Protocol C3511004

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

Statistical Analysis Plan
(SAP)

[redacted]

Version: 4

Date: 15 Apr 2024

TABLE OF CONTENTS

LIST OF TABLES

1. VERSION HISTORY

Table 1. Summary of Changes

Version / Date	Associated Protocol Amendment	Rationale	Specific Changes
4 / 15 Apr 2024		Added supplementary analyses with prespecified thresholds	• Added supplementary analyses based on the proportion of participants achieving a ≥4-fold rise in hSBA titers (and composite response for MenB) against prespecified LCI thresholds at 1 month after the second dose of MenABCWY in Group 2 (Section 6.3.1.1.2 and Section 6.3.1.3.2).
3 / 17 Nov 2021		Updated to reflect inputs from the Clinical Team	• Allowed some flexibility on whether the exploratory endpoints analyses of the percentage of participants with hSBA titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains will be reported. This flexibility will not extend to reporting of the primary endpoint of percentage of participants achieving hSBA titers ≥ LLOQ and ≥1:4. • Removed planned analyses of hSBA GMTs for each of the 4 primary MenB test strains and for each of the ACWY test strains at 13 months after the first dose of MenABCWY in Group 2. • Removed neuroinflammatory and autoimmune conditions summaries for the analysis interval table (Table 5). • Changed the information for the ACWY assay from qualified to validated (Table 8). • Removed the sensitivity analysis for alternative definition of composite response in Section 3.3. • Modified the analysis population for the demographic and baseline characteristics summary in Section 6.5.3. • Replaced some study conduct tables with listings in Section 6.5.4.
2 / 13 May 2021	Amendment 1 07 Jan 2021	Updated to reflect protocol amendment 1	• Added estimands for the immunogenicity analysis of the blood drawn after the saline injection in Group 2, per CBER feedback. • Updated the estimands/objectives to reflect the modified study design per protocol amendment 1. • 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visit for Group 2) and the associated immunogenicity objectives/estimands from the study design, as Visit 11 is no longer applicable. • Reduced the planned statistical analyses from 3 (after Visit 5, after Visit 10, and at the end of the study) to 2 (after Visit 5 and at the end of the study).

Table 1. Summary of Changes

Version / Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Added validated LOD and LLOQ details for the MenB strains; qualified the LOD and LLOQ details for the MenACWY serogroups. • Added a note in Section 7.1 to reflect the possibility of a SAP amendment due to the pandemic. • Moved the discussion of the analysis methods from Section 5.2.1.1 to Section 3.3.
1 / 22 Jul 2020	Original 04 Feb 2020	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3511004. A brief description of the study design and the study objectives are given. Subsequent sections include analysis populations and the definitions of the immunogenicity and safety endpoints, followed by details around statistical analysis and reporting. A list of tables, listings, and figures, mock-up tables, listings, and figures, and programming rules are prepared separately based on the methods described in this document. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. Table 2 shows the study design.

Table 2. Study Design

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.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1. Primary Objectives

- To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule.
- To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 36-month schedule.
- To describe the safety profile of MenABCWY when administered on a 0- and 12-month and a 0- and 36-month schedule.

2.1.2. Secondary Objectives

- 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.
- 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.
- To describe the persistence of the MenB response following 2 doses of MenABCWY administered on a 0- and 12-month schedule.
- 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.

2.1.3. Exploratory Objectives

- To further describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule.
- To further describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 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.
- 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.

Appendix 1 shows how the study estimands and endpoints relate to each objective.

2.1.4. Primary Estimands

- **Primary Immunogenicity Estimands**

For the first objective (to describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule), the primary estimand has the following attributes:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary: 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).

For the second objective (to describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 36-month schedule), the primary estimand has the following attributes:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary: 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).

The planned analyses for the primary endpoints as related to the estimands are outlined in Section 6.1.

- **Primary Safety Estimands**

For the primary safety objective to describe the safety profile of MenABCWY when administered on a 0- and 12-month and 0- and 36-month schedule as measured by AEs, SAEs, MAEs, NDCMCs, and immediate AEs, the estimand has the following attributes:

- Population: Participants receiving at least 1 dose of study intervention.
- Variable: AEs, SAEs, MAEs, NDCMCs, and immediate AEs.
- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.
- Population-level summaries:
  - 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.
      - 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.

For the primary safety objective to describe the safety profile of MenABCWY when administered on a 0- and 12-month and 0- and 36-month schedule as measured by days missing school or work because of AEs, the estimand has the following attributes:

- Population: Participants receiving at least 1 dose of study intervention.
- Variable: Days missing from school or work because of AEs.
- Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.
- Population-level summary: The percentage of participants who missed days of school and/or work because of AEs occurring within 6 months after Vaccinations 1 and 2 and within 1 month after Vaccination 3.

