Protocol C3511001

A PHASE 3, RANDOMIZED, ACTIVE-CONTROLLED, OBSERVER-BLINDED TRIAL TO ASSESS THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MenABCWY IN HEALTHY PARTICIPANTS ≥10 TO <26 YEARS OF AGE

Statistical Analysis Plan (SAP)

Version: 3

Date: 13 Jul 2022

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF TABLES 5
APPENDICES 5
1. VERSION HISTORY 6
2. INTRODUCTION 7
2.1. Study Objectives, Endpoints, and Estimands 8
2.1.1. Primary Objectives 8
2.1.2. Secondary Objectives 8
2.1.3. Tertiary/Exploratory Objectives 8
2.1.4. Primary Estimands 9
2.1.5. Secondary Estimands 13
2.1.6. Additional Estimands 14
2.2. Study Design 16
2.3. Schedule of Activities (SoA) 18
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 20
3.1. Primary Endpoints 20
3.1.1. Primary Immunogenicity Endpoints 20
3.1.2. Primary Safety Endpoints 20
3.2. Secondary Endpoints 20
3.2.1. Secondary Immunogenicity Endpoints 20
3.3. Tertiary/Exploratory Endpoints 20
3.4. Baseline Variables 21
3.4.1. Demographic, Medical History, and Baseline Characteristic Variables 21
3.4.2. Previous Vaccinations 21
3.5. Safety Endpoints 22
3.5.1. Adverse Events 22
3.5.1.1. Analysis Intervals 23
3.5.2. Reactogenicity Data 24
3.5.2.1. Local Reactions Endpoints 24
3.5.2.2. Systemic Events Endpoints 26

3.5.2.3. Use of Antipyretic Medication 28
3.5.3. Pregnancy Testing 28
3.5.4. Laboratory Data 28
3.5.5. Medical Device Errors 28
3.6. Study Conduct 28
3.6.1. E-Diary Completion 28
3.6.2. Nonstudy Vaccines and Concomitant Medications 29
4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS) 30
4.1. Vaccine/Stratum Misallocation 31
5. GENERAL METHODOLOGY AND CONVENTIONS 32
5.1. Hypotheses and Decision Rules 32
5.2. General Methods 34
5.2.1. Analyses for Binary Endpoints 34
5.2.1.1. Immunogenicity Data 34
5.2.1.2. Safety Data 36
5.2.2. Analyses for Continuous Endpoints 37
5.2.2.1. Geometric Mean Titers 37
5.2.2.2. Reverse Cumulative Distribution Curves 37
5.2.2.3. Days Missed 37
5.3. Methods to Manage Missing Data 37
5.3.1. Safety Data 37
5.3.1.1. Reactogenicity Data 37
5.3.2. Immunogenicity Data 38
6. ANALYSES AND SUMMARIES 39
6.1. Primary Endpoints 39
6.1.1. Primary Immunogenicity Endpoints 39
6.1.1.1. hSBA Titer for Each of the MenACWY Test Strains for ACWY-Naïve Participants 39
6.1.1.2. hSBA Titer for Each of the MenACWY Test Strains for ACWY-Experienced Participants 39
6.1.1.3. Primary MenB Test Strain Evaluation (A22, A56, B24, and B44) 40
6.1.2. Primary Safety Endpoints 41
6.1.2.1. Local Reactions Within 7 Days After Vaccination 41

6.1.2.2. Systemic Events Within 7 Days After Vaccination 41
6.1.2.3. Use of Antipyretic Medications Within 7 Days After Vaccination 42
6.1.2.4. Serious Adverse Events, Medically Attended Adverse Events, and Newly Diagnosed Chronic Medical Conditions 42
6.1.2.5. Adverse Events 42
6.1.2.6. Immediate Adverse Events 43
6.1.2.7. Days Missing School or Work 43
6.2. Secondary Endpoints 43
6.2.1. Secondary Immunogenicity Endpoints 43
6.2.1.1. hSBA Titer for Each of the MenACWY Test Strains for ACWY-Naïve Participants 44
6.2.1.2. hSBA Titer for Each of the MenACWY Test Strains for ACWY-Experienced Participants 44
6.3. Other Endpoints 45
6.3.1. Tertiary/Exploratory Endpoints 45
6.3.1.1. hSBA Titer for Each of the MenACWY Test Strains 45
6.3.1.2. Primary MenB Test Strain Evaluations (A22, A56, B24, and B44) 47
6.3.1.3. Secondary MenB Test Strain Evaluation 47
6.3.1.4. Positive Predictive Value Analyses 48
6.3.1.5. Exploratory Analyses for the Relationship Between Pre– and Post–Vaccination 2 hSBA Titers 48
6.4. Subset Analyses 48
6.5. Baseline and Other Summaries and Analyses 49
6.5.1. Study Conduct and Participant Disposition 49
6.5.2. Vaccine Exposure 49
6.5.3. Demographic, Medical History, and Baseline Characteristics 49
6.5.4. E-Diary Completion 50
6.5.5. Concomitant Medications and Nondrug Treatments 50
6.6. Safety Summaries and Analyses 50
6.6.1. Adverse Events 50
6.6.1.1. Related Events 50
6.6.1.2. Severe Events 51

6.6.1.3. Neuroinflammatory and Autoimmune Conditions....51
6.6.1.4. AEs Leading to Study Withdrawal....51
6.6.1.5. Death....51
6.6.2. Reactogenicity Data....51
6.6.3. Physical Examination....51
7. INTERIM ANALYSES....51
7.1. Introduction....51
7.2. Data Monitoring Committee....51
8. REFERENCES....52
9. APPENDICES....53

