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
f. Please refer to Section 8.3.1.

Group 2 (0- and 36-Month Schedule)								
Visit Identifier Abbreviations used in this table may be found in Appendix 7	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**[a]	**Visit 8**	**Visit 9**	**Visit 10**
Visit Description	**Vaccination 1**	**1 Month Post–Vaccination 1 Blood Draw**	**Safety Telephone Contact 1**	**Vaccination 2**	**1 Month Post–Vaccination 2 Blood Draw**	**Safety Telephone Contact 2**	**Vaccination 3**	**1 Month Post–Vaccination 3 Blood Draw**
Approximate Month	**0**	**1**	**6**	**12**	**13**	**24**	**36**	**37**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**168 to 196 Days After Visit 1**	**336 to 394 Days After Visit 1**	**28 to 42 Days After Visit 4**	**336 to 394 Days After Visit 4**	**700 to 756 Days After Visit 4**	**28 to 42 Days After Visit 9**
Informed consent	X							
Review eligibility criteria	X							
Demography	X							
Confirm continued eligibility[b]		X	X	X	X	X	X	X
Medical history	X							
Physical examination	X			X			X	
Record previous PRP-OMP vaccinations	X							
Urine pregnancy test for female participants (obtain results prior to vaccination)	X			X			X	
Oral temperature (prior to vaccination)	X			X			X	
Randomization	X							
Obtain blood sample (~25 mL)	X	X			X			X
Study intervention administration and observation[c]	X			X			X	
Record nonstudy vaccinations[d]		X	X	X	X	X	X	X
Provide the participant with a contact card	X							
Provide the participant with a memory aid		X			X			
Complete Study Visit/ Telephone Contact AE Checklist[e]		X	X	X	X	X	X	X

Group 2 (0- and 36-Month Schedule)								
Visit Identifier Abbreviations used in this table may be found in Appendix 7	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[a]**	**Visit 8**	**Visit 9**	**Visit 10**
Visit Description	**Vaccination 1**	**1 Month Post–Vaccination 1 Blood Draw**	**Safety Telephone Contact 1**	**Vaccination 2**	**1 Month Post–Vaccination 2 Blood Draw**	**Safety Telephone Contact 2**	**Vaccination 3**	**1 Month Post–Vaccination 3 Blood Draw**
Approximate Month	**0**	**1**	**6**	**12**	**13**	**24**	**36**	**37**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**168 to 196 Days After Visit 1**	**336 to 394 Days After Visit 1**	**28 to 42 Days After Visit 4**	**336 to 394 Days After Visit 4**	**700 to 756 Days After Visit 4**	**28 to 42 Days After Visit 9**
Record concomitant medications used to treat AEs	X	X	X	X	X	X	X	X
(S)AE collection appropriate for the visit[f]	X	X	X	X	X	X	X	X

Note: A safety follow-up telephone contact should occur for all participants who withdraw from the study within 6 months after any vaccination. Refer to Section 8.11.3.

a. Visits 6 and 7 will not be conducted for participants in Group 2.
b. Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements, as appropriate.
c. Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions.
d. Record nonstudy vaccinations as described in Section 6.5.
e. Checklist includes questions regarding NDCMCs, MAEs, and missed days of school or work, as well as neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
f. Please refer to Section 8.3.1.

2. INTRODUCTION

Bivalent rLP2086 (120 µg) and MenACWY-TT (5 µg of each of the 4 meningococcal capsular polysaccharides A, C, W-135, and Y conjugated to 44 µg of tetanus toxoid) are available commercially as Trumenba and Nimenrix, respectively.

Trumenba is composed of 2 recombinant lipidated fHBP variants from MenB, one from fHBP subfamily A (A05) and one from subfamily B (B01), and is indicated for active immunization to prevent invasive disease caused by MenB. Trumenba is approved for use in individuals 10 through 25 years of age in the United States and individuals 10 years of age and older in Europe and other locations.

Nimenrix is composed of capsular polysaccharides from each of the A, C, W, and Y groups of *Neisseria meningitidis* conjugated to tetanus toxoid, is indicated for active immunization of individuals 6 weeks of age and older against IMD caused by *N meningitidis* groups A, C, W-135, and Y, and is approved in Europe and other locations.

Pfizer intends to develop a pentavalent meningococcal vaccine (MenABCWY) by combining bivalent rLP2086 (supplied as a high-fill volume PFS) and MenACWY-TT (supplied as a single-dose vial containing lyophilized powder to be reconstituted for injection); the resultant MenABCWY is administered as a 0.5-mL dose via intramuscular injection. The target indication for the candidate pentavalent vaccine is active immunization to prevent invasive disease caused by *N meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age, regardless of prior exposure to a conjugated ACWY quadrivalent meningococcal vaccine.

2.1. Study Rationale

In Study B1971057, an FIH and POC study for MenABCWY, 543 participants received MenABCWY on a 0- and 6-month schedule. Results from B1971057 indicated MenABCWY, when given on a 0- and 6-month schedule, is well tolerated with an acceptable safety profile and also provides a high degree of protective immune responses without interference among all 5 serogroup components tested. These results are comparable to Phase 2 and 3 bivalent rLP2086 studies, which demonstrate that by increasing the interval between 2 doses, immune responses are enhanced. Study B1971057 also demonstrated that 1 dose of MenACWY-TT (Nimenrix), as a component of MenABCWY, provides protective immune responses in a high proportion of those vaccinated, consistent with Phase 3 data supporting licensure of Nimenrix.

The aim of this Phase 2b descriptive study is to assess the potential utility of MenABCWY in the framework of current US meningococcal vaccination practices, which are based on ACIP recommendations. The ACIP recommends that children 11 to 12 years of age should receive a MenACWY conjugate vaccination with a booster dose at 16 years of age and that adolescents and young adults 16 to 23 years of age may be vaccinated with a 2- or 3-dose series MenB vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. A single dose of MenACWY conjugate provides protection in early adolescence, but the second dose is required to extend that protection into late adolescence

and early adulthood.[1] Therefore, a minimum of 2 doses of an ACWY conjugate vaccine and 2 doses of a serogroup B vaccine are recommended to provide comprehensive protection against IMD in the United States during the specific periods of adolescence and young adulthood when there is an increased risk of IMD. This study is therefore designed to describe the short-term immunogenicity and safety of 2 doses of MenABCWY separated by either 12 or 36 months during adolescence, and immunopersistence up to 24 months after completing 2 doses separated by a 12-month interval, to provide insight as to whether 1 dose of MenABCWY in early adolescence could support a recommendation for serogroups A, C, W, and Y protection during early adolescence followed by a second dose at least 12 to 36 months later to provide protection against all 5 serogroups (A, C, W, Y, and B) during later adolescence and early adulthood. All study participants will receive 1 dose of MenACWY TT (Nimenrix), as a component of MenABCWY at Visit 1 which, as demonstrated in Study B1971057, provides protective immune responses in a high proportion of those vaccinated, consistent with Phase 3 data supporting licensure of Nimenrix. Demonstration of safety and both short-term immunogenicity and longer-term immunopersistence of MenABCWY could provide a simplified 2-dose alternative to the current 4-dose regimen recommended for comprehensive IMD protection in the United States.

Data obtained from prior studies supporting the licensure of the 2 vaccines comprising MenABCWY (Nimenrix and Trumenba) support a favorable benefit-risk assessment for continued study of MenABCWY.

2.2. Background

2.2.1. Background of the Disease and Medical Need

N meningitidis is an obligate human pathogen that colonizes the upper respiratory tract, which, in some individuals, can cause serious, life-threatening IMD, which clinically presents as septicemia, meningitis, or both.[2] *N meningitidis* serogroups A, B, C, W, and Y are 5 of the 6 meningococcal serogroups that cause the vast majority of meningococcal disease globally,[3] and disease incidence is highest in infants and children younger than 5 years of age, adolescents and young adults (16 to 21 years of age), and older adults (≥65 years of age).[4] In the United States, meningococcal disease is primarily caused by groups B, C, W, and Y, which are responsible for approximately 83% of disease across all ages.[5]

Current preventive vaccination strategies generally require separate immunizations at different times for an ACWY conjugate vaccine as well as a separate serogroup B vaccine. In the United States, MenACWY vaccination rates among adolescents 13 to 17 years of age are estimated to be 86.6% for ≥1 dose and 50.8% for ≥2 doses, and MenB vaccination coverage among 17-year-olds approaches only 17.2%.[6] This suggests that adherence to ACIP guidelines for prevention of IMD decreases with increasing age and, for serogroup B, suggests the weakness of the recommendation. This is the trend despite the fact that in the United States, MenB now exceeds all other serogroups in incidence, accounting for about 66% of IMD among individuals 11 to 23 years of age, despite high vaccination rates in targeted adolescents.[5] These data support the idea that all 5 serogroups contribute to disease

in adolescents and young adults and that a multivalent vaccine incorporating serogroup B would have significant public health utility.

A 2-dose MenABCWY vaccination series with at least a 12- to 36-month interval between doses that provides protection against serogroups A, C, W, and Y from early adolescence and protection against serogroup B after the second dose later in adolescence might also provide a simplified approach to comprehensive vaccination against IMD. A 2-dose MenABCWY vaccination series may also lead to increased adherence compared to the current recommendations for MenACWY vaccination in early adolescence, with a booster in late adolescence and a 2-dose MenB vaccination series in later adolescence, requiring a total of 4 doses (2 each of a MenACWY conjugate and a MenB vaccine) to achieve comprehensive protection during adolescence and early adulthood.