2.1.5. Secondary Estimands

For the secondary objective 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, the estimand has the following attributes:

After 1 dose of MenABCWY:

- Population: Participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the ACWY test strains.
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary: 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).

After 2 doses of MenABCWY:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the ACWY test strains.
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary: 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 second dose of MenABCWY in Group 1 (0- and 12-month schedule).

For the secondary objective 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, the estimand has the following attributes:

After 1 dose of MenABCWY:

- Population: Participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the ACWY test strains.
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary: 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).

After 2 doses of MenABCWY:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the ACWY test strains.
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary: 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 second dose of MenABCWY Group 2 (0- and 36-month schedule).

For the secondary objective to describe the persistence of the MenB response following 2 doses of MenABCWY administered on a 0- and 12-month schedule, the estimand has the following attributes:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary: 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).

For the secondary objective 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, the estimand has the following attributes:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the ACWY test strains.
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary: 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).

2.1.6. Exploratory Estimands

For the exploratory objective to further describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule, the estimand has the following attributes:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

- Population-level summary:

  - 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).

    - 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.

For the exploratory objective to further describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 36-month schedule, the estimand has the following attributes:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).

- Variable: hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

- Population-level summary:
    - 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 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).
    - 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.
        - 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.

For the exploratory objective to further describe the immune response for MenB induced by 2 doses of MenABCWY administered on both dose schedules, the endpoints related to the percentage of participants with hSBA titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 may not be reported. This will not extend to reporting of the primary endpoint of percentage of participants achieving hSBA titers ≥ LLOQ and ≥1:4. In addition, the endpoint related to hSBA GMTs for each of the 4 primary MenB test strains at 13 months after the first dose of MenABCWY in Group 2 will not be reported.

For the exploratory objective 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, the estimand has the following attributes:

After 1 dose of MenABCWY:

- Population: Participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the ACWY test strains.
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary:
  - 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.

After 2 doses of MenABCWY:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the ACWY test strains.
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary:
  - 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).
  - 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).

- 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.

For the exploratory objective 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, the estimand has the following attributes:

After 1 dose of MenABCWY:

- Population: Participants receiving 1 dose of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).

- Variable: hSBA titer for each of the ACWY test strains.

- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

- Population-level summary:

- 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 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).

- 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).

    - 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.

For the exploratory objective to further describe the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY administered on a 0- and 36-month schedule, the endpoint related to hSBA GMTs for each of the ACWY test strains at 13 months after the first dose of MenABCWY in Group 2 will not be reported.

After 2 doses of MenABCWY:

- Population: Participants receiving 2 doses of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the ACWY test strains.
- Intercurrent event(s): Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- Population-level summary:
    - 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.

2.2. Study 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 Table 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. Each participant will participate in the study for approximately 37 months. Approximately 300 participants will be enrolled in the study.

2.2.1. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. 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	**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			

Group 1 (0- and 12-Month Schedule)							
Visit Identifier	**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**
Randomization	X						
Obtain blood sample (~25 mL)	X	X			X	X	X
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

Group 1 (0- and 12-Month Schedule)							
Visit Identifier	**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**
(S)AE collection appropriate for the visit[f]	X	X	X	X	X	X	X

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition; PRP-OMP = polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein.
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 8.1.1.3 in the protocol.

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 in the protocol.
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 in the protocol.

Group 2 (0- and 36-Month Schedule)								
Visit Identifier	**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

Group 2 (0- and 36-Month Schedule)								
Visit Identifier	**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**
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
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

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition; PRP-OMP = polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein.

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 8.1.1.3 in the protocol.

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 in the protocol.
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 in the protocol.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Appendix 1 shows how the study estimands and endpoints relate to each objective.

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoints

- hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

3.1.2. Primary Safety Endpoints

- AEs, SAEs, MAEs, NDCMCs, and immediate AEs.
- Days missing from school or work because of AEs.