LIST OF TABLES

Table 1. Summary of Changes....6
Table 2. Study Design....7
Table 3. Schedule of Activities (SoA)....18
Table 4. Summary of Adverse Event Collection....22
Table 5. Analysis Intervals for AEs, SAEs, MAEs, NDCMCs, and Days Missing School or Work Because of AEs....23
Table 6. Analysis Intervals for Immediate AEs....24
Table 7. Analysis Interval for Reactogenicity Data....24
Table 8. Derived Variables for Local Reactions....25
Table 9. Grading of Redness and Swelling....25
Table 10. Grading of Pain at Injection Site....25
Table 11. Grading of Systemic Events....27
Table 12. Severity Scale for Fever....27
Table 13. Validated hSBA LOD and LLOQ for MenB Primary Strains....34
Table 14. Validated hSBA LOD and LLOQ for MenACWY Serogroups....35

APPENDICES

Appendix 1. Objectives, Estimands, and Endpoints....53
Appendix 2. List of Abbreviations....60

1. VERSION HISTORY

Table 1. Summary of Changes

Version / Date	Associated Protocol Amendment	Rationale	Specific Changes
1 / 02 Jun 2020	Original 12 Dec 2019	N/A	N/A
2 / 02 Mar 2022	Amendment 1 30 Apr 2021	Table reduction initiative, including removal of redundancy.	• Removed the analyses from: Section 2.1.6, Section 6.3.1.1.1, Section 6.3.1.2.1, Section 6.3.1.1.3, and Appendix 1 (Section 9) for the exploratory endpoints 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 and the MenACWY test strains. The endpoints of percentage of participants achieving an hSBA titer ≥ LLOQ and ≥1:4 (MenB) are not affected. • Replaced some study conduct tables with listings throughout Section 6.5. • Removed the sensitivity analysis for an alternative definition of composite response in Section 5.2.1.1.
		Addition of new analyses.	• Added additional exploratory analyses to investigate the relationship between pre– and post–Vaccination 2 MenACWY hSBA titers in the MenABCWY groups in Section 6.3.1.5.
		Addition of clarifications for analyses.	• Added the data handling method for participants randomized to the safety subset but for whom immunogenicity data are collected. • Removed special handling of participants who received a monovalent C vaccine in Section 4.1. • In Section 2.1.2, Section 2.1.5, Section 3.2.1., Section 6.2.1.3, Sectiun 6.3.1.3, and Appendix 1 (Section 9), added that the reporting on the evaluation of the secondary MenB test strains will be done only if requested. • Updated the temperature scale of severity for fever (Table 12) in Section 3.5.2.2 to allow for consistency in severity designation between temperatures recorded in °F and °C scales.

		Administrative changes.	Updated Section 2.2 Study Design and Table 2 according to protocol amendment.
3/ 13 Jul 2022	Amendment 2 13 Jun 2022	Modifications in the definitions of the immunogenicity analysis populations. Administrative changes to be consistent with protocol amendment 2.	• Extended the window for the post–Vaccination 1 blood draw visit (Visit 2) and the post–Vaccination 2 blood draw visit (Visit 4) to "28 to 49 days" after the previous vaccination visit in the definitions of the post–Vaccination 1 evaluable immunogenicity population and the post–Vaccination 2 evaluable immunogenicity population in Section 4. • Moved secondary MenB strain immunogenicity objectives from secondary immunogenicity objectives to tertiary/exploratory objectives.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3511001. 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

		Vaccination 1	Follow-up Visit 1[a]	Vaccination 2	Follow-up Visit 2[a]	Telephone Contact
	Approximate Month	**0**	**1**	**6**	**7**	**12**
	Visit Number	**1**	**2**	**3**	**4**	**5**
ACWY-naïve participants	Group 1 (n=450)	MenABCWY + Saline		MenABCWY		
	Group 2 (n=225)	Trumenba + MenACWY-CRM		Trumenba		
ACWY-experienced participants	Group 3 (n=675)	MenABCWY + Saline		MenABCWY		
	Group 4 (n=338)	Trumenba + MenACWY-CRM		Trumenba		
	Blood draw (Groups 1-4 only)	25 mL	25 mL		25 mL or 50 mL	

Table 2. Study Design

		Vaccination 1	Follow-up Visit 1[a]	Vaccination 2	Follow-up Visit 2[a]	Telephone Contact
ACWY-naïve participants	Group 5 (n=500)	MenABCWY + Saline		MenABCWY		
	Group 6 (n=50)	Trumenba + MenACWY-CRM		Trumenba		
ACWY-experienced participants	Group 7 (n=125)	MenABCWY + Saline		MenABCWY		
	Group 8 (n=50)	Trumenba + MenACWY-CRM		Trumenba		

a. Follow-up Visits 1 and 2 will be a telephone contacts for safety-assessment-only participants in Groups 5 through 8, for whom blood samples will not be obtained.

2.1. Study Objectives, Endpoints, and Estimands

For this study and throughout the SAP, ACWY-experienced is defined as receiving a US-licensed MenACWY vaccine at least 4 years prior to enrollment.

2.1.1. Primary Objectives

- To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM in both ACWY-naïve and ACWY-experienced participants, separately.

- To demonstrate that the immune response for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba®.

- To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs.

2.1.2. Secondary Objectives

To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.

2.1.3. Tertiary/Exploratory Objectives

- To describe the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.

- To describe the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.

- To describe the immune response for MenB, as measured by hSBA performed with primary MenB test strains, induced by 2 doses of MenABCWY compared to the immune response induced by 2 doses of Trumenba.

- To describe the immune response for MenB, as measured by hSBA performed with secondary MenB test strains, induced by 2 doses of MenABCWY.

The tertiary/exploratory objective related to secondary MenB test strains induced by 2 doses of MenABCWY will be reported if requested/required.

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

2.1.4. Primary Estimands

- **Primary Immunogenicity Estimands**

For the primary, secondary, and exploratory estimands below, ACWY-experienced is defined as receiving a US-licensed MenACWY vaccine at least 4 years prior to enrollment.

For the primary estimands to demonstrate the immunogenicity objectives for noninferiority, the estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. This addresses the objective of estimating the maximum potential difference between 2 groups, since the impact of noncompliance is likely to diminish the observed difference between the 2 groups.