Improving vaccination rates for older adolescents and young adults against all 5 serogroups over currently observed rates is particularly important given the recent shifts in disease incidence across age groups. Older adolescents and young adults, particularly those attending college, are clearly at higher risk than their younger counterparts. During 2017, the incidence of IMD in the United States in young adolescents (11 to 15 years of age) was 0.04, while at the same time was much higher, at 0.2, in 16- to 23-year-olds.[5] Although the overall incidence of endemic IMD is quite low, it can rise significantly during epidemics, particularly on US college campuses, where it has been as high as 21.1 to 134 per 100,000 in data reported in 2014.[7,8] These cases of IMD are not inconsequential. Among 7924 cases of IMD occurring in the United States from 2006 through 2015, the overall case fatality rate was 14.9% and, when stratified by adolescent age group, case fatality rates were 11.5% for 11- to 15-year-olds, 14.3% for 16- to 20-year-olds, and 16.7% for 21- to 25-year-olds.[9] Among survivors, significant long-term sequelae, such as limb loss, neurological disability, and deafness, can also occur.[4] A different approach that could provide broader serogroup coverage with 1 vaccine, administered in fewer doses to enhance adherence, could fill some of the gaps encountered with operational implementation of the currently recommended IMD immunization strategy and reduce overall incidence of IMD as well as morbidity and mortality due to IMD among adolescents and young adults in the United States.

This study is designed to evaluate such an approach with investigational pentavalent vaccine, MenABCWY, which could potentially fulfill the unmet need for broader protection with a single vaccine against IMD from early adolescence through young adulthood for serogroups A, C, W, and Y and from late adolescence through early adulthood for serogroup B, that is more durable in the setting of the disease's changing epidemiology.

2.2.2. Prior Clinical Experience

2.2.2.1. Trumenba (Bivalent rLP2086)

Trumenba was approved in the United States on 29 October 2014, under 21 CFR 601 Subpart E - Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses, for active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by MenB.

Trumenba was subsequently approved in the EU on 24 May 2017 for active immunization of individuals 10 years of age and older to prevent IMD caused by MenB. Trumenba has received marketing authorization in 45 countries and is currently marketed in 22 countries.

Approval of Trumenba in the United States was based on the demonstration of safety and a serological correlate that showed in Phase 2 studies the induction of serum bactericidal activity against 4 serogroup B strains that are representative of prevalent US strains. These were measured using hSBAs. As a requirement of licensure, Phase 3 studies were conducted to confirm the safety and immune responses associated with the 3-dose schedule. Subsequently, both Phase 2 studies and 1 Phase 3 study have been conducted to confirm safety and immunogenicity of a 2-dose schedule.

As of 28 April 2019, it is estimated that 23,586 participants have participated in the Trumenba CDP: 12,027 participants were exposed to Trumenba alone; a total of 5202 participants received Trumenba in combination with DTaP-Hib; HBV-IPV/Prevenar® (32); DTaP-IPV (372); HPV4 (992); MCV4-Tdap (884); MenACWY-CRM (1057); or saline (1865); 543 participants received bivalent rLP2086 mixed with MenACWY-TT (Nimenrix) as a single injection in Study B1971057; and 5847 participants received control. The estimated cumulative worldwide unit distribution for Trumenba from launch through 28 April 2019 is approximately 3,367,496 doses.

A licensure persistence-of-immunity and booster study, B1971033, showed that persistence of immunity after the 2- and 3-dose primary Trumenba series schedules utilized in Studies B1971010 and B1971012 follows a similar pattern over 4 years; antibody levels declined by Year 1 and remained stable through Year 4, regardless of the primary series schedule. The immune responses following a booster dose with Trumenba 4 years after the primary Trumenba series resulted in generally higher hSBA titers compared to 1 month following the primary series, irrespective of whether participants received a 2-dose or 3-dose series, demonstrating a robust anamnestic response. Protective hSBA titers (hSBA ≥ LLOQ) also persisted in a high proportion of booster recipients (57.5% to 82.8%, depending on test strain) for up to 2 years after the booster dose.

2.2.2.2. Nimenrix (MenACWY-TT)

Nimenrix was first licensed for use in the EU on 20 April 2012 for the active immunization of individuals 12 months of age and above against IMD caused by *N meningitidis* serogroups A, C, W-135, and Y. On 12 December 2016, the indication of Nimenrix was extended in Europe to infants 6 weeks of age and older. Nimenrix has received marketing authorization in 83 countries and is currently marketed in 59 countries.

Nimenrix is not licensed in the United States, though there is an open IND application. Licensure outside of the United States was based on safety and demonstration of immunologic noninferiority (based mainly on comparing proportions of participants with rSBA of at least 1:8) to licensed meningococcal vaccines.

Cumulatively, it is estimated that 21,520 participants have participated in the Nimenrix CDP. Worldwide distribution for Nimenrix from launch through 19 April 2019 is approximately 16,124,606 doses.

The immunogenicity studies conducted in participants 12 months of age and above demonstrate that 1 dose of MenACWY-TT induces a response that is similar to or higher than the response induced by licensed meningococcal vaccines used as control and that the vaccine is able to induce immunologic memory against the 4 meningococcal serogroups in individuals vaccinated as toddlers 12 to 14 months of age, historically an age group that is not responsive to meningococcal polysaccharide vaccines. Follow-up studies demonstrate that persistence of the responses elicited by the vaccine is similar to or higher than persistence of those elicited by the licensed meningococcal polysaccharide vaccines Meningitec® and Mencevax® when assessed using the GSK rSBA. Additionally, immunopersistence data through 10 years following MenACWY-TT vaccination indicate that a high proportion of vacinees remain protected at that time.

2.2.2.3. Pentavalent Meningococcal Vaccine (MenABCWY)

MenABCWY is an investigational pentavalent meningococcal vaccine consisting of bivalent rLP2086 (supplied as a high-fill volume PFS) and MenACWY-TT, which are administered as a single injection after reconstituting the MenACWY-TT components with the bivalent rLP2086 suspension. MenABCWY has been administered to 543 individuals participating in Study B1971057.

Results from B1971057 demonstrated the immunogenicity and safety of MenABCWY in adolescents and young adults. This was a randomized, active-controlled, observer-blinded multicenter trial in which approximately 1600 participants ≥10 to <26 years of age were randomly assigned to receive either MenABCWY (n=543) on a 0- and 6-month schedule, or Trumenba on a 0- and 6-month schedule and MenACWY-CRM (n=1057) at the same time as the first dose of Trumenba. All participants were naïve to any MenB vaccine prior to enrollment and approximately half were naïve to MenACWY vaccination while the other half were considered ACWY-experienced, having had no more than 1 previous ACWY component vaccine at least 4 years prior to enrollment. Stage 1, which included the vaccination phase of the primary series, is now complete. Stage 2, which evaluates immunopersistence and safety and immunogenicity of a booster dose 4 years after completing the primary series, is ongoing.

Immunogenicity noninferiority evaluations of hSBA responses to the MenACWY component of MenABCWY showed that MenABCWY, both after 1 and 2 doses, was noninferior to a single dose of MenACWY-CRM by 3 different statistical methods for individuals who were either ACWY-naïve or ACWY-experienced. One and 2 doses of MenABCWY were noninferior to 1 dose of MenACWY-CRM. Pertinent to the study described herein, for ACWY-naïve participants, the percentage-of-responder (≥4-fold rise) differences between a single dose of MenABCWY compared to a single dose of MenACWY-CRM were 1.1% (-2.1, 3.7) for serogroup A, 5.5% (-1.3, 11.9) for C, 10.7% (4.9, 16.1) for W, and 14.1% (8.1, 19.7) for Y. Similarly, noninferiority was also established for the ≥4-fold rise in the

percentage of responders after 2 doses of MenABCWY compared to a single dose of MenACWY-CRM for ACWY-naïve participants, for whom the percentage-of-responder differences were 1.1% (-2.2, 3.8) for serogroup A, 26.5% (21.6, 31.1) for C, 21.5% (17.1, 25.8) for W, and 22.9% (17.7, 27.6) for Y. MenABCWY, whether given as a single dose or as a 2-dose series separated by 6 months, was noninferior to a single dose of MenACWY-CRM, regardless of prior ACWY experience.

For the MenB component of MenABCWY, hSBA responses after the second dose were noninferior to those for Trumenba. Noninferiority was established for the percentage of responders who achieved a ≥4-fold rise in hSBA titer over baseline among MenABCWY recipients compared with Trumenba recipients for the 4 primary test strains: A22, A56, B24, and B44.

Reactogenicity data were collected for 7 days following each vaccination by e-diaries, applying the same methodology used in the Trumenba development program. Local and systemic reactogenicity was similar between MenABCWY and Trumenba/MenACWY-CRM recipients, with injection site pain (93.4% vs 91.1%) being the most common local reaction after any vaccination, followed by swelling (26.0% vs 22.4%) and redness (24.5% vs 21.1%). No significant differences among MenABCWY recipients who were considered either ACWY-naïve or ACWY-experienced were observed.

During the vaccination phase (from the first vaccination through 1 month after the second vaccination), similar proportions of participants receiving MenABCWY reported any AE (39.2%) compared to Trumenba + MenACWY-CRM recipients (40.7%), and the 2 groups were also similar between ACWY-naïve and ACWY-experienced MenABCWY recipients. During the same period, similar proportions of participants reported SAEs (1.1% vs 0.8%, respectively), MAEs (26.2% vs 26.7%, respectively), and NDCMCs (0.4% vs 0.8%, respectively). Based on the immunogenicity and safety results from Study B1971057 outlined above, the benefit-risk profile for MenABCWY generated by Phase 2 Study B1971057 is favorable.

2.3. Benefit/Risk Assessment

Common AEs noted after vaccination with Trumenba (licensed in the US, EU, and other countries) and Nimenrix (licensed in the EU and other non-US countries) are primarily related to reactogenicity, including local reactions (pain, swelling, redness around the injection site) and systemic events (headache, fatigue, myalgias, arthralgias, nausea/vomiting, diarrhea, chills, fever). As noted above, the MenABCWY profile from the Phase 2 portion of Study B1971057 is consistent with these 2 licensed products.