3.2. Secondary Endpoints

3.2.1. Secondary Immunogenicity Endpoints

- hSBA titer for each of the MenACWY test strains.
- hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

3.3. Exploratory Endpoints

- hSBA titer for each of the MenACWY test strains.
- hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

hSBA titers assessed for either MenB or MenACWY will be analyzed as below:

hSBA titers ≥ LLOQ will be derived as follows:

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

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

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

Similarly, for all hSBA titers assessed, binary variables of assay results at each visit where assay titers are analyzed, and that achieve specific thresholds, will be derived as follows:

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

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

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

The threshold values for MenB hSBA titers are:

- ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128

For the exploratory objective to further describe the immune response for MenB induced by 2 doses of MenABCWY administered on both dose schedules, the endpoints related to the percentage of participants with hSBA titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 may not be reported. This will not extend to reporting of the primary endpoint of percentage of participants achieving hSBA titers ≥ LLOQ and ≥1:4.

A composite response will be computed at Visit 5 (1 month after the second dose of MenABCWY in Group 1) and Visit 10 (1 month after the second dose of MenABCWY in Group 2). The composite response is defined as participants who have assay results that are ≥ LLOQ for all 4 of the primary MenB strains at the same visit. The composite response will be computed as follows:

= •, if the assay result is missing, indeterminate, or otherwise unavailable for at least 1 of the 4 MenB primary strains;

= 1, if all 4 MenB primary strains have assay results ≥ LLOQ at the same visit;

= 0, if not all 4 MenB primary strains have assay results ≥ LLOQ.

The 4-fold response in assay titers from baseline (Visit 1, before vaccination) to 1 month after Vaccination 1 (Visit 2) and 1 month after the second dose of MenABCWY (Visit 5 for Group 1 and Visit 10 for Group 2) will be defined as follows:

- 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 (ie, hSBA titer of 1:8), 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 4-fold response variable for the MenB and MenACWY strains will be computed as follows:

= •, if the assay result at baseline or specific time point is missing, indeterminate, or otherwise unavailable;

= 1, if the assay result meets 1 of the 3 definitions for a 4-fold response;

= 0, if the assay result does not meet 1 of the 3 definitions for a 4-fold response.

3.4. Baseline Variables

3.4.1. Demographic, Medical History, and Baseline Characteristic Variables

Demographic variables collected at Visit 1 include sex, race, ethnicity, and date of birth. Race collected includes:

- Black or African American
- American Indian or Alaska Native
- Asian
- Native Hawaiian or other Pacific Islander
- White
- Not reported

Ethnicity collected includes:

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

For countries where full date of birth is collected, age at the time of first vaccination and age at randomization will be derived based on birthday. For example, if the first vaccination date is 1 day before the participant's thirteenth birthday, the participant is 12 years old.

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

Physical examination will be assessed prior to vaccination at Visit 1 (Groups 1 and 2) and each body system examined will be recorded in the CRF as normal, abnormal, or not done. Additional physical examination prior to Vaccination 2 (Groups 1 and 2) and Vaccination 3 (Group 2 only) will also be recorded on the CRF, but with fewer body systems.

3.4.2. Previous Vaccinations

For participants who have ever received a PRP-OMP vaccine, the name of the vaccine and date of administration will be recorded on the CRF.

3.5. Safety Endpoints

3.5.1. Adverse Events

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.

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

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, 6 months after the first dose of MenABCWY), 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, MAEs, and NDCMCs, 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 3.

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, 6 months after the first dose of MenABCWY), 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, 12 months after the placebo dose), 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 4.

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.

Table 3. 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]		

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition.
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 4. 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]		←	→

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition.
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.

3.5.1.1. Analysis Intervals

There will be 11 analysis intervals for the AE data collected via CRF (Table 5). The analysis populations used for these intervals are described in detail in Section 4.

For Vaccination 1 (Visit 1), MenABCWY will be administered to participants in both Groups 1 and 2. For Vaccination 2 (Visit 4), MenABCWY will be administered to Group 1 participants; saline will be administered to Group 2 participants. For Vaccination 3 (Visit 9), MenABCWY will be administered to Group 2 participants.

Table 5. Analysis Intervals for AEs, SAEs, MAEs, NDCMCs, and Days Missing School or Work Because of AEs