For the first primary objective (to demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, for ACWY-naïve and ACWY-experienced participants separately), there are 2 primary estimands with the following attributes (ACWY-naïve and ACWY-experienced participants separately):

For ACWY-naïve participants:

- Population: ACWY-naïve participants receiving at least 1 dose (Group 2) of MenACWY-CRM or 2 doses (Group 1) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).

- Variable: hSBA titer for each of the MenACWY test strains (MenA, MenC, MenW, and MenY).

- 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: Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each MenACWY test strain, 1 month after Vaccination 2 in Group 1 compared to 1 month after Vaccination 1 in Group 2.

- 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 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 ACWY-experienced participants:

- Population: ACWY-experienced participants receiving at least 1 dose (Group 4) of MenACWY-CRM or 2 doses (Group 3) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).

- Variable: hSBA titer for each of the MenACWY 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:

  - Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each MenACWY test strain, 1 month after Vaccination 2 in Group 3 compared to 1 month after Vaccination 1 in Group 4.

    - 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 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 second primary objective (to demonstrate that the immune response for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba), the estimand has the following attributes:

- Population: Participants receiving at least 2 doses of investigational product 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:

  - Differences in 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), in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2.

  - Difference in 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, in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2.

    - 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 hypothesis and decision rules, refer to Section 5.1. The planned analyses for the primary endpoints as they relate to the estimands are discussed in Section 6.1. Populations used for the analysis are described in Section 4. Details on handling vaccine and/or stratum misallocations are described in Section 4.1.

- **Primary Safety Estimands**

  For the primary safety objective to describe the safety profile of MenABCWY, as measured by local reactions, systemic events, and the use of antipyretic medications, the estimand has the following attributes:

  - Population: Participants receiving at least 1 dose of investigational product, expressed as MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined).

  - Variables: Local reactions (pain, redness, and swelling), systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain), and use of antipyretic medication.

  - Intercurrent event(s): Participants will be analyzed according to the vaccine they actually received. Missing e-diary data will not be imputed.

- Population-level summary: Percentages of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after vaccination in the MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined).

For the primary safety objective to describe the safety profile of MenABCWY, as measured by AEs, SAEs, MAEs, NDCMCs, and immediate AEs, the estimands have the following attributes:

- Population: Participants receiving at least 1 dose of investigational product, expressed as MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined).

- Variables: AEs, SAEs, MAEs, NDCMCs, immediate AEs, and days missing 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 summaries:

  - The percentages 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 vaccination.

    - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]).

  - The percentages 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 phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5]).

    - Throughout the study (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5]).

  - The percentage of participants reporting at least 1 immediate AE.

  - The percentage of participants who missed days of school and/or work because of AEs.

2.1.5. Secondary Estimands

For the first secondary objective (to demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately), there are 2 estimands with the following attributes:

For ACWY-naïve participants:

- Population: ACWY-naïve participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the MenACWY 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: Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each MenACWY test strain, 1 month after Vaccination 1 in Group 1 compared to Group 2.
    - 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 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 ACWY-experienced participants:

- Population: ACWY-experienced participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titer for each of the MenACWY 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: Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each MenACWY test strain, 1 month after Vaccination 1 in Group 3 compared to Group 4.
    - 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 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.

2.1.6. Additional Estimands

For the first tertiary/exploratory objective (to describe the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately), the estimand has the following attributes:

- Population: ACWY-naïve and ACWY-experienced participants separately who have received at least 1 dose (Groups 2 and 4) of MenACWY-CRM or 2 doses (Groups 1 and 3) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants).

- Variable: hSBA titers for each MenACWY strain.

- 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 ≥1:8 for each MenACWY test strain, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3.

  - The percentage of participants achieving hSBA titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each MenACWY test strain, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3.

  - hSBA GMTs for each of the MenACWY test strains, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3.

The second tertiary/exploratory objective (to describe the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately), the estimand has the following attributes:

- Population: ACWY-naïve and ACWY-experienced participants separately who have received at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants).

- Variable: hSBA titers for each MenACWY strain.
- 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 ≥1:8 for each MenACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4.
  - The percentage of participants achieving hSBA titers of ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each MenACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4.
  - hSBA GMTs for each of the MenACWY test strains, at baseline and 1 month after Vaccination 1 in Groups 1 through 4.

The third tertiary/exploratory objective (to describe the immune response for MenB, as measured by hSBA performed with primary MenB test strains, induced by 2 doses of MenABCWY compared to the immune response induced by 2 doses of Trumenba), the estimand has the following attributes:

- Population: Participants receiving at least 2 doses of investigational product 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:
  - Percentage and associated 95% CI for each of the primary MenB strains for participants achieving an hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2.
  - Percentage and associated 95% CI for each of the primary MenB strains for participants achieving defined hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2.
  - hSBA GMTs and associated 95% CIs for each of the 4 primary MenB test strains in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2.

For the tertiary/exploratory objective to further describe the immune response, the endpoints related to the percentage of participants with hSBA titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the MenACWY and primary MenB test strains will not be reported. The endpoints of percentage of participants achieving an hSBA titer ≥ LLOQ and ≥1:4 (MenB) are not affected.

For the last tertiary/exploratory objective (to describe the immune response for MenB, as measured by hSBA performed with secondary MenB test strains, induced by 2 doses of MenABCWY), the estimand has the following attributes:

- Population: Participants receiving at least 2 doses of investigational product who are in compliance with the key protocol criteria (evaluable participants).
- Variable: hSBA titers for each MenB secondary strain.
- 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:
  - Percentage of participants with hSBA titer ≥ LLOQ for each secondary MenB test strain in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2.
  - Percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each secondary MenB test strain in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2.
  - hSBA GMTs and associated 95% CI for each secondary MenB test strain in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2.

The tertiary/exploratory objective related to secondary MenB test strains induced by 2 doses of MenABCWY will be reported if requested/required.