As with any vaccine, an allergic reaction may occur. Symptoms of an allergic reaction can include swelling of the lips, mouth, and throat, which may cause difficulty in swallowing or breathing; skin rash; swelling of the hands, feet, and ankles; dizziness; and fainting. A severe allergic shock (anaphylactic shock) may occur. There may also be additional risks related to the vaccines administered in the study that are unknown at this time.

Risks that may be associated with study procedures include risk from blood sampling, such as feeling faint, dizziness, fainting, pain, swelling, bruising, and infection in the vicinity of the vein from where blood is taken.

Safety assessments described in this protocol and ongoing safety data reviews by the investigator, and the sponsor's global medical monitor, the internal safety data review subcommittee, the internal risk management committee, and the E-DMC will serve to monitor and mitigate these risks.

In Phase 2 Study B1971057, MenABCWY provided a high degree of immunologic protection against IMD caused by *N meningitidis* serogroups A, B, C, W, and Y based on the proportions of participants achieving hSBA titers ≥ LLOQ for each serogroup (≥1:8 for serogroups A, C, W, and Y and ≥1:8 or ≥1:16 for serogroup B, depending on the test strain), which are higher than the accepted surrogate marker for protective immunity (hSBA titer ≥1:4). Additionally, MenABCWY was statistically noninferior to Trumenba for the B component and MenACWY-CRM for the ACWY components in both ACWY-naïve participants and ACWY-experienced participants. This Phase 2b study is one of several studies comprising the MenABCWY development program, which if successful, could provide a broadly protective, safe, comprehensive, and first-in-class meningococcal vaccine that could contribute significantly to a simplified vaccination program for the prevention of IMD.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of MenABCWY may be found in the IB, 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) – MenABCWY Vaccination		
Potential risks associated with MenABCWY in the age group for this study include the following: transient injection site pain, injection site redness, injection site swelling, headache, fatigue/drowsiness, muscle pain, joint pain, nausea, vomiting, chills, diarrhea, allergic reactions, decreased/lost appetite, dizziness, fainting, hypoesthesia, pruritus, rash, pain in extremity, injection site hematoma, injection site warmth, injection site anesthesia, and extensive limb swelling at the injection site.	The potential risks are based on product labeling for bivalent rLP2086 and MenACWY-TT and B1971057 FIH study results.	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 the first vaccination or AEs considered by the investigator to present increased risk to the participant if rechallenged with the second vaccination or who develop exclusionary conditions during the conduct of the study will be excluded from further vaccinations.
Study Procedures – Venipuncture		
Venipuncture will be performed during the study.	There is a risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site and an overall risk of dizziness and fainting associated with the procedure.	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. Participants will be placed in the supine position prior to and directly after phlebotomy to minimize risk of dizziness or fainting associated with phlebotomy.

2.3.2. Benefit Assessment

Based on the known degree of protective immunogenicity afforded by licensed vaccines Trumenba and Nimenrix, as well as the data for investigational vaccine MenABCWY from Phase 2 Study B1971057, the potential benefits of participation in this study and receipt of all vaccination doses include potential protection against IMD caused by *N meningitidis* serogroups A, C, W, and Y after a single dose and extended protection for a yet-to-be determined period of time after administration of a second dose 12 to 36 months after the initial dose. Participation in the study and receipt of all scheduled vaccinations will also potentially provide protection against invasive meningococcal B disease after the second dose of MenABCWY.

Other benefits to the individual participant may include physical examination by a medical provider at the start of the study and prior to each study vaccination, 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

Taking into account the measures taken to minimize risk in participants of this study, the potential risks identified in association with MenABCWY primarily include well-established local and systemic vaccination reactions, which are mostly mild to moderate in severity and transient in nature, or minor complications expected from needlesticks (vaccination or venipuncture), and are justified by the anticipated benefits (protective immunity against IMD) that may be afforded to participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 36-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule).	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
Primary Safety:	**Primary Safety:**	**Primary Safety:**

To describe the safety profile of MenABCWY when administered on a 0- and 12-month and a 0- and 36-month schedule.	In participants receiving at least 1 dose of study intervention:
	• The percentage of participants reporting at least 1 AE, at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods:
	  • 30 Days after each vaccination.
	  • 30 Days after any MenABCWY vaccination.
	  • During the Vaccination 1, 2, and 3 vaccination phases:
	  o From Vaccination 1 (Visit 1) through 1 month after Vaccination 1 (Visit 2) in Groups 1 and 2.
		• AEs, SAEs, MAEs, NDCMCs, and immediate AEs.
		• Days missing from school or work because of AEs.

Objectives	Estimands	Endpoints
	○ From Vaccination 2 (Visit 4) through 1 month after Vaccination 2 (Visit 5) in Groups 1 and 2. ○ From Vaccination 3 (Visit 9) through 1 month after Vaccination 3 (Visit 10) in Group 2. • The percentage of participants reporting at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods: • During the follow-up phases: ○ From 1 month after Vaccination 1 (Visit 2) through 6 months after Vaccination 1 (Visit 3) in Groups 1 and 2. ○ From 1 month after Vaccination 2 (Visit 5) through 6 months after Vaccination 2 in Groups 1 and 2. • 6 Months after Vaccinations 1 and 2: ○ From Vaccination 1 (Visit 1) through 6 months after Vaccination 1 (Visit 3) in Groups 1 and 2. ○ From Vaccination 2 (Visit 4) through 6 months after Vaccination 2 in Groups 1 and 2. • The percentage of participants reporting at least 1 immediate AE after each vaccination. • The percentage of participants with missed days of school or work due to AEs occurring within 6 months after Vaccinations 1 and 2 and within 1 month after Vaccination 3.	
Secondary Immunogenicity:	**Secondary Immunogenicity:**	**Secondary Immunogenicity:**
To describe the immune response for MenA, MenC, MenW, and MenY induced by 1 and 2 doses of MenABCWY administered on a 0- and 12-month schedule.	In participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (ie, hSBA titer of ≥1:8) for each ACWY test strain at baseline and	• hSBA titer for each of the MenACWY test strains.

Objectives	Estimands	Endpoints
	1 month after the first dose of MenABCWY in Group 1 (0- and 12-month schedule). In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each ACWY test strain at baseline and 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	
To describe the immune response for MenA, MenC, MenW, and MenY induced by 1 and 2 doses of MenABCWY administered on a 0- and 36-month schedule.	In participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (ie, hSBA titer of ≥1:8) for each ACWY test strain at baseline and 1 month after the first dose of MenABCWY Group 2 (0- and 36-month schedule), In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each ACWY test strain at baseline and 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule).	• hSBA titer for each of the MenACWY test strains.
To describe the persistence of the MenB response following 2 doses of MenABCWY administered on a 0- and 12-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the 4 primary MenB test strains at 12 months and 24 months after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
To describe the persistence of the MenA, MenC, MenW, and MenY response following 2 doses of MenABCWY when	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants):	• hSBA titer for each of the MenACWY test strains.

Objectives	Estimands	Endpoints
administered on a 0- and 12-month schedule.	• The percentage of participants achieving an hSBA titer ≥ LLOQ for each ACWY test strain at 12 and 24 months after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	
Exploratory Immunogenicity:	**Exploratory Immunogenicity:**	**Exploratory Immunogenicity:**
To further describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule). • hSBA GMTs for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule). • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for all 4 primary MenB test strains combined (composite response) at baseline and 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule). • The percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each of the 4 primary MenB test strains at 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule). o For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. o For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ.	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

Objectives	Estimands	Endpoints
	○ For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.	
To further describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 36-month schedule.	In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule). • hSBA GMTs for each of the 4 primary MenB test strains at baseline, 13 months after the first dose of MenABCWY, and 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule). • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for all 4 primary MenB test strains combined (composite response) at baseline and 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule). • The percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each of the 4 primary MenB test strains at 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule). ○ For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. ○ For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ.	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

Objectives	Estimands	Endpoints
	○ For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer. • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the 4 primary MenB test strains at 13 months after the first dose of MenABCWY in Group 2 (0- and 36-month schedule).	
To further describe the immune response for MenA, MenC, MenW, and MenY induced by 1 and 2 doses of MenABCWY administered on a 0- and 12-month schedule.	In participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • hSBA GMTs for each ACWY test strain at baseline and 1 month after the first dose of MenABCWY in Group 1 (0- and 12-month schedule). • The percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain at 1 month after the first dose of MenABCWY in Group 1 (0- and 12-month schedule). ○ For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. ○ For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ. ○ For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer. In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • hSBA GMTs for each ACWY test strain at baseline and 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule).	• hSBA titer for each of the MenACWY test strains.

Objectives	Estimands	Endpoints
	• The percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain at 1 month after the second dose of MenABCWY in Group 1 (0- and 12-month schedule). o For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. o For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ. o For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.	
To further describe the immune response for MenA, MenC, MenW, and MenY induced by 1 and 2 doses of MenABCWY administered on a 0- and 36-month schedule.	In participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • hSBA GMTs for each ACWY test strain at baseline, 1 month after the first dose of MenABCWY, and 13 months after the first dose of MenABCWY in Group 2 (0- and 36-month schedule). • The percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain at 1 month after the first dose of MenABCWY in Group 2 (0- and 36-month schedule). o For participants with a baseline hSBA titer below LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. o For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ.	• hSBA titer for each of the MenACWY test strains.

Objectives	Estimands	Endpoints
	○ For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer. • The percentage of participants achieving an hSBA titer ≥ LLOQ for each ACWY test strain at 13 months after the first dose of MenABCWY in Group 2 (0- and 36-month schedule). In participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • hSBA GMTs for each ACWY test strain at baseline and 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule). • The percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain at 1 month after the second dose of MenABCWY in Group 2 (0- and 36-month schedule). ○ For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. ○ For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ. ○ For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, randomized, observer-blinded, multicenter trial in which approximately 300 US participants ≥11 to <15 years of age will be randomly assigned at a 1:1 ratio to receive MenABCWY either on a 0- and 12-month schedule (Group 1) or a 0- and 36-month schedule (Group 2) as shown in Section 1.2. All participants will be naïve to any meningococcal vaccine prior to enrollment.