Interval #	Group	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)	Safety Data
1	Groups 1, 2	Within 30 days after Vaccination 1	Vax 1 safety	Vax 1 date (Visit 1 for Groups 1, 2)	Vax 1 date (Visit 1 for Groups 1, 2) + 30 days	AEs, SAEs, MAEs, NDCMCs
2	Groups 1, 2	Within 30 days after Vaccination 2	Vax 2 safety	Vax 2 date (Visit 4 for Groups 1, 2)	Vax 2 date (Visit 4 for Groups 1, 2) + 30 days	AEs, SAEs, MAEs, NDCMCs
3	Group 2	Within 30 days after Vaccination 3	Vax 3 safety	Vax 3 date (Visit 9 for Group 2)	Vax 3 date (Visit 9 for Groups 1, 2) + 30 days	AEs, SAEs, MAEs, NDCMCs
4	Groups 1, 2	Within 30 days after any MenABCWY vaccination	Safety	Vax 1 date (for Groups 1, 2) or Vax 2 date (for Group 1) or Vax 3 date (for Group 2)	Vax 1 date (Groups 1, 2) + 30 days or Vax 2 date (Group 1) + 30 days or Vax 3 date (Group 2) + 30 days	AEs, SAEs, MAEs, NDCMCs
5	Groups 1, 2	Vaccination 1 vaccination phase	Vax 1 safety	Visit 1 date	Visit 2 date (or end of vaccination day)	AEs, SAEs, MAEs, NDCMCs
6	Groups 1, 2	Vaccination 2 vaccination phase	Vax 2 safety	Visit 4 date	Visit 5 date (or end of vaccination day)	AEs, SAEs, MAEs, NDCMCs
7	Group 2	Vaccination 3 vaccination phase	Vax 3 safety	Visit 9 date	Visit 10 date (or end of vaccination day)	AEs, SAEs, MAEs, NDCMCs, days missing school or work because of AEs
8	Groups 1, 2	During follow-up phase 1	Follow-up safety 1	Visit 2 date + 1, or end of vaccination date + 1 for early withdrawal participants	6 Months after Vax 1 date (Visit 3)	SAEs, MAEs, NDCMCs
9	Groups 1, 2	During follow-up phase 2	Follow-up safety 2	Visit 5 date + 1, or end of vaccination date + 1 for early withdrawal participants	6 Months after Vax 2 date	SAEs, MAEs, NDCMCs

Table 5. Analysis Intervals for AEs, SAEs, MAEs, NDCMCs, and Days Missing School or Work Because of AEs

Interval #	Group	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)	Safety Data
10	Groups 1, 2	6 Months after Vaccination 1	Vax 1 safety	Vax 1 date (Groups 1, 2)	6 Months after Vax 1 date	SAEs, MAEs, NDCMCs, days missing school or work because of AEs
11	Groups 1, 2	6 Months after Vaccination 2	Vax 2 safety	Vax 2 date (Groups 1, 2)	6 Months after Vax 2 date	SAEs, MAEs, NDCMCs, days missing school or work because of AEs

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition; Vax = vaccination.
Note: 183 Days will be used as the duration for programmatic determination of 6 months for Interval 11.

Three analysis intervals will be applied to immediate AEs (Table 6).

Table 6. Analysis Intervals for Immediate AEs

Interval #	Group	Analysis Interval	Analysis Population	Interval Start Date/Time (Inclusive)	Interval Stop Date/Time (Inclusive)
1	Groups 1, 2	Vaccination 1	Vax 1 safety	Vax 1 time	Vax 1 time + 30 minutes
2	Groups 1, 2	Vaccination 2	Vax 2 safety	Vax 2 time	Vax 2 time + 30 minutes
3	Group 2	Vaccination 3	Vax 3 safety	Vax 3 time	Vax 3 time + 30 minutes

Abbreviation: Vax = vaccination.

3.5.2. Pregnancy Testing

The results of the urine pregnancy tests collected at Visits 1, 4, and 9 (Group 2 only) will be recorded.

3.5.3. Laboratory Data

Laboratory assessments will not be collected for this study.

3.5.4. Medical Device Errors

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

3.6. Study Conduct

3.6.1. Nonstudy Vaccines and Concomitant Medications

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD up to 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 will be collected from the signing of the ICD up to the end of study participation.

Concomitant vaccines and medications permitted during the study include:

- 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.

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

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to study intervention (as-randomized), also termed intent-to-treat (ITT) population	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 population	1. All randomized participants. 2. Eligible throughout Visit 2. 3. Received the study intervention at Visit 1 as randomized. 4. 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). 5. Had at least 1 valid and determinate MenA/C/W/Y assay result at Visit 2. 6. Had received no prohibited vaccines or treatment through Visit 2. 7. Had no important protocol deviations through Visit 2.
Post–Vaccination 2 evaluable population	1. All randomized participants. 2. Eligible throughout 1 month after the second dose of MenABCWY. 3. Received the study intervention at Visit 1 (for Groups 1 and 2) and Visit 4 (for Group 1) and Visit 9 (for Group 2) as randomized. 4. 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).