2.2. Study Design

This is a Phase 3, randomized, active-controlled, observer-blinded multicenter trial in which approximately 2413 participants ≥10 to <26 years of age will be randomly assigned to receive either MenABCWY and saline, or Trumenba and MenACWY-CRM. The study will include evaluation of both ACWY-naïve and ACWY-experienced individuals. All participants will be naïve to any meningococcal group B vaccine prior to enrollment. ACWY-experienced is defined as receiving a US-licensed MenACWY vaccine at least 4 years prior to enrollment. Table 2 illustrates the study design.

Participants in Groups 1 through 4 will be considered an immunogenicity subset and will contribute to both the safety and immunogenicity analyses; these participants will have blood drawn prior to Vaccination 1 and 1 month after Vaccinations 1 and 2. Participants in Groups 5 through 8 will be considered a safety subset and will contribute to the safety analysis only, and will not have blood drawn for immunogenicity evaluations.

Randomization will be stratified by prior vaccination history. Overall, approximately 1225 ACWY-naïve and 1188 ACWY-experienced participants (having received 1 dose of Menactra or Menveo ≥4 years prior to the date of randomization) will be enrolled. Of these total participants, up to 675 ACWY-naïve and 1013 ACWY-experienced participants will contribute to the immunogenicity subset.

Participants enrolled in the immunogenicity subset will contribute to both the immunogenicity and safety evaluations. Additionally, participants will be enrolled in a safety subset that will contribute exclusively to the safety evaluation. Numbers enrolled in the safety subset will therefore be based on numbers needed to achieve an overall number of enrolled participants, all of whom will contribute to the safety evaluation. The numbers to be enrolled by group across immunogenicity and safety subsets as stated in the protocol (Protocol amendment 1, Section 1.2 and Table 1) are estimates only.

Additionally, randomization will be stratified by geographic region. The overall participant distribution by region will be approximately 80% from the US and approximately 20% from other regions. Among the participants in the immunogenicity subset, approximately 80% will be enrolled in US investigative sites, and approximately 20% will be enrolled in other regions. Regional or safety/immunogenicity group enrollment shifts may be necessary based on the availability of participants with specific characteristics (age group or ACWY experience) in a given location based on local immunization practices. However, these minor shifts from the originally targeted numbers will not deviate from original targets to a degree that will impact the overall study design or endpoint assessments of the study.

Enrollment targets will also be adjusted to achieve appropriate representation by age group (participants 10 to <18 years old and participants 18 to <26 years old) within each subset, and by MenACWY stratum within each subset.

Each participant will participate in the study for approximately 12 months. Approximately 2413 participants will be enrolled.

A portion of the projected number of participant enrollment slots may be moved from the safety subset to the immunogenicity subset to achieve appropriate regional distribution for the overall study population and the immunogenicity subset. This determination will be made by the sponsor while still blinded. The sponsor may decide to proceed with less than full enrollment if an assessment of power shows that it is sufficient to meet the primary objectives. This assessment will be done in a completely blinded fashion before any participants are unblinded or the immunogenicity data are accessed.

2.3. Schedule of Activities (SoA)

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

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.

Table 3. Schedule of Activities (SoA)

Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Visit Description	**Vaccination 1**	**Follow-up Visit 1[a]**	**Vaccination 2**	**Follow-up Visit 2[a]**	**Telephone Contact**
Approximate Month	**0**	**1**	**6**	**7**	**6 Months After Last Study Vaccination**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days After Last Vaccination**
Informed consent	X				
Review eligibility criteria	X				
Demography	X				
Confirm continued eligibility[b]		X	X	X	
Medical history and physical examination	X				
Record previous PRP-OMP vaccinations	X				
Record any previous meningococcal vaccinations	X				
Urine pregnancy test for female participants (obtain results prior to vaccination)	X		X		
Oral temperature (prior to vaccination)	X		X		
Randomization	X				
Obtain blood sample for participants in the immunogenicity subset (Groups 1-4 only) prior to vaccination	25 mL	25 mL		25 mL	
Investigational product administration and observation[c]	X		X		

Table 3. Schedule of Activities (SoA)

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Visit Description	**Vaccination 1**	**Follow-up Visit 1[a]**	**Vaccination 2**	**Follow-up Visit 2[a]**	**Telephone Contact**
Approximate Month	**0**	**1**	**6**	**7**	**6 Months After Last Study Vaccination**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days After Last Vaccination**
Record nonstudy vaccinations		X	X	X	
Provide participant with an e-diary, caliper, measuring tape/ruler, and digital thermometer, if necessary, and provide instructions on use	X		X		
Review and collect e-diary		X		X	
Assess reactogenicity and record use of antipyretic medications[d]	Days 1 to 7		Days 1 to 7		
Provide the participant with a contact card	X				
Provide the participant with a memory aid			X		
Complete Study Visit/Telephone Contact AE Checklist[e]		X	X	X	X
Record concomitant medications used to treat AEs	X	X	X	X	X
(S)AE collection appropriate for the visit[f]	X	X	X	X	X

Abbreviations: e-diary = electronic diary; PRP-OMP = polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein.

a. Follow-up Visits 1 and 2 will be telephone contacts for safety-assessment-only participants in Groups 5 through 8, for whom blood samples will not be obtained.
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 investigational product administration for any acute reactions.
d. Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the participant in order to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that were ongoing on the last day that the e-diary was completed.
e. Checklist includes questions regarding newly diagnosed chronic medical conditions, medically attended adverse events, and missed days of school or work, as well as about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
f. Please refer to Section 8.3.1 of the protocol.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Appendix 1 shows how the study estimands and endpoints relate to each objective. Section 6 describes the planned analyses and summaries.

3.1. Primary Endpoints

3.1.1. Primary 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).

3.1.2. Primary Safety Endpoints

- Local reactions (pain, redness, and swelling).
- Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain).
- Use of antipyretic medications within 7 days after each vaccination visit.
- 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.