Participants will have blood drawn prior to Vaccination 1 and 1 month after each vaccination. Additionally, to facilitate the description of antibody persistence after 2 doses of MenABCWY, participants in Group 1 (0- and 12-month schedule) will have blood drawn at 12 and 24 months after the second dose of MenABCWY. The sponsor will be blinded to dosing schedule assignment through Month 13 (1 month after the second dose of MenABCWY in Group 1 [0- and 12-month schedule]), after which the dosing schedule assignment for all participants will be unblinded. The second dose of MenABCWY in Group 2 (0- and 36-month schedule) will be administered in an open-label manner.

4.1.1. Approximate Duration of Participation for Each Participant

Each participant will participate in the study for approximately 37 months.

4.1.2. Approximate Number of Participants

Approximately 300 participants will be enrolled in the study.

4.2. Scientific Rationale for Study Design

In Study B1971057, an FIH and POC study for MenABCWY, 543 participants received MenABCWY on a 0- and 6-month schedule. Results from Study B1971057 indicated MenABCWY is well tolerated with an acceptable safety profile and also provides a high degree of protective immune responses without interference among all 5 serogroup components tested.

The aim of this Phase 2b study is to describe the immunogenicity and safety of 2 doses of MenABCWY separated by either 12 or 36 months during adolescence, and the persistence of bactericidal responses up to 24 months after completing 2 doses of MenABCWY separated by a 12-month interval, to provide insight as to whether 1 dose of MenABCWY in early adolescence (≥11 to <15 years of age) could meet safety and immunogenicity requirements to support a recommendation for serogroups A, C, W, and Y protection during early adolescence, followed by a second dose at least 12 to 36 months later to provide protection against all 5 serogroups (A, C, W, Y, and B) during later adolescence (≥15 to <19 years of age). This will allow us to assess the potential utility of MenABCWY in the framework of current US meningococcal vaccination practices, which are based on ACIP recommendations. Demonstration of safety and both short-term immunogenicity and longer-term immunopersistence of MenABCWY could provide a simplified 2-dose

alternative to the current 4-dose regimen recommended for comprehensive IMD protection in the United States.

Refer to Section 2.1 for further detail about the rationale of the study design.

Data obtained from prior studies evaluating MenABCWY, MenACWY-TT (Nimenrix), and bivalent rLP2086 (Trumenba) support a favorable benefit-risk assessment for continued study of MenABCWY.

Bivalent rLP2086 and MenACWY-TT are approved for active immunization against IMD caused by serogroup B and ACWY, respectively, without any contraceptive precautions. There is no suspicion of human genotoxicity or teratogenicity based on the intended pharmacology and World Health Organization guidance.[10] The same is expected for both products when administered together as a single dose of MenABCWY. See Appendix 4 for contraceptive requirements.

4.3. Justification for Dose

Bivalent rLP2086 (120 µg, meningococcal group B vaccine) and MenACWY-TT (5 µg of each of the 4 meningococcal capsular polysaccharides A, C, W-135, and Y conjugated to 44 µg of tetanus toxoid) are available commercially as Trumenba and Nimenrix, respectively. Trumenba is indicated for active immunization to prevent invasive disease caused by MenB and is approved for use in Europe in individuals 10 years of age and older and in the US in individuals 10 through 25 years of age. Nimenrix is indicated for active immunization to prevent invasive disease caused by MenA, MenC, MenW, and MenY and is approved for use in Europe and a number of ex-US countries in individuals 6 weeks of age and older. Trumenba is supplied as a 0.5-mL dose PFS, while Nimenrix is supplied as a single-dose vial containing lyophilized powder to be reconstituted for injection.

MenABCWY consists of bivalent rLP2086, supplied as a high-fill volume PFS, which is used to reconstitute MenACWY-TT, and 0.5 mL of the resultant MenABCWY is administered via intramuscular injection.

The safety, tolerability, and immunogenicity of Trumenba and Nimenrix when used separately are well established in adolescents and young adults. Results from Study B1971057, which evaluated MenABCWY on a 0- and 6-month schedule in adolescents and young adults, showed no clinically significant difference in the tolerability or safety of MenABCWY when compared with Trumenba. Furthermore, no interference was demonstrated for either MenB or ACWY responses when compared with licensed vaccines Trumenba and Menveo in the United States and the EU. Therefore, Pfizer is proceeding with adolescent and adult Phase 3 development of MenABCWY with the dose used in Study B1971057.

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 participants ≥11 through <15 years of age at the time of randomization.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Participants who have never received a prior dose of any meningococcal vaccine. Written confirmation of vaccination history must be obtained prior to randomization.

4. Available for the entire study period and can be reached by telephone.

5. Healthy participant as determined by medical history, physical examination, and judgment of the investigator.

6. Male and female participants of childbearing potential must agree to use a highly effective method of contraception for at least 28 days after the last study vaccination. A participant is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active (Appendix 4).

7. Negative urine pregnancy test for all female participants; pregnancy test is not applicable to male participants.

Informed Consent:

8. Participants whose parent(s)/legal guardian 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. A known or suspected defect of the immune system that would prevent an immune response to the vaccine, such as participants with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, intravenous, or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy. Participants with terminal complement deficiency are excluded from participation in this study. Please refer to the ISF for additional details.

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

5. Significant neurological disorder or history of seizure (excluding simple febrile seizure).

6. Any neuroinflammatory or autoimmune condition, including, but not limited to, transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.

7. Recent (within the past year) hospitalization for psychiatric illness.

8. Other medical or psychiatric condition, including recent (within the past year) 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.

Prior/Concomitant Therapy:

9. Participants receiving any allergen immunotherapy with a nonlicensed product or receiving allergen immunotherapy with a licensed product and are not on stable maintenance doses.

10. Receipt of any blood products, including immunoglobulin, within 6 months before the first study vaccination.

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

Prior/Concurrent Clinical Study Experience:

12. 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:

13. Children or grandchildren who are direct descendants of investigational site staff members or Pfizer employees directly involved in the conduct of the study.

14. Pregnant female participants; breastfeeding female participants; fertile male participants and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant's parent(s)/legal guardian, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

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

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

5.5.1. Criteria for Temporarily Delaying Vaccine Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the conditions have resolved and the participant is eligible for vaccination:

1. Current febrile illness (temperature ≥38.0°C [100.4°F]) or other acute illness within 48 hours before study intervention administration.

2. Participant has received any nonlive vaccine (or intramuscular/sublingual allergen immunotherapy) within 14 days, or any live vaccine within 28 days, before study intervention administration.

3. Participant is less than 5 days into a course of systemic antibiotic therapy.

4. Participant has received systemic (oral, intravenous, or intramuscular) corticosteroid therapy within the previous 28 days.

If a participant meets any delay criteria for vaccination, all study procedures, including blood sample collection relating to that visit, if required, should be delayed until the day of vaccination. When required, blood samples must always be collected prior to vaccination, on the day of vaccination.

5.5.2. Criteria for Temporarily Delaying Immunogenicity Blood Draw

The following condition is temporary or self-limiting, and blood may be drawn once the condition has resolved and the participant is eligible for blood collection:

1. Participant has received systemic antibiotic therapy within the last 5 days (must have a full 5-day interval between the date of the last dose and the 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, study intervention refers to MenABCWY, consisting of bivalent rLP2086 and MenACWY-TT (Nimenrix), or placebo.

6.1. Study Intervention(s) Administered

MenACWY-TT, supplied as a single-dose vial containing lyophilized powder, will be reconstituted with bivalent rLP2086 supplied as a high-fill volume PFS, as detailed in the IP manual, and 0.5 mL of the resultant MenABCWY will be administered via intramuscular injection. The final MenABCWY composition includes rLP2086 subfamily A and B proteins formulated at 120 µg/mL/subfamily, purified capsular polysaccharides of

N meningitidis serogroups A, C, W, and Y at a concentration of 10 µg/mL/polysaccharide type conjugated to tetanus toxoid [redacted], in [redacted] histidine [redacted] sodium chloride, 0.5 mg/mL aluminum as $AlPO_4$, 0.035 mg/mL polysorbate 80, and [redacted] sucrose.

The placebo is sterile normal saline solution for injection and will be administered as a 0.5-mL intramuscular injection.

Intervention Name	MenABCWY	Placebo (Normal Saline)
Dose Formulation	MenACWY-TT will be reconstituted with bivalent rLP2086, supplied as a high-fill volume PFS	Sterile normal saline solution for injection
Dosage Level(s)	0.5-mL dose at Visits 1 and 4 (Group 1) or at Visits 1 and 9 (Group 2)	0.5-mL dose at Visit 4 (Group 2)
Route of Administration	Intramuscular	Intramuscular
IMP or NIMP	IMP	IMP
Sourcing	Pfizer	Pfizer
Packaging and Labeling	Each MenABCWY kit will consist of a vial of MenACWY-TT, bivalent rLP2086 high-fill volume PFS, and vial adaptor. Kits will be packaged in a carton and labeled as required per country requirement. Kits provided for Visits 1 and 4 will include a blinded label and a tamper evident seal. Kits provided for Visit 9 will include an open label and a tamper evident seal.	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton and labeled as required per country requirement. Kits provided for Visit 4 will include a blinded label and a tamper evident seal.

6.1.1. 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.

Table 1 describes the administration details for each vaccine. Each vaccine will be administered as a 0.5-mL dose in the upper deltoid muscle of the left or right arm.

Table 1. Study Intervention Administration Schedule

Study Intervention	Group(s)	Visit(s)
MenABCWY	1	1 and 4
MenABCWY	2	1 and 9
Placebo	2	4

6.1.2. Medical Devices

1. In this study, medical devices being used will be the vial adaptor and PFS for MenABCWY and the PFS only for placebo.

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 unblinded personnel throughout the clinical investigation (see Section 8.3.6) and appropriately managed by the sponsor.