Defined Population for Analysis	Description
	5. 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). 6. Had received no prohibited vaccines or treatment through Visit 5 (Group 1) or Visit 10 (Group 2). 7. Had no important protocol deviations through Visit 5 (Group 1) or Visit 10 (Group 2).
Post–Vaccination 1 mITT population	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 population	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.
Vaccination 1 safety population	This population will include participants who received the first dose of study intervention at Visit 1 and for whom safety information from Visit 1 up to Visit 4 is available in Groups 1 and 2.
Vaccination 2 safety population	This population will include participants who received the second dose of study intervention at Visit 4 (MenABCWY for Group 1, saline for Group 2) and for whom safety information from Visit 4 up to Visit 7 (for Group 1) or Visit 9 (for Group 2) is available.
Vaccination 3 safety population	This population will include participants who received the third dose of study intervention at Visit 9 (MenABCWY for Group 2) and for whom safety information from Visit 9 through Visit 10 is available.
Follow-up safety population 1	This population will include participants who received the first dose of study intervention and for whom safety information from Visit 2 up to Visit 4 in Groups 1 and 2 is available.
Follow-up safety population 2	This population will include participants who received the second dose of study intervention (MenABCWY for Group 1, saline for Group 2) and for whom safety information from Visit 5 up to Visit 7 (for Group 1) or Visit 9 (for Group 2) is available.

For determination of the evaluable population(s), items 1 through 5 will be computerized checks of the data, while items 6 and 7 will be determined by clinical review. 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 receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The global medical monitor from the sponsor will identify those participants with a protocol deviation prior to unblinding of the study.

For participants withdrawn early, they will be included in the respective follow-up population, in case they have any type of AEs in the respective AE follow-up intervals.

For Analysis 1 (per Section 7.1), the post–Vaccination 1 evaluable population will be fully defined for both Groups 1 and 2. Similarly, the post–Vaccination 2 evaluable population will be fully defined for Group 1 for Analysis 1. The final determination of the protocol

deviations, and hence the post–Vaccination 2 evaluable population for Group 2, will be completed for the final analysis.

4.1. Vaccine Misallocation

- Vaccinated but not randomized: These participants will be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received, but will be excluded from immunogenicity analyses.

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

- Randomized but received incorrect vaccine: These participants will be included in the mITT population for immunogenicity analyses if data are available and will be reported under the vaccine group based on the randomized vaccine. These participants will also be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses specified in the protocol. All safety and immunogenicity analyses will be descriptively summarized.

5.1.1. Statistical Decision Rules

Not applicable.

5.2. General Methods

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

5.2.1. Analyses for Binary Endpoints

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

5.2.1.1. Immunogenicity Data

Each MenB (Table 7) and MenACWY (Table 8) strain has a validated LLOQ value defined.

Table 7. Validated hSBA LOD and LLOQ for MenB Primary Strains

Strain Type	Strain Variant	LOD	LLOQ
Primary	A22	1:4	1:16
	A56	1:4	1:8
	B24	1:4	1:8
	B44	1:4	1:8

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenB = *Neisseria meningitidis* group B.

Table 8. Validated hSBA LOD and LLOQ for MenACWY Serogroups

Serogroup	LOD	LLOQ
MenA	1:4	1:8
MenC	1:4	1:8
MenW	1:4	1:8
MenY	1:4	1:8

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; MenA, MenC, MenW, or MenY = *Neisseria meningitidis* group A, group C, group W, or group Y; MenACWY = *Neisseria meningitidis* groups A, C, W, and Y.

5.2.1.2. Safety Data

All safety endpoints will be summarized with percentages and 95% exact CIs (Clopper-Pearson method) for each group. The CIs presented for the safety data will not be used to test hypotheses but will be used to determine which events may need further clinical investigation.

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Geometric Mean Titers

GMTs will be computed for each hSBA titer for MenB and MenACWY strains. If the hSBA result is below LLOQ, it will be set to ½ the LLOQ for the GMT calculation. The assay results at each blood sampling time point will be (natural-log) logarithmically transformed for analysis. GMTs are obtained by log transformations of indicated values, averaging the log values, then exponentiating the result. The associated 2-sided 95% CIs are obtained by exponentiating the limits of CIs for the mean logarithm of the hSBA titers (based on the Student t distribution).

5.2.2.2. Reverse Cumulative Distribution Curves

RCDCs for MenB and MenACWY strains for a combination of available time points and Groups 1 and 2 may be generated.

5.2.2.3. Days Missed

Days in which a participant missed school and/or work will be captured on the AE checklist. The data captured at each visit will be summarized and the total number of missed days of school and/or work will be obtained.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms on handling missing AE dates will be applied according to Pfizer safety rules.