3.3. Tertiary/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 titer for each of the secondary MenB test strains.

The tertiary/exploratory immunogenicity endpoint related to secondary MenB test strains induced by 2 doses of MenABCWY will be reported if requested/required.

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

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 13th 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 and each body system examined will be recorded in the CRF as normal, abnormal, or not done.

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.

Similarly, for participants who have received any prior meningococcal vaccines or vaccines containing 1 or more MenACWY groups, the trade name and date of administration will be recorded on the CRF.

3.5. Safety Endpoints

3.5.1. Adverse Events

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.6.1).

Tier 1 events: These are prespecified events of clinical importance. There is no Tier 1 event identified for MenABCWY at this stage.

Tier 2 events: These are events that are not Tier 1 but are "relatively common." A MedDRA PT is defined as a Tier 2 event if there are at least 4 participants in at least 1 combined group reporting the event.

Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

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

The time period for actively eliciting and collecting (S)AEs, MAEs, and NDCMCs for each participant is outlined in Table 4.

Table 4. Summary of Adverse Event Collection

	Visits 1-4	Visit 5
Approximate Month	**0-7**	**12**
Nonserious AEs	ICD through and including Visit 4 (1 month after Vaccination 2)	
SAEs	ICD through and including Visit 4 (1 month after Vaccination 2)	Since Visit 4
MAEs	ICD through and including Visit 4 (1 month after Vaccination 2)	Since Visit 4
NDCMCs	ICD through and including Visit 4 (1 month after Vaccination 2)	Since Visit 4

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

An MAE is defined as a nonserious AE that results in an evaluation at a medical facility, and participants who missed days of school or work because of an AE will be captured via the AE checklist (See Table 3). Neuroinflammatory and autoimmune conditions will also be captured via the AE checklist. An NDCMC is defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects.

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant/parent(s)/legal guardian begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 4. At Visit 5, the participant will be contacted by telephone to inquire about SAEs, MAEs, and NDCMCs since Visit 4.

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

Medical occurrences that begin before the start of investigational product administration but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

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

3.5.1.1. Analysis Intervals

There will be 6 analysis intervals for the AE data collected via the CRF (Table 5).
The analysis populations used for these intervals are described in detail in Section 4.

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

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

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

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

Table 6. Analysis Intervals for Immediate AEs

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

3.5.2. Reactogenicity Data

Reactogenicity data are solicited AEs. The reactogenicity data collected from the study e-diary will include: local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain), and use of antipyretic medication.

The e-diary will record reactogenicity data from Day 1 to Day 7 starting on the day of each vaccination (Day 1), following investigational product administration. Local reactions at the site of investigational product administration only on the left arm will be recorded.

Three analysis intervals will be applied to reactogenicity data (Table 7).

Table 7. Analysis Interval for Reactogenicity Data

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

3.5.2.1. Local Reactions Endpoints

For each local reaction, the derivation of whether or not the specific reaction occurred on each day and "any day (Days 1-7)" will be made. The variable will be calculated for each vaccination as well as overall reactions for any vaccination. The derivation of this variable is given in Table 8.

Table 8. Derived Variables for Local Reactions

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

a. For redness and swelling, "mild," "moderate, and "severe" categories are based on the caliper size reported from the e-diary and defined in Table 9.
b. For redness and swelling, "none" means 0 to 4 caliper units reported in the e-diary.

A caliper (measuring device) is used to measure the redness or swelling of the injection site area. Caliper units (range: 1-21+) are converted to centimeters according to 1 caliper unit = 0.5 centimeters and then categorized as none, mild, moderate, or severe based on the grading scale of local reactions in Table 9. Pain at the injection site will be assessed by the participant/parent/legal guardian according to the grading scale in Table 10.

Table 9. Grading of Redness and Swelling

None	0 to 2.0 cm (0 to 4 caliper units)
Mild	>2.0 to 5.0 cm (5 to 10 caliper units)
Moderate	>5.0 to 10.0 cm (11 to 20 caliper units)
Severe	>10.0 cm (>20 caliper units)

Table 10. Grading of Pain at Injection Site

None	No pain
Mild	Does not interfere with activity
Moderate	Interferes with activity
Severe	Prevents daily activity

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

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

For participants experiencing any local reactions (or those with derived reaction presence in Table 8), the maximum duration (last day of reaction - first day of reaction + 1) will be derived for the study vaccination. Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the participant diary-recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing.

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

Participants with no reported reaction have no duration.

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

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

3.5.2.2. Systemic Events Endpoints

Participants will be asked to assess the severity of each event according to Table 11.

Table 11. Grading of Systemic Events

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires IV hydration
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Fatigue	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Muscle pain (other than muscle pain at the injection site)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity

Abbreviation: IV = intravenous.

Oral temperature will be collected in the e-diary, daily, for 7 days after each vaccination and at any time during the 7 days when fever is suspected. The highest temperature for each day will be recorded in the e-diary. The protocol defines fever as an oral temperature ≥38.0°C (≥100.4°F). Fever will be scaled as shown in Table 12.

Table 12. Severity Scale for Fever

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

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

1. Each systemic event on each day (Days 1-7) after each vaccination.
2. Each systemic event on any day (Days 1-7) after each vaccination and any vaccination.
3. Any systemic event on any day (Days 1-7) after each vaccination and after any vaccination.
4. Maximum severity of each systemic event on any day (Days 1-7) after each vaccination and any vaccination.
5. Maximum duration of each systemic event after each vaccination.

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

3.5.2.3. Use of Antipyretic Medication

The use of antipyretic medication will be recorded in the e-diary for 7 days (Day 1 to Day 7) after each vaccination.

The following variables will be derived:

1. Use of antipyretic medication on each day (Days 1-7) after each vaccination.
2. Use of antipyretic medication on any day (Days 1-7) after each vaccination and any vaccination.
3. Maximum duration of use of antipyretic medication after each vaccination.