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 to the study site after required regulatory and legal documents have been received by the sponsor. These will be shipped at +2°C to +8°C. 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 once reconstituted.

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. Used needles and syringes should be disposed of according to local practice. 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.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an unblinded, appropriately qualified, 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. All participants will remain blinded to whether they received MenABCWY or placebo at Vaccination 2 through and including Visit 5 (1 month after Vaccination 2). All participants will be unblinded prior to the time that Group 2 participants receive the second dose of MenABCWY at Month 36 in an open-label manner.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system that is accessible 24 hours a day, 365 days a year. Having logged in, the site personnel (study coordinator or specified designee) will be required to enter or select certain information, including, but not limited to, the user's ID and password, protocol number, participant number, and date of birth of the participant. The site personnel will then be provided with a participant randomization number and DU or container number. The randomization number and the date on which the randomization number was assigned will be recorded on the CRF. Once participant numbers, DU numbers, and randomization numbers have been assigned, they cannot be reassigned. The IRT system will provide a confirmation report containing the participant randomization number and DU or container number assigned. The confirmation report must be stored in the site's files.

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

6.3.2. Blinding of Site Personnel

In this observer-blinded study, the study staff dispensing, preparing, and administering the vaccine will be unblinded. All other study and site personnel, including the investigator, investigator staff, participants, and participants' parent(s)/legal guardian, will be blinded to study intervention assignments through and including Visit 5 (Vaccinations 1 and 2). In particular, the individuals who evaluate participant safety will be blinded. Because the study vaccine and placebo are different in physical appearance, the study vaccine syringes will be administered in a manner that prevents the study participants from identifying the vaccine type based on its appearance. The second dose of MenABCWY for participants in Group 2 (Vaccination 3) will be given in an open-label manner.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). An unblinded clinician who is not a direct member of the study team will review unblinded protocol deviations. All other study team members will remain blinded to the vaccine assigned/received through and including Visit 5 (1 month after Vaccination 2). All laboratory testing personnel performing serology assays will remain blinded to vaccine assigned/received and to visit number throughout the study.

6.3.4. Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should only be broken in emergency situations for reasons of participant safety.

In case of an emergency, when knowledge of the study intervention assignment is required for the medical management of an individual participant, it may be unblinded. The investigator must notify a member of the study team immediately after determining that it is necessary to unblind the assignment. The investigator must also indicate in source documents that the blind was broken and provide the date and reason for breaking the blind. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

6.3.5. Planned Unblinding

Pfizer will release unblinding information to the investigators after all participants have completed the blood draw at Visit 5 (1 month after the second dose of MenABCWY in Group 1 [0- and 12-month schedule] or 1 month after placebo in Group 2 [0- and 36-month schedule]). Additional information is included in the ISF.

The second dose of MenABCWY in Group 2 (0- and 36-month schedule) will be administered in an open-label manner.

6.4. Study Intervention Compliance

All doses of study intervention will be administered by the appropriately 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 approximately 6 months after Vaccinations 1 and 2, within approximately 1 month after Vaccination 3 (Group 2 only), and within 28 days before administration of study intervention at Visit 4 and Visit 9 will be recorded on the CRF. The name and date of administration for any nonstudy meningococcal vaccine received, which is exclusionary, will be collected from the signing of the ICD up to the end of study participation.

The name, start and stop dates, and route of administration for concomitant medications (prescription and nonprescription) used to treat an AE from the signing of the ICD to the final visit will be recorded in the CRF.

6.5.1. Prohibited During the Study

- Receipt of any blood products, including immunoglobulin, in the period 6 months before any blood draw.

- Nonstudy meningococcal vaccines.

- Nonlive or live nonstudy vaccines are not permitted 14 and 28 days, respectively, before or after any study vaccination.

- Intramuscular/sublingual allergen immunotherapy is not permitted within 14 days before or after any study vaccination.

- Systemic (oral, intravenous, or intramuscular) corticosteroid therapy within 28 days before or after any study vaccination.

6.5.2. Permitted During the Study

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed. In such situations, effort should be made to appropriately plan the administration of study intervention around dosing of the pandemic vaccine.

- Nonstudy vaccines (other than any meningococcal vaccines) that are part of recommended immunization schedules are allowed anytime during the study but should not be administered within 14 days (for nonlive vaccines) and 28 days (for live vaccines) before or after administration of study intervention.

- Antipyretic and other pain medication to treat symptoms following administration of study intervention is permitted.

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

- Topical antibiotics are permitted.

- Topical and inhaled corticosteroids are permitted.

- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

6.5.3. Prior Treatments

If the participant is known to have ever received a PRP-OMP vaccine, the name of the vaccine and date of administration will be recorded on the CRF.

6.5.4. Prohibited Prior Treatments

Receipt of any blood products, including immunoglobulin, within 6 months before the first study vaccination.

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 or participant request; 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 the collection of safety information. See the SoA and Section 8.11.3 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.

Premature termination of this study may occur because of a regulatory authority decision, change in the opinion of the IRB/EC, or study intervention safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of MenABCWY at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact the parent(s)/guardian of all participants and the hospital pharmacy (if applicable) immediately. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

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:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Parent(s)/legal guardian or participant request;

- Protocol violation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant's parent(s)/legal guardian. All attempts to contact the parent(s)/legal guardian 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 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, his/her parent(s)/legal guardian 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 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.

A final telephone contact 6 months after the last vaccination (Section 8.11.3) for the collection of safety information should be completed for all participants who withdraw or have been withdrawn within 6 months after administration of study intervention, unless consent for further contact has been withdrawn or the participant is lost to follow-up. Participant withdrawal should be explained in the source documents and should include whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or postvaccination study follow-up.

If the participant is withdrawn from the study and his/her parent(s)/legal guardian 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.

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.

7.2.1. Withdrawal of Consent

Participants whose parent(s)/legal guardian requests to discontinue 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 specifically withdraws consent for any further contact with him or her or persons previously authorized by the parent(s)/legal guardian to provide this information. The participant's parent(s)/legal guardian 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 is unable to be contacted by the study site.

The following actions must be taken if a participant's parent(s)/legal guardian fails to respond to a safety telephone call or return to the clinic for a required study visit:

- The site must attempt to contact the participant's parent(s)/legal guardian and reschedule the missed visit as soon as possible and counsel the participant's parent(s)/legal guardian on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant's parent(s)/legal guardian wishes for the participant 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 (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 continue to be unreachable, the participant 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 complete 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. Options for alternative measures that may be taken for some study visits in case of a public emergency are described in Appendix 8.

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.

The total blood sampling volume for individual participants in this study is approximately 125 mL for Group 1 (0- and 12-month schedule) and 100 mL for Group 2 (0- and 36-month schedule). The actual collection times of blood sampling may change.

8.1. Efficacy and/or Immunogenicity Assessments

To facilitate immunogenicity analyses, participants will have approximately 25 mL of blood collected at 4 or 5 visits during the study as described in Section 8.11 and the SoA. Sera obtained at all study visits will be used in immunogenicity assays. LOD and LLOQ titers for these assays will be detailed in the SAP.

8.1.1. MenA, MenC, MenW, and MenY Serum Bactericidal Assays

For assessment of the immune response to the ACWY components of MenABCWY, test strains specific for each of the ACWY groups (A [PMB277], C [PMB3204], W [PMB6270], Y [PMB3385]) will be used in the hSBAs for determination of the immunogenicity endpoints in this study. Sera obtained from participants in Groups 1 and 2 at all study visits will be used in hSBAs for the ACWY test strains.

8.1.2. MenB Serum Bactericidal Assays

For assessment of the immune response to the B component of MenABCWY, 4 primary MenB test strains, PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), will be used in the hSBAs for determination of the immunogenicity endpoints in this study.

Sera obtained from participants in Group 1 at Visits 1, 5, 6, and 7, and from participants in Group 2 at Visits 1, 5, and 10 will be used in hSBAs for the 4 primary MenB test strains.

8.1.3. Biological Samples

Blood 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 or the participant's parent(s)/legal guardian 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.

A mechanism (eg, appropriate wording within the study ICD) will be established that enables testing of serum samples obtained during the study to assess for the preexistence of select AEs reported during study participation.

8.2. Safety Assessments

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.

Any participant who receives at least 1 dose of study intervention will be included in the evaluation for safety. The following safety parameters will be assessed as described in Section 8.11 and in the SoA:

- Physical examination;
- AEs and SAEs.

A medical history will be obtained, and a physical examination will be performed on all participants at Visit 1 to establish a baseline. When taking the medical history and performing the physical examination, particular care must be taken to note any neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Significant medical history and observations from the physical examination will be documented on the CRF. In addition, a urine pregnancy test will be performed on all female participants.

Immediate AEs, defined as AEs occurring within the first 30 minutes after study intervention administration, will be assessed and documented on the AE CRF. The time of onset will be recorded for any AEs that occur on the same day as study intervention administration.

MAEs and NDCMCs will also be assessed throughout the study and documented on the appropriate AE CRF. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. 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.

AEs (serious and nonserious), NDCMCs, and visits to other medical facilities will be assessed at study visits as specified in the SoA and reported as defined in Section 8.3. AE-related hospitalizations, visits to other medical facilities, medication use, and days of school or work missed will be collected and recorded in the CRF. Hospitalizations and visits to medical facilities not associated with an AE, such as elective hospitalizations, healthcare visits for preventive care, or routine physical examinations, will not be collected. Non–AE-related concomitant medications and days of school or work missed not associated with an AE will not be collected. A Study Visit/Telephone Contact AE Checklist will be used as a guide, completed at each scheduled study visit/telephone contact after Visit 1, and included in the source documentation. Please refer to the ISF for details.