5.3.2. Immunogenicity Data

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

For the hSBA assay results, the following values will be set to missing: QNS (insufficient sera), indeterminate results, and not done. Participants without blood draw (ie, dropout) will also have missing data for immunogenicity.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Immunogenicity Endpoints

6.1.1.1. hSBA Titer for Each of the Primary MenB Test Strains (A22, A56, B24, and B44), Group 1 (0- and 12-Month Schedule)

6.1.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 2 evaluable population for Group 1.
- Analysis methodology: Exact 2-sided 95% CIs for the percentages using the Clopper-Pearson method.
- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized.
- 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 Group 1 based on the post–Vaccination 2 evaluable population.

6.1.1.1.2. Sensitivity/Supplementary Analyses

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

6.1.1.2. hSBA Titer for Each of the Primary MenB Test Strains (A22, A56, B24, and B44), Group 2 (0- and 36-Month Schedule)

6.1.1.2.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 2 evaluable population for Group 2.
- Analysis methodology: Exact 2-sided 95% CIs for the percentages using the Clopper-Pearson method.
- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized.
- 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 Group 2 based on the post–Vaccination 2 evaluable population.

6.1.1.2.2. Sensitivity/Supplementary Analyses

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

6.1.2. Primary Safety Endpoints

6.1.2.1. Serious Adverse Events, Medically Attended Events, and Newly Diagnosed Chronic Medical Conditions

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics and Clopper-Pearson CIs.
- Intercurrent events and missing data: Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.
- For each group, the numbers and percentages of participants with MAEs, SAEs, and NDCMCs for the 11 analysis intervals defined in Table 5 will be summarized. For the events during the vaccination phase, follow-up phase, and 6 months after Vaccinations 1 and 2, the (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.1.2.2. Adverse Events

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics and Clopper-Pearson CIs.
- Intercurrent events and missing data: Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.
- For each group, the numbers of participants with AEs for the first 7 analysis intervals defined in Table 5 will be summarized. The (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

  Nonserious AEs are not required to be reported during the follow-up phase; however, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data will be listed separately.

6.1.2.3. Immediate Adverse Events

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics and Clopper-Pearson CIs.
- Intercurrent events and missing data: Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.
- The number and percentage of participants reporting AEs occurring within the 30-minute observation period immediately after vaccination will be summarized according to the 3 analysis intervals defined in Table 6. These summaries will include 95% Clopper-Pearson CIs.

6.1.2.4. Days Missing School or Work

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics and Clopper-Pearson CIs.
- Intercurrent events and missing data: Participants will be analyzed according to the vaccine they actually received. Missing AE dates will be handled according to the Pfizer safety rules.
- The percentage of participants with missed days of school and/or work will be descriptively summarized according to Intervals 7, 10, and 11 in Table 5.

6.2. Secondary Endpoints

6.2.1. Secondary Immunogenicity Endpoints

6.2.1.1. hSBA Titer for Each of the MenACWY Test Strains

6.2.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 1 and Post–Vaccination 2 evaluable populations for Groups 1 and 2.
- Analysis methodology: Exact 2-sided 95% CIs for the percentages using the Clopper-Pearson method.
- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized.
- The percentage of participants in Group 1 (0- and 12-month schedule) and Group 2 (0- and 36-month schedule) separately and combined with hSBA titers ≥ LLOQ for each of the ACWY test strains at baseline and at 1 month after the first dose of MenABCWY may 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.

6.2.1.1.2. Supplemental Analysis

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

6.2.1.2. hSBA Titer for Each of the Primary MenB Test Strains (A22, A56, B24, and B44), Group 1 (0- and 12-Month Schedule)

6.2.1.2.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 2 evaluable population for Group 1.
- Analysis methodology: Exact 2-sided 95% CIs for the percentages using the Clopper-Pearson method.
- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized.

- 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.

6.2.1.2.2. Supplemental Analysis

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

6.2.1.3. hSBA Titer for Each of the MenACWY Test Strains, Group 1 (0- and 12-Month Schedule)

6.2.1.3.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 2 evaluable population for Group 1.
- Analysis methodology: Exact 2-sided 95% CIs for the percentages using the Clopper-Pearson method.
- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized.
- 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.

6.2.1.3.2. Supplemental Analysis

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

6.3. Exploratory Endpoints

6.3.1. Exploratory Immunogenicity Endpoints

6.3.1.1. hSBA Titer for Each of the Primary MenB Test Strains (A22, A56, B24, and B44)

6.3.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 2 evaluable populations for Groups 1 and 2.
- Analysis methodology: Exact 2-sided 95% CIs for the percentages using the Clopper-Pearson method.

- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized.

- 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 for each group, separately. The percentage of participants with hSBA titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 may not be reported out.

- MenB hSBA GMTs for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY for Groups 1 and 2, separately.

- 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 for each group, separately.

- 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.

- 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 each group, separately.

    - 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.

6.3.1.1.2. Supplemental Analysis

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

One additional supplementary analysis without hypothesis testing will be performed to assess the lower bound of the 2-sided 95% CI for the percentage of participants achieving at least a 4-fold rise from baseline in hSBA titers for each of the 4 primary MenB test strains and composite response against the prespecified LCI thresholds at 1 month following the second dose of MenABCWY for Group 2. The LCI thresholds for a 4-fold rise from baseline and composite response for MenB are listed for reference in Table 9.

Table 9. LCI Thresholds for MenB and Composite Response

	Strain Type	LCI Thresholds
hSBA titer fold rise ≥4 from baseline	A22	75%
	A56	85%
	B24	65%
	B44	75%
Composite response (hSBA titer ≥ LLOQ for all 4 primary strains combined)		70%

6.3.1.2. hSBA Titer for Each of the MenACWY Test Strains (After Vaccination 1)

6.3.1.2.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 1 evaluable populations for Groups 1 and 2.
- Analysis methodology: Exact 2-sided 95% CIs for the percentages using the Clopper-Pearson method.
- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized.
- hSBA GMTs for each ACWY test strain at baseline and 1 month after the first dose of MenABCWY for each group, separately and combined, may be summarized.
- 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).
- 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 each group, separately and combined, may be summarized.
    - 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 (ie, an hSBA titer of 1:8), 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.

6.3.1.2.2. Supplemental Analysis

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

6.3.1.3. hSBA Titer for Each of the MenACWY Test Strains (After Vaccination 2 of MenABCWY)

6.3.1.3.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 2 evaluable populations for Groups 1 and 2.
- Analysis methodology: Exact 2-sided 95% CIs for the percentages using the Clopper-Pearson method.
- Intercurrent events and missing data: Missing serology results will not be imputed. Participants will be summarized according to the vaccine group to which they were randomized.
- hSBA GMTs for each ACWY test strain at baseline and 1 month after the second dose of MenABCWY for each group, separately.
- 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 each group, separately.
    - 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 (ie, an hSBA titer of 1:8), 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.

6.3.1.3.2. Supplemental Analysis

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

One additional supplementary analysis without hypothesis testing will be performed to assess the lower bound of the 2-sided 95% CI for the percentage of participants achieving at least a 4-fold rise from baseline in each ACWY test strain against the prespecified LCI thresholds at 1 month following the second dose of MenABCWY for Group 2. The LCI thresholds for MenACWY are listed for reference in Table 10.

Table 10. LCI Thresholds for MenACWY

	Serogroup	LCI Thresholds
hSBA titer fold rise ≥4 from baseline	MenA	75%
	MenC	75%
	MenW	75%
	MenY	75%

6.4. Subset Analyses

Subgroup analyses may be performed on the primary and secondary immunogenicity and safety endpoints described in Section 6.1 and Section 6.2. No subgroup analysis is planned for rare events (endpoints with less than 1% of participants in any group). Subgroups include sex and race. If a subgroup variable (eg, race) does not have more than 1 group with greater than 5% of participants in the group, the corresponding subset analyses may not be reported.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct and Participant Disposition

All participants in the ITT population will be included in the disposition summaries. Summaries will be displayed by randomized vaccine group separately (Group 1 and Group 2).

Disposition summaries include:

- N and % of participants included in each study population (ITT, post–Vaccination 1 mITT, post–Vaccination 2 mITT, post–Vaccination 1 evaluable, post–Vaccination 2 evaluable).
- N and % of participants receiving each vaccination.
- N and % of participants completing vaccination phases and follow-up phases.
- N and % of participants who withdrew during the vaccination phases and reasons for withdrawal.
- N and % of participants who withdrew during the follow-up phases and reasons for withdrawal.

For each blood draw, the number and percentage of participants randomized, vaccinated at each visit (Visits 1 and 4 for Group 1; Visits 1, 4, and 9 for Group 2), and providing blood samples within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated by randomized vaccine group, and total population.

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

6.5.2. Study Vaccination Exposure

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

6.5.3. Demographic, Medical History, and Baseline Characteristics

The safety population will be used to generate the demographic and baseline characteristics summary. All summaries will be presented for each randomized vaccine group separately, and the total population.

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

The listings of medical history and baseline physical examination may be provided.