3.5.3. Pregnancy Testing

The results of the urine pregnancy tests collected at Visits 1 and 3 will be recorded.

3.5.4. Laboratory Data

Laboratory assessments will not be collected for this study.

3.5.5. Medical Device Errors

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

3.6. Study Conduct

3.6.1. E-Diary Completion

For any given day, an e-diary will be transmitted and considered complete if all expected data (the 3 local reactions, the 9 systemic events including fever, and the use of antipyretic medications) are available. If all data are missing for all items on the e-diary, for all days following vaccination, the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all days are available (ie, not missing) and data are valid. Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

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

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

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

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

3.6.2. Nonstudy Vaccines and Concomitant Medications

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

Permitted during the study include:

Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed. However, while prioritizing standard clinical care, efforts should be made not to administer nonstudy vaccines within 14 days (for nonlive vaccines) or 28 days (for live vaccines) as specified below (see exception below for any COVID-19 vaccination).Guidance provided by the CDC states that COVID-19 vaccines and other vaccines may now be administered without regard to timing. Because of the COVID-19 pandemic and the ongoing COVID-19 vaccinations at the time of study recruitment, participants will be allowed to receive any authorized (nonexperimental) COVID-19 vaccination within 8 days of investigational product administration (ie, not permitted 7 days before or after any study vaccination).

- 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) of investigational product administration.

- Antipyretic and other pain medication to treat symptoms following investigational product administration 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.

The name, start and stop dates, and route of administration for concomitant medications (prescription and nonprescription) used to treat an AE (excluding events recorded only in the e-diary) from the signing of the ICD through Visit 5 will be recorded in the CRF.

Treatments will be categories 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 investigational product (as randomized), also termed the 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.
mITT	All participants who received at least 1 study vaccination and have at least 1 valid and determinate MenB or MenACWY assay result available at any time point from Visit 1 to Visit 4.
Safety	All randomized participants who receive at least 1 dose of the investigational product 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 immunogenicity population	1. Were randomized to the study group of interest. 2. Were eligible through Visit 2, ie, fulfilling all of the inclusion criteria and none of the exclusion criteria at each visit where eligibility criteria are collected and confirmed. 3. Received the investigational products at Visit 1 as randomized. 4. Had blood drawn for assay testing within the required time frames at Months 0 (Visit 1: before Vaccination 1) and - (Visit 2: 1 month after the first vaccination: window 28-49 days). 5. Had at least 1 valid and determinate MenACWY 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 immunogenicity population	1. Were randomized to the study group of interest. 2. Were eligible through Visit 4, ie, fulfilling all of the inclusion criteria and none of the exclusion criteria at each visit where eligibility criteria are collected and confirmed. 3. Received the investigational products at Visit 1 and Visit 3 as randomized. 4. Had blood drawn for assay testing within the required time frames at Months 0 (Visit 1: before Vaccination 1) and 7 (Visit 4: 1 month after the second vaccination: window 28-49 days). 5. Had at least 1 valid and determinate MenACWY or MenB assay result at Visit 4. 6. Had received no prohibited vaccines or treatment through Visit 4. 7. Had no important protocol deviations through Visit 4.

Defined Population for Analysis	Description
Vaccination 1 safety population	This population will include participants who received the first dose of investigational product at Visit 1 and for whom safety information is available from Visit 1 to prior to Visit 3.
Vaccination 2 safety population	This population will include participants who received the second dose of investigational product at Visit 3 and for whom safety information is available from Visit 3 to Visit 4.
Follow-up safety population	This population will include participants who received at least 1 dose of investigational product and for whom safety information is available from after Visit 4 through Visit 5.

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

Participants withdrawn early will be included in the follow-up safety population, in case they have any type of AEs in the AE follow-up interval.

4.1. Vaccine/Stratum Misallocation

- Randomized into the wrong MenACWY stratum: These participants will be included in the safety population for the safety analysis and will be reported under the MenACWY stratum according to true MenACWY history. These participants will also be included in the mITT population for immunogenicity analyses if data are available, and will be reported under the MenACWY stratum according to their true MenACWY history (MenACWY experience recorded on the CRF for prior MenACWY history). However, these participants will be excluded from the analyses using evaluable immunogenicity population(s) for the MenACWY endpoints, but included in the analyses using evaluable immunogenicity population(s) for the MenB endpoints. A participant's true MenACWY history (naïve/experienced) will be ascertained programmatically from the prior meningococcal vaccine data set in the clinical database before the planned unblinding. Serogroups contained within the prior meningococcal vaccine received will be determined by the sponsor's global medical monitor.

- Participants randomized to the safety subset but for whom immunogenicity data are collected according to the CRF: These participants will be reported according to their true immunogenicity subset per the CRF. A participant's true immunogenicity/safety assignment will be ascertained programmatically in the clinical database before the planned unblinding. These participants will be included in the safety population and the mITT population. For the evaluable populations, they will be excluded.

- 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 population 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

The primary immunogenicity objectives are:

- To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, for ACWY-naïve and ACWY-experienced participants separately.

- To demonstrate that the immune response for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba.

The primary objectives of noninferiority will be met if:

- The lower limit of the 2-sided 95% CI for the difference in seroresponders (Group 1 - Group 2) is > -10% for all of the MenACWY test strains at 1 month after the second vaccination for Group 1 and at 1 month after the first vaccination for Group 2; and

- The lower limit of the 2-sided 95% CI for the difference in seroresponders (Group 3 - Group 4) is > -10% for all of the MenACWY test strains at 1 month after the second vaccination for Group 3 and at 1 month after the first vaccination for Group 4; and

- The lower limit of the 2-sided 95% CI for the differences in 4-fold rises and composite responses (Groups 1+3 - Groups 2+4) is > -10% for all of the primary MenB test strains at 1 month after the second vaccination.