The participant's parent(s)/legal guardian will be given a memory aid at Visits 2 and 5. The memory aid will be used to remind parent(s)/legal guardian to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The parent(s)/legal guardian may use the memory aid as needed during the telephone contact at Visits 3 and 8 or the follow-up visits at Visits 6, 7, and 10 to prompt recall of events. These may be used to assist in reporting and discussion of events with study staff, but these memory aids will not be considered source documents and will not be collected at study visits. Only information collected by study staff as part of a study visit or telephone contact will be included in the source documents and entered into the CRF.

In addition, AEs and SAEs will be collected as defined in Section 8.3.

8.2.1. Pregnancy Testing

Urine pregnancy tests will have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in all female participants at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study for safety follow-up.

In the case of a positive confirmed pregnancy at Visit 1, the participant will not be eligible for participation.

8.3. Adverse Events and Serious Adverse Events

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 6. Device deficiencies are covered in Section 8.3.6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent[s]/legal guardian).

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/parent/legal guardian 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

For all participants, information about AEs will be collected for events occurring within approximately 1 month after each vaccination, and information about SAEs, including hospitalizations, MAEs, and NDCMCs, will be collected for events occurring approximately 6 months after Vaccinations 1 and 2, and within approximately 1 month after Vaccination 3. Information about AEs and SAEs, including hospitalizations and MAEs will be collected for events occurring within 48 hours after each antibody persistence blood draw.

Details for the collection of AE and SAE information for participants in each vaccine group are described below.

Group 1 (0- and 12-month schedule)

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 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 (1 month after the first dose of MenABCWY), and from Visit 4 (second dose of MenABCWY) to Visit 5 (1 month after the second dose of MenABCWY).

At Visit 3 (safety telephone contact), the participant's parent(s)/legal guardian will be contacted by telephone to inquire about SAEs, MAEs, and NDCMCs since Visit 2.

At Visit 6 (12-month antibody persistence visit), information about SAEs, MAEs, and NDCMCs will be collected for events within 6 months after Visit 4 (second dose of MenABCWY).

During the antibody persistence phase (Visits 6 and 7), information about AEs and SAEs, including hospitalizations and MAEs, will be collected for events occurring within 48 hours after each antibody persistence blood draw.

AE collection for Group 1 (0- and 12-month schedule) is summarized in Table 2.

Group 2 (0- and 36-month schedule)

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 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 (1 month after the first dose of MenABCWY), and from Visit 4 (placebo dose) to Visit 5 (1 month after the placebo dose) and from Visit 9 (second dose of MenABCWY) to Visit 10 (1 month after the second dose of MenABCWY).

At Visit 3 (safety telephone contact), the participant's parent(s)/legal guardian will be contacted by telephone to inquire about SAEs, MAEs, and NDCMCs since Visit 2.

At Visit 8 (safety telephone contact), the participant's parent(s)/legal guardian will be contacted by telephone to inquire about SAEs, MAEs, and NDCMCs within 6 months after Visit 4 (placebo dose).

AE collection for Group 2 (0- and 36-month schedule) is summarized in Table 3.

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 or withdrawn early from 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.

Table 2. Summary of Adverse Event Collection for Group 1 (0- and 12-Month Schedule)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]
Visit Description	**Vaccination 1**	**1 Month Post–Vaccination 1 Blood Draw**	**Safety Telephone Contact 1**	**Vaccination 2**	**1 Month Post–Vaccination 2 Blood Draw**	**12-Month Antibody Persistence Visit**	**24-Month Antibody Persistence Visit**
Approximate Month	**0**	**1**	**6**	**12**	**13**	**24**	**36**
Nonserious AEs	←	→		←	→	Within 48 hours after blood draw	Within 48 hours after blood draw
SAEs	←	→		←	→ [b,c]		Within 48 hours after blood draw
MAEs	←	→		←	→ [b,c]		Within 48 hours after blood draw
NDCMCs	←	→		←	→ [b]		

Note: The arrows represent the time periods for safety data collection.
a. Visits 8, 9, and 10 will not be conducted for Group 1 participants.
b. Events occurring within 6 months after Vaccination 2.
c. Events occurring within 48 hours after the Visit 6 blood draw.

Table 3. Summary of Adverse Event Collection for Group 2 (0- and 36-Month Schedule)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 8	Visit 9	Visit 10
Visit Description	**Vaccination 1**	**1 Month Post–Vaccination 1 Blood Draw**	**Safety Telephone Contact 1**	**Vaccination 2**	**1 Month Post–Vaccination 2 Blood Draw**	**Safety Telephone Contact 2**	**Vaccination 3**	**1 Month Post–Vaccination 3 Blood Draw**
Approximate Month	**0**	**1**	**6**	**12**	**13**	**24**	**36**	**37**
Nonserious AEs	◄——►			◄——►			◄——►	
SAEs	◄——►			◄——► [b]			◄——►	
MAEs	◄——►			◄——► [b]			◄——►	
NDCMCs	◄——►			◄——► [b]			◄——►	

Note: The arrows represent the time periods for safety data collection.

a. Visits 6 and 7 will not be conducted for participants in Group 2.

b. Events occurring within 6 months after Vaccination 2..

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 period, 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's parent(s)/legal guardian.

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's parent(s)/legal guardian 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 toward 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, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and 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 participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- 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 EDP:
    - 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 a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until the pregnancy is completed (or terminated) for pregnancies that initiate within 6 months after administration of study intervention.

- 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 investigator site file.

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 investigator site file.

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 investigator site file.

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 is reportable to Pfizer Safety only if associated with an SAE.

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 unblinded site staff are 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 6.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Sections 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 6.

8.3.9.2. Follow-up of Medical Device Deficiencies

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

The unblinded site staff are 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 unblinded site staff.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the unblinded site staff determine 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.

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 Section 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 study settings 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.

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.

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.**

8.4. Treatment of Overdose

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

Pfizer 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

Immunogenicity assessments are described in 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

8.11.1. Group 1 (0- and 12-Month Schedule)

8.11.1.1. Visit 1 (Day 1), Vaccination 1

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Obtain written informed consent, and assent if appropriate, before performing study-specific procedures. The date of informed consent will be recorded on the CRF.
- Record the participant's demographic information (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.
- Record previous PRP-OMP vaccinations as described in Section 6.5.3.
- Perform a physical examination 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 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.
- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of vaccination, prior to administration of study intervention, measure and record the participant's oral temperature.
- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.

- If a participant is eligible for the study, assign a randomization number and an investigational product container number via the IRT, or an equivalent system.

- On the day of vaccination, prior to administration of study intervention, collect a blood sample (approximately 25 mL). Collect the blood sample only if the participant is eligible for vaccination on the same day.

- The unblinded administrator administers a single 0.5-mL intramuscular injection of MenABCWY into the upper deltoid muscle of the arm. The time of study intervention administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).

- Record AEs as described in Section 8.3 and the SoA. Time of onset will be recorded for any AEs that occur on the same day as study intervention administration.

- Record concomitant medications used to treat AEs as described in Section 6.5.

- Provide the parent(s)/legal guardian with a contact card (Section 10.1.10).

- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.

- Complete the CRF, and update the study intervention accountability records.

8.11.1.2. Visit 2, Month 1 (1 Month [28 to 42 Days] After Visit 1), 1-Month Post–Vaccination 1 Blood Draw

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.

- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of blood draw criteria as described in Section 5.5.2.

- Complete the Study Visit/Telephone Contact AE Checklist to:

  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.

  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.

- Record AEs as described in Section 8.3 and the SoA.

- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.

- Record concomitant medications used to treat AEs as described in Section 6.5.

- Record nonstudy vaccinations as described in Section 6.5.

- Collect a blood sample (approximately 25 mL).

- Provide the parent(s)/legal guardian with a memory aid. Instruct the parent(s)/legal guardian to use the memory aid between Visits 2 and 3 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF for additional details.

- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule a telephone contact, and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.

- Complete the CRFs.

8.11.1.3. Visit 3, Month 6 (6 Months [168 to 196 Days] After Visit 1), Safety Telephone Contact 1

- Contact the parent(s)/legal guardian by telephone.

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.

- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7.

- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.11.1.4. Visit 4, Month 12 (12 Months [336 to 394 Days] After Visit 1), Vaccination 2

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of vaccination criteria as described in Section 5.5.1.
- Perform a brief physical examination of the participant's general appearance, skin, ears, throat, heart, lungs, abdomen, and lymph nodes. Record any AEs as described in Section 8.3.
- Complete the Study Visit/Telephone Contact AE Checklist to:

  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.

  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.

- Record AEs as described in Section 8.3 and the SoA. Time of onset will be recorded for any AEs that occur on the same day as study intervention administration.

- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.

- Record concomitant medications used to treat AEs as described in Section 6.5.

- Record nonstudy vaccinations as described in Section 6.5.

- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the study intervention.

- On the day of vaccination, prior to administration of study intervention, measure and record the participant's oral temperature.

- The unblinded administrator administers a single 0.5-mL intramuscular injection of MenABCWY into the upper deltoid muscle of the arm. The time of study intervention administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).

- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.

- Complete the CRFs.

8.11.1.5. Visit 5, Month 13 (1 Month [28 to 42 Days] After Visit 4), 1-Month Post–Vaccination 2 Blood Draw

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of blood draw criteria as described in Section 5.5.2.
- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect a blood sample (approximately 25 mL).
- Provide the parent(s)/legal guardian with a memory aid. Instruct the parent(s)/legal guardian to use the memory aid between Visits 5 and 6 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF for additional details.
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.

- Complete the CRFs.

8.11.1.6. Visit 6, Month 24 (12 Months [336 to 394 Days] After Visit 4), 12-Month Antibody Persistence Visit

Visit 6 must not be performed until the investigator is unblinded. The Visit 6 window may be extended for individual participants by up to 60 days, at the discretion of the sponsor, to ensure unblinded information is available.

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of blood draw criteria as described in Section 5.5.2.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect a blood sample (approximately 25 mL).
- Ask the parent(s)/legal guardian to contact the investigator about any AEs occurring during the 48-hour period after the blood draw.
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.
- Complete the CRFs.