6.5.4. Concomitant Medications and Nondrug Treatments

The listings of nonstudy vaccines and concomitant medications captured throughout the study will be provided according to the WHO Drug Dictionary.

6.6. Safety Summaries and Analyses

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

6.6.1. Adverse Events

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

Analyses and summaries of primary AE endpoints are described in detail in Section 6.1.2.

6.6.1.1. Related Events

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

6.6.1.2. Severe Events

AEs deemed severe by the investigator may be summarized separately. The denominator for the percentages will be the appropriate safety population.

6.6.1.3. Neuroinflammatory and Autoimmune Conditions

A list of PTs to include all of the neuroinflammatory and autoimmune conditions will be provided by the medical monitor prior to database lock for each analysis. These events can be SAEs or AEs.

6.6.1.4. AEs Leading to Study Withdrawal

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

6.6.1.5. Death

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

6.6.2. Physical Examination

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

7. INTERIM ANALYSES

7.1. Introduction

No interim analysis is planned for the study.

Statistical analyses will be performed when the following data are available:

> Analysis 1: Participants have completed Visit 5 (1 month after the second dose of MenABCWY in Group 1 [0- and 12-month schedule]). Immunogenicity data for Visits 1, 2, and 5 for participants from Groups 1 and 2 will be included in Analysis 1. Safety data for all participants from Groups 1 and 2 for Visits 1 through 5 will be included in Analysis 1.

A final analysis will be done after all the available data have been collected.

The study team will remain blinded until all participants have completed Visit 5. The impact of COVID-19 will be assessed prior to the Analysis 1 time point. The SAP may be amended accordingly to account for this impact, if any.

7.2. Interim Analyses and Summaries

7.2.1. Data Monitoring Committee

This study will use an E-DMC.

An independent statistician will provide unblinded safety reports to the E-DMC for review. Safety data will be reviewed by the E-DMC throughout the study.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

8. REFERENCES

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

9. APPENDICES

Appendix 1. Objectives, Estimands, and Endpoints

Study objectives, estimands, and endpoints as described in the protocol. The endpoints related to the percentage of participants with hSBA titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for the 4 primary MenB test strains in the exploratory endpoints may not be reported. This will not extend to reporting of the primary endpoint of percentage of participants achieving hSBA titers ≥ LLOQ and ≥1:4. The endpoints related to hSBA GMTs for each of the 4 primary MenB test strains and for each of the ACWY test strains at 13 months after the first dose of MenABCWY in Group 2 will not be reported.

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.	• AEs, SAEs, MAEs, NDCMCs, and immediate AEs. • Days missing from school or work because of AEs.

Objectives	Estimands	Endpoints

	• 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.
	  o From Vaccination 2 (Visit 4) through 1 month after Vaccination 2 (Visit 5) in Groups 1 and 2.
	  o 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:
	  o From 1 month after Vaccination 1 (Visit 2) through 6 months after Vaccination 1 (Visit 3) in Groups 1 and 2.
	  o 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:
	  o From Vaccination 1 (Visit 1) through 6 months after Vaccination 1 (Visit 3) in Groups 1 and 2.
	  o 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.	

Objectives	Estimands	Endpoints
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). 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).	• hSBA titer for each of the MenACWY test strains.
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.

Objectives	Estimands	Endpoints
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 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 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.
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	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

Objectives	Estimands	Endpoints
	1 month after the second 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.	
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).	• 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 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 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 titer for each of the MenACWY test strains.

Objectives	Estimands	Endpoints
	• 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). • 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.	

Appendix 2. List of Abbreviations

Abbreviation	Term
ACWY	meningococcal group A, C, W, and Y
AE	adverse event
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CRF	case report form
E-DMC	external data monitoring committee
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
IRT	interactive response technology
ITT	intent-to-treat
LCI	lower limits of the confidence interval
LLOQ	lower limit of quantitation
LOD	limit of detection
MAE	medically attended adverse event
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
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
PRP-OMP	polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein
PT	preferred term
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	system organ class
US	United States
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

Document Approval Record

Document Name:	C3511004 Statistical Analysis Plan V4 Clean Copy, 15 Apr 2024
Document Title:	A PHASE 2b, RANDOMIZED, OBSERVER-BLINDED TRIAL TO DES CRIBE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MenABCWY ADMINISTERED ON 2 DIFFERENT DOSING SCHEDUL ES IN HEALTHY PARTICIPANTS ≥11 TO <15 YEARS OF AGE

Signed By:	Date(GMT)	Signing Capacity
PPD	15-Apr-2024 15:24:21	Final Approval