For the MenACWY noninferiority evaluation in ACWY-naïve participants, the immune response will be evaluated at 1 month following Vaccination 2 for Group 1 and at 1 month following Vaccination 1 for Group 2. The null hypothesis (H_0) for each MenACWY serogroup for noninferiority is as follows:

H_0: $\pi_{G1} - \pi_{G2} \leq -10\%$

where π_{G1} and π_{G2} are the percentages of participants who achieve a 4-fold rise in hSBA titers for MenA, MenC, MenW, and MenY.

π_{G1} and π_{G2} represent Group 1 and Group 2 participants, respectively.

For the MenACWY noninferiority evaluation in ACWY-experienced participants, the immune response will be evaluated at 1 month following Vaccination 2 for Group 3 and at 1 month following Vaccination 1 for Group 4 participants.

The null hypothesis (H_0) for each MenACWY serogroup for noninferiority is as follows:

H_0: $\pi_{G3} - \pi_{G4} \leq -10\%$

where π_{G3} and π_{G4} are the percentages of participants who achieve a 4-fold rise in hSBA titers for MenA, MenC, MenW, and MenY.

π_{G3} and π_{G4} represent Group 3 and Group 4 participants, respectively.

The null hypothesis (H_0) for noninferiority for each primary MenB test strain is as follows:

H_0: $\pi_{G1+G3} - \pi_{G2+G4} \leq -10\%$

where π_{G1+G3} and π_{G2+G4} are the percentages of 4-fold rises and composite responses for Groups 1 and 3 combined and for Groups 2 and 4 combined, respectively, at 1 month after the second vaccination.

The primary hypotheses for MenACWY endpoints and the primary hypotheses for MenB endpoints will be tested simultaneously. The primary objectives of noninferiority will be met only if all statistical criteria for the objectives were met. Therefore, the multiplicity of primary objectives does not require an alpha adjustment.

The secondary objective with hypothesis testing is:

- To demonstrate that the immune response induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, for ACWY-naïve and ACWY-experienced participants separately.

Hypothesis testing for the secondary objective will be performed only if the primary objectives are successful.

The secondary objective of noninferiority will be met if:

- The lower limit of the 2-sided 95% CI for the difference in seroresponders (Group 1 - Group 2) is > -10% for all of the MenACWY test strains (at 1 month after the first vaccination for Group 1 and at 1 month after the first vaccination for Group 2); and

- The lower limit of the 2-sided 95% CI for the difference in seroresponders (Group 3 - Group 4) is > -10% for all of the MenACWY test strains (at 1 month after the first vaccination for Group 3 and at 1 month after the first vaccination for Group 4).

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, and for difference in 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.

For both Tier 1 and Tier 2 events, the 95% CIs for the difference in percentage of participants reporting the events between MenABCWY and Trumenba combined groups will be calculated using the Miettinen and Nurminen method.[2] There are no Tier 1 events identified for MenABCWY at this stage.

5.2.1.1. Immunogenicity Data

Each MenB strain has a validated LLOQ value defined (Table 13). Each MenACWY serogroup has a qualified LLOQ value defined (Table 14).

Table 13. 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 14. 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; MenACWY = *Neisseria meningitidis* group A, C, W, and Y.

For the immunogenicity subset, all hSBA titers assessed for either MenB or MenACWY will be analyzed as below:

At each visit where assay titers are available (Visits 1, 2, and 4), participants with 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 at which 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 and MenACWY titers are:

- ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for MenB hSBA titers
- ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for MenACWY hSBA titers

A composite response will be computed at 1 month after Vaccination 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.

= •, 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, prevaccination) to 1 month after Vaccinations 1 and 2 (Visits 2 and 4) 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, a 4-fold response is defined as an hSBA titer of ≥4 times 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:

= •, if the assay result at baseline or the 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.

5.2.1.2. Safety Data

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

For both Tier 1 and Tier 2 events (AEs by PTs during the vaccination period), the 95% CIs for the difference in percentage of participants reporting the events between MenABCWY and Trumenba combined groups will be calculated using the Miettinen and Nurminen method.

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. No adjustment for multiplicity is needed. There are no Tier 1 events identified for MenABCWY.

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Geometric Mean Titers

GMTs will be computed for each hSBA titer for the 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 vaccine groups 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.

5.3.1.1. Reactogenicity Data

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

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

Based on data from available studies, the missing data on reactogenicity are minimal, which is consistent with Li et al (2011).[3] No sensitivity analysis is planned for reactogenicity data.

5.3.2. Immunogenicity Data

As assay data are expected to be missing completely at random, the primary analysis for the primary objectives will be based upon the observed, determinate observations. No imputation will be performed. The proportion of participants with missing immunogenicity data may be summarized at each blood sampling visit for 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.

If 10% or more of the participants in any group have missing hSBA data for the MenB or MenACWY strains for non–withdrawal-related reasons, a sensitivity analysis using an MMRM in the immunogenicity subset may be applied for each strain (GMT). For the MenACWY strains, the ACWY-naïve and ACWY-experienced participants will be analyzed separately. For the primary MenB strains, Groups 1 and 3 combined will be described against Groups 2 and 4 combined.

The MMRM uses maximum likelihood estimation and it is under the assumption that the missingness is at random (MAR). To account for the intraparticipant correlation among the repeated measures, an unstructured covariance matrix will be used. In case the model does not converge, further covariance structures will be explored (ie, first-order autoregressive, compound symmetry). Independent variables (race, sex, etc) may be dropped from the model because of nonconvergence.

Log (hSBA) = randomized group(s) + race + sex + geographic location (US; ex-US) + age at randomization + visit. The intercept will be set as random effect.

In addition to type III analysis output, least-squares GMTs at each visit will be summarized for each strain.

These analyses will use the mITT population, using ½ LLOQ to set the hSBA values below LLOQ.