8.11.1.7. Visit 7, Month 36, (24 Months [700 to 756 Days] After Visit 4), 24-Month Antibody Persistence Visit

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of blood draw criteria as described in Section 5.5.2.
- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Collect a blood sample (approximately 25 mL).
- Ask the parent(s)/legal guardian to contact the investigator about any AEs occurring during the 48-hour period after the blood draw.
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Complete the source documents.
- Complete the CRFs.

8.11.2. Group 2 (0- and 36-Month Schedule)

8.11.2.1. Visit 1 (Day 1), Vaccination 1

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Obtain written informed consent, and assent if appropriate, before performing study-specific procedures. The date of informed consent will be recorded on the CRF.
- Record the participant's demographic information (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.
- Record previous PRP-OMP vaccinations as described in Section 6.5.
- Perform a physical examination 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 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.
- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of vaccination, prior to administration of study intervention, measure and record the participant's oral temperature.
- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- If a participant is eligible for the study, assign a randomization number and an investigational product container number via the IRT, or an equivalent system.
- On the day of vaccination, prior to administration of study intervention, collect a blood sample (approximately 25 mL). Collect the blood sample only if the participant is eligible for vaccination on the same day.

- The unblinded administrator administers a single 0.5-mL intramuscular injection of MenABCWY into the upper deltoid muscle of the arm. The time of study intervention administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).

- Record AEs as described in Section 8.3 and the SoA. Time of onset will be recorded for any AEs that occur on the same day as study intervention administration.

- Record concomitant medications used to treat AEs as described in Section 6.5.

- Provide the parent(s)/legal guardian with a contact card (Section 10.1.10).

- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.

- Complete the CRF, and update the study intervention accountability records.

8.11.2.2. Visit 2, Month 1 (1 Month [28 to 42 Days] After Visit 1), 1-Month Post–Vaccination 1 Blood Draw

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.

- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of blood draw criteria as described in Section 5.5.2.

- Complete the Study Visit/Telephone Contact AE Checklist to:

  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.

  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.

- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect a blood sample (approximately 25 mL).
- Provide the parent(s)/legal guardian with a memory aid. Instruct the parent(s)/legal guardian to use the memory aid between Visits 2 and 3 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF for additional details.
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule a telephone contact, and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.11.2.3. Visit 3, Month 6 (6 Months [168 to 196 Days] After Visit 1), Safety Telephone Contact 1

- Contact the parent(s)/legal guardian by telephone.
- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.

- Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.

- Record AEs as described in Section 8.3 and the SoA.

- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.

- Record concomitant medications used to treat AEs as described in Section 6.5.

- Record nonstudy vaccinations as described in Section 6.5.

- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.

- Complete the CRFs.

8.11.2.4. Visit 4, Month 12 (12 Months [336 to 394 Days] After Visit 1), Vaccination 2

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.

- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of vaccination criteria as described in Section 5.5.1.

- Perform a brief physical examination of the participant's general appearance, skin, ears, throat, heart, lungs, abdomen, and lymph nodes.

- Complete the Study Visit/Telephone Contact AE Checklist to:

  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.

  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.

- Record AEs as described in Section 8.3 and the SoA. Time of onset will be recorded for any AEs that occur on the same day as study intervention administration.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the study intervention.
- On the day of vaccination, prior to administration of study intervention, measure and record the participant's oral temperature.
- The unblinded administrator administers a single 0.5-mL intramuscular injection of saline placebo into the upper deltoid muscle of the arm. The time of study intervention administration will be recorded on the CRF.
- Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.11.2.5. Visit 5, Month 13 (1 Month [28 to 42 Days] After Visit 4), 1-Month Post–Vaccination 2 Blood Draw

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of blood draw criteria as described in Section 5.5.2.

- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect a blood sample (approximately 25 mL).
- Provide the parent(s)/legal guardian with a memory aid. Instruct the parent(s)/legal guardian to use the memory aid between Visits 5 and 10 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF for additional details.
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next study visit as an in-person visit to maintain blinding, and confirm that it is scheduled within the time window per the protocol. Convert the scheduled next study visit to a telephone contact after the study-planned unblinding occurs.
- Complete the source documents.
- Complete the CRFs.

8.11.2.6. Visit 8, Month 24 (12 Months [336 to 394 Days] After Visit 4), Safety Telephone Contact 2

Visit 8 must not be performed until the investigator is unblinded. The Visit 8 window may be extended for individual participants by up to 60 days, at the discretion of the sponsor, to ensure unblinded information is available.

- Contact the parent(s)/legal guardian by telephone.
- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.11.2.7. Visit 9, Month 36 (24 Months [700 to 756 Days] After Visit 4), Vaccination 3

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of vaccination criteria as described in Section 5.5.1.

- Perform a brief physical examination of the participant's general appearance, skin, ears, throat, heart, lungs, abdomen, and lymph nodes. Record any AEs as described in Section 8.3.

- Complete the Study Visit/Telephone Contact AE Checklist to:

  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.

  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.

- Record AEs as described in Section 8.3 and the SoA. Time of onset will be recorded for any AEs that occur on the same day as study intervention administration.

- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.

- Record concomitant medications used to treat AEs as described in Section 6.5.

- Record nonstudy vaccinations as described in Section 6.5.

- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the study intervention.

- On the day of vaccination, prior to administration of study intervention, measure and record the participant's oral temperature.

- Administer a single 0.5-mL intramuscular injection of MenABCWY into the upper deltoid muscle of the arm. The time of study intervention administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).

- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.
- Complete the CRFs.

8.11.2.8. Visit 10, Month 37 (1 Month [28 to 42 Days] After Visit 9), 1-Month Post–Vaccination 3 Blood Draw

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of blood draw criteria as described in Section 5.5.2.
- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect a blood sample (approximately 25 mL).
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Complete the source documents.
- Complete the CRFs.

8.11.3. Final Telephone Contact for Participants Who Withdraw From the Study

- This telephone contact should occur if a participant withdraws or is withdrawn from the study within 6 months after Vaccinations 1 and 2, or within 1 month after Vaccination 3; this contact should be attempted for all participants who have withdrawn from the study within the specified timeframe after receiving any study vaccination, unless they have withdrawn consent.

- Contact the parent(s)/legal guardian or the participant by telephone.

- Complete the Study Visit/Telephone Contact AE Checklist to:

    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.

    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.

- Report any SAEs to the sponsor as defined in Section 8.3.

- Record AEs as described in Section 8.3 and the SoA.

- Record concomitant medications used to treat AEs as described in Section 6.5.

- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.

- Record nonstudy vaccinations as described in Section 6.5.

- Complete the source documents.

- Complete the CRFs.

8.12. Unscheduled Visits

An unscheduled telephone contact or visit may be scheduled for further assessment of any AE. The symptom that prompted the visit should be assessed by a medically qualified member of the study staff. Findings should be recorded on the CRF.

For the purpose of assessments performed during unscheduled visits, a medically qualified member of the study staff is a study physician or a study nurse, as applicable to the investigator's local practice.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described 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, and exploratory objective are described in the table in Section 3. The estimands to evaluate the immunogenicity objectives are based on evaluable populations (see Section 9.3 for 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 in each vaccine group. Assuming up to 20% exclusion rate from the applicable evaluable population, there will be approximately 120 evaluable participants in each vaccine group.

Table 4 shows the expected half-width of the 95% CI by percentage of participants achieving an hSBA titer ≥ LLOQ for each test strain.

Table 4. Expected Half-Width of 95% CIs by Percentage of Participants Achieving an hSBA Titer ≥ LLOQ for Each Test Strain

Percentage of Participants	Number of Participants per Group	Expected Half-Width of 95% CI (%)
60	120	9.1
70	120	8.5
80	120	7.5
90	120	5.8

The probability of observing at least 1 occurrence of any AE for true event percentages between 0.1% and 2.0%, when MenABCWY 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 populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants who are assigned a randomization number in the IRT system.
Evaluable	Defined according to post–Vaccination 1 evaluable and post–Vaccination 2 evaluable criteria.
Modified intent-to-treat (mITT)	Defined according to post–Vaccination 1 and post–Vaccination 2 criteria.
Safety	All randomized participants who receive at least 1 dose of the study intervention and have safety data reported after vaccination. Participants will be analyzed according to the vaccine they actually received.

Defined Population for Analysis	Description
Post–Vaccination 1 evaluable	All randomized participants who were: • eligible throughout Visit 2, • received the investigational product at Visit 1 as randomized, • had blood drawn for assay testing within the required time frames at Month 0 (Visit 1; before Vaccination 1) and Month 1 (Visit 2; 1 month after the first vaccination: window 28-42 days), • had at least 1 valid and determinate MenA/C/W/Y assay result at Visit 2, • had received no prohibited vaccines or treatment through Visit 2, and • had no important protocol deviations through Visit 2. An important 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

Defined Population for Analysis	Description
	medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine).
Post–Vaccination 2 evaluable	All randomized participants who were: • eligible throughout 1 month after the second dose of MenABCWY, • received the investigational product at Visit 1 (for Groups 1 and 2) and Visit 4 (for Group 1) and Visit 9 (for Group 2) as randomized, • had blood drawn for assay testing within the required time frames at Month 0 (Visit 1; before Vaccination 1) and at 1 month after the second MenABCWY vaccination (Visit 5 for Group 1 and Visit 10 for Group 2: window 28-42 days), • had at least 1 valid and determinate MenA/C/W/Y or MenB assay result at 1 month after the second MenABCWY vaccination (Visit 5 for Group 1 and Visit 10 for Group 2), • had received no prohibited vaccines or treatment through Visit 5 (Group 1) or Visit 10 (Group 2), and • had no important protocol deviations through Visit 5 (Group 1) or Visit 10 (Group 2). An important 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 suspected decrease in potency of the vaccine).
Post–Vaccination 1 mITT	All participants who received at least 1 study vaccination and had at least 1 valid and determinate MenB or MenA/C/W/Y assay result available at any time point from Visit 1 to Visit 2.
Post–Vaccination 2 mITT	All participants who received at least 1 study vaccination and had at least 1 valid and determinate MenB or MenA/C/W/Y assay result available at any time point from Visit 1 to Visit 5 for Group 1 and from Visit 1 to Visit 10 for Group 2.

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, secondary, and exploratory endpoints.

9.4.1. Immunogenicity Analyses

Primary	For each of the 4 primary MenB test strains, the percentage of participants with an hSBA titer ≥ LLOQ at baseline and at 1 month after the second dose of MenABCWY will be calculated for each vaccine group. Exact 2-sided 95% CIs for the percentages will be provided using the Clopper-Pearson method.

	The primary analysis for the primary MenB strains is based on the post–Vaccination 2 evaluable population. A supportive analysis will be performed based on the applicable mITT population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary	The percentage of participants in Group 1 (0- and 12-month schedule) with hSBA titers ≥ LLOQ for each of the primary MenB test strains at 12 and 24 months after the second dose of MenABCWY will be summarized using the post–Vaccination 2 evaluable population. The percentage of participants in Group 1 with hSBA titers ≥ LLOQ for each of the ACWY test strains at 12 and 24 months after the second dose of MenABCWY will be summarized using the post–Vaccination 2 evaluable population. The percentage of participants in Group 1 (0- and 12-month schedule) and Group 2 (0- and 36-month schedule) separately with hSBA titers ≥ LLOQ for each of the ACWY test strains at baseline and at 1 month after the first dose of MenABCWY will be summarized using the post–Vaccination 1 evaluable population. The percentage of participants in Groups 1 and 2 separately with hSBA titers ≥ LLOQ for each of the ACWY test strains at baseline and at 1 month after the second dose of MenABCWY will be summarized using the post–Vaccination 2 evaluable population. Reverse cumulative distribution functions will be provided for both MenA/C/W/Y strains (1 month after the first and second dose of MenABCWY) and MenB strains (1 month after the second dose of MenABCWY) for each vaccine group. Supportive analyses will be done using the applicable mITT population. Exact 2-sided 95% CIs for the percentages will be provided using the Clopper-Pearson method. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Exploratory	The following analyses for the primary MenB test strains are based on the post–Vaccination 2 evaluable population for Groups 1 and 2 (separately): • The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY. • MenB hSBA GMTs for each of the 4 primary MenB test strains at baseline, 13 months after the first dose of MenABCWY (Group 2 only), and 1 month after the second dose of MenABCWY. • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for all primary MenB test strains combined (composite response) at baseline and 1 month after the second dose of MenABCWY. • The percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each of the 4 primary MenB test strains at 1 month after the second dose of MenABCWY.

	○ For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. ○ For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ. ○ For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer. • The percentage of participants with hSBA titers ≥ LLOQ for each of the 4 primary MenB test strains at 13 months after the first dose of MenABCWY (Group 2 only). The following analyses for the ACWY test strains are based on the post–Vaccination 2 evaluable population for Groups 1 and 2 (separately): • hSBA GMTs for each ACWY test strain at baseline and 1 month after the second dose of MenABCWY. • The percentage of participants achieving at least a 4-fold rise in hSBA titers from baseline for each ACWY test strain at 1 month after the second dose of MenABCWY. ○ For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as a participant with an hSBA titer of ≥1:16. ○ For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, an hSBA titer of 1:8), a 4-fold response is defined as a participant with an hSBA titer of ≥4 times LLOQ. ○ For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as a participant with an hSBA titer of ≥4 times the baseline titer. The following analyses for the ACWY test strains are based on the post–Vaccination 1 evaluable population for Groups 1 and 2 (separately): • hSBA GMTs for each ACWY test strain at baseline, 1 month after the first dose of MenABCWY, and 13 months after the first dose of MenABCWY (Group 2 only). • The percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain at 1 month after the first dose of MenABCWY. ○ For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as a participant with an hSBA titer of ≥1:16.

	○ For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, an hSBA titer of 1:8), a 4-fold response is defined as a participant with an hSBA titer of ≥4 times the LLOQ. ○ For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as a participant with an hSBA titer of ≥4 times the baseline titer. • The percentage of participants with hSBA titers ≥ LLOQ for each ACWY test strain at 13 months after the first dose of MenABCWY (Group 2 only). Percentages will be presented with 2-sided 95% CIs using the Clopper-Pearson method. Geometric means and their 2-sided 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 done using the applicable mITT population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population. Separate safety populations will be defined for each vaccination visit and follow-up phase, and will be detailed in the SAP.

Endpoint	**Statistical Analysis Methods**
Primary	The percentage of participants reporting at least 1 SAE, the percentage of participants reporting at least 1 MAE, and the percentage of participants reporting at least 1 NDCMC will be descriptively summarized (percentages and associated Clopper-Pearson 95% CIs) by vaccination group for each time period defined in Section 3. All AEs and SAEs will be categorized according to the latest version of MedDRA. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. 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. AEs, SAEs, MAEs, and NDCMCs will be summarized by vaccine group. Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules. Detailed analyses for each safety endpoint will be addressed in the SAP.

9.5. Interim Analyses

No interim analysis is planned in this study.

9.5.1. Analysis Timing

The study team will remain blinded until all participants have completed Visit 5, after which time select data will be reported, including immunogenicity data for Group 1. A final analysis will be done after all available data have been collected.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

An independent statistical center will provide unblinded safety reports to the DMC for review. Safety data will be reviewed by the DMC throughout the study. No alpha adjustments will be made to the immunogenicity summaries (CIs) for these periodic safety assessments.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses, to regulatory authorities, as appropriate.

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 and answer all questions regarding the study. The participant's parent(s)/legal guardian 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 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 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 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.

The participant's parent(s)/legal guardian 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 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 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.

A study-specific assent form will be provided to pediatric participants as required by local regulations. It is to be understood as the adolescent's will to participate in a trial after having received age-appropriate information and is sometimes also referred to as "knowing agreement." If the study includes minor participants who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant's parent(s)/legal guardian the objectives of the additional research. The participant's parent(s)/legal guardian will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

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 ID. 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 EU 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 onsite 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 systems 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 sponsor or designee/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 investigator site file.

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 and meet the requirements as per Section 8.3.8.1. 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 an NDCMC

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

10.3.3. 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.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious 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:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or 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.

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.
- 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.

10.3.5. 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: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention:

- Refrain from donating sperm.

  PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

   - Documented bilateral salpingectomy;

   - Documented bilateral oophorectomy.

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

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

     - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

     - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: 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.

10.6. Appendix 6: 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).

10.6.1. 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 AE related to the use of an investigational medical device. This definition includes any AEs 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.

10.6.2. 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 ADE that has resulted in any of the consequences characteristic of an SAE.
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.

10.6.3. 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.

10.6.4. 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, or designee, 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: AEs/SAEs on the appropriate form of the CRF, medical device deficiencies via the medical device complaint submission form.
- 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.
- 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.

10.6.5. 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.

10.6.6. 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.

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
ACWY	meningococcal group A, C, W, and Y
ADE	adverse device effect
AE	adverse event
$AlPO_4$	aluminum phosphate
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine (Trumenba)
CDP	clinical development program
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CRF	case report form
CRM	cross-reactive material
CRO	contract research organization
CSR	clinical study report
DILI	drug-induced liver injury
DMC	data monitoring committee
DTaP-Hib	diphtheria, tetanus, and acellular pertussis and *Haemophilus influenzae* type b vaccine
DTaP-IPV	diphtheria, tetanus, and acellular pertussis and inactivated poliomyelitis virus vaccine
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
fHBP	factor H binding protein
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMT	geometric mean titer

Abbreviation	Term
GSK	GlaxoSmithKline
HBV-IPV	hepatitis B virus and inactivated poliomyelitis virus vaccine
HIPAA	Health Insurance Portability and Accountability Act
HPV4	human papillomavirus vaccine
HRT	hormone replacement therapy
hSBA	serum bactericidal assay using human complement
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IND	investigational new drug
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
LOD	limit of detection
MAE	medically attended adverse event
MCV4-Tdap	quadrivalent meningococcal polysaccharide conjugate and tetanus, diphtheria, and acellular pertussis vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* group A
MenA/C/W/Y	*Neisseria meningitidis* group A, C, W, and/or Y
MenABCWY	*Neisseria meningitidis* group A, B, C, W, and Y vaccine
MenACWY	meningococcal groups A, C, W, and Y conjugate vaccine
MenACWY-CRM	meningococcal group A, C, W-135, and Y conjugate vaccine (Menveo)
MenACWY-TT	meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (Nimenrix)
MenB	*Neisseria meningitidis* group B
MenC	*Neisseria meningitidis* group C
MenW	*Neisseria meningitidis* group W
MenY	*Neisseria meningitidis* group Y
mITT	modified intent-to-treat
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product

Abbreviation	Term
PACL	protocol administrative change letter
PFS	prefilled syringe
POC	proof of concept
PRP-OMP	polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein
PT/INR	prothrombin time/international normalized ratio
rLP2086	recombinant lipoprotein 2086
rSBA	serum bactericidal assay using rabbit complement
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
CCI	[redacted]
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
WOCBP	woman/women of childbearing potential

10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic in the US and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.8.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, and video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications used to treat an AE since the last contact. Refer to Section 6.5.
- Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

In addition to the above, procedures outlined for a typical safety telephone contact (see Section 8.11.1.3) may be performed during a telehealth visit. Study participants must be reminded to promptly notify site staff about any change in their health status.

10.8.2. Home Health Visits

A home healthcare service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Ensure that the participant continues to be eligible for the study and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7 and none of the temporary delay of blood draw criteria as described in Section 5.5.2.

- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in Section 8.3 and the SoA.
- Review AEs that were ongoing since the previous visit, and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect a blood sample (approximately 25 mL).
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window indicated in the protocol.
- Complete the source documents.
- Complete the CRFs.

10.8.3. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

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