Similar to GMT, a GLIMMIX will be used. The response variables are binary variables (composite response and 4-fold response), and a logit link will be used. The model will be similar to above. As the 4-fold responses will not have a response at Visit 1, the GLIMMIX will use baseline hSBA titer as covariate and blood sampling time points at Visits 2 and 4 as repeated dependent variables. The composite response analyses will be similar to the GMT analyses, with composite responses at all 3 visits modeled as dependent variables. This analysis will only be applied to the mITT population. The model-estimated response rates and the 95% CIs will be summarized. The groups for the ACWY-naïve and ACWY-experienced participants will be similar to the GMT analysis.

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

Section 2 describes the estimands for each of the study objectives and Section 5.1 includes further details about the hypothesis testing for the primary and first secondary objectives. Below are the planned analysis by endpoints.

6.1. Primary Endpoints

6.1.1. Primary Immunogenicity Endpoints

6.1.1.1. hSBA Titer for Each of the MenACWY Test Strains for ACWY-Naïve Participants

6.1.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: ACWY-naïve participants: Post–Vaccination 1 evaluable population for Group 2 and post–Vaccination 2 evaluable population for Group 1.
- Analysis methodology: 95% CI for the difference in the percentage of seroresponders (defined as participants achieving a 4-fold rise from baseline for each MenACWY test strain) calculated by the Miettinen and Nurminen procedure.
- 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 95% CIs for the difference in the percentage of seroresponders, defined as participants achieving a 4-fold rise from baseline for each MenACWY test strain, 1 month after Vaccination 2 in Group 1 compared to 1 month after Vaccination 1 in Group 2 will be calculated using the Miettinen and Nurminen method. The lower limit of the CI will be used in the hypothesis test for noninferiority as detailed in Section 5.1. Exact 2-sided 95% CIs for the percentages of seroresponders will be provided using the Clopper-Pearson method.

6.1.1.1.2. Sensitivity/Supplementary Analyses

The main analysis will also be performed on the mITT population.

6.1.1.2. hSBA Titer for Each of the MenACWY Test Strains for ACWY-Experienced Participants

6.1.1.2.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: ACWY-experienced participants: Post–Vaccination 1 evaluable population for Group 4 and post–Vaccination 2 evaluable population for Group 3.

- Analysis methodology: 95% CI for the difference in the percentage of seroresponders, calculated by the Miettinen and Nurminen procedure.

- 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 95% CIs for the difference in the percentage of seroresponders, defined as participants achieving a 4-fold rise from baseline for each MenACWY test strain, 1 month after Vaccination 2 in Group 3 compared to 1 month after Vaccination 1 in Group 4 will be calculated using the Miettinen and Nurminen method. The lower limit of the CI will be used in the hypothesis test for noninferiority as detailed in Section 5.1. Exact 2-sided 95% CIs for the percentages of seroresponders will be provided using the Clopper-Pearson method.

6.1.1.2.2. Sensitivity/Supplementary Analyses

The main analysis will also be performed on the mITT population.

6.1.1.3. Primary MenB Test Strain Evaluation (A22, A56, B24, and B44)

6.1.1.3.1. Main Analysis

- Estimand strategy: Hypothetical.

- Analysis set: Post–Vaccination 2 evaluable population.

- Analysis methodology: 95% CI for the difference in the percentage of the 4-fold rises and composite responses, calculated by the Miettinen and Nurminen procedure.

- 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 95% CIs for the difference in 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), in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2 will be calculated using the Miettinen and Nurminen method. The lower limit of the CI will be used in the hypothesis test for noninferiority as detailed in Section 5.1.

- The 95% CIs for the difference in 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, in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2 will be calculated using the Miettinen and Nurminen method. The lower limit of the CI will be used in the hypothesis test for noninferiority as detailed in Section 5.1.

Exact 2-sided 95% CIs for the percentages of participants achieving 4-fold rises, and composite responses, will be provided using the Clopper-Pearson method.

6.1.1.3.2. Sensitivity/Supplementary Analysis

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

6.1.2. Primary Safety Endpoints

Safety endpoints will be summarized by MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined). The reactogenicity data may also be summarized by true MenACWY history (naïve/experienced).

6.1.2.1. Local Reactions Within 7 Days After Vaccination

- 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 e-diary data will not be imputed.
- For each group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of each local reaction on any day (Days 1-7) after vaccination.
  - Presence or absence of any local reaction on any day (Days 1-7) after vaccination.
  - Maximum severity of each local reaction on any day (Days 1-7) after vaccination.

6.1.2.2. Systemic Events Within 7 Days After Vaccination

- 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 e-diary data will not be imputed.
- For each group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of each systemic event on any day (Days 1-7) after vaccination.
  - Presence or absence of any systemic event on any day (Days 1-7) after vaccination.
  - Maximum severity of each systemic event on any day (Days 1-7) after vaccination.

6.1.2.3. Use of Antipyretic Medications Within 7 Days After Vaccination

- 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 e-diary data will not be imputed.
- For each group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Use of antipyretic medication on any day (Days 1-7) after vaccination.

6.1.2.4. Serious Adverse Events, Medically Attended Adverse 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 percentage of participants with MAEs, SAEs, and NDCMCs for each of the analysis intervals defined in Table 4 will be summarized. For the events during the vaccination and follow-up phase, the (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

6.1.2.5. Adverse Events

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive summary statistics and Clopper-Pearson CIs. The Miettinen and Nurminen procedure to calculate the 95% CI of the difference in percentages for Tier 1 and Tier 2 events.
- 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 4 analysis intervals defined in Table 4 will be summarized. The (n), %, and 95% CI may be presented for any event, for each SOC, and for each PT within each SOC.

For both Tier 1 and Tier 2 events (AEs by PTs during the vaccination period), the 95% CIs for the difference in the percentage of participants reporting the events between the MenABCWY and Trumenba combined groups will be calculated using the Miettinen and Nurminen method. Descriptive summary statistics (counts and percentages and associated Clopper-Pearson 95% CIs) will be provided for all events. There is no Tier 1 event identified for MenABCWY at this stage. The difference in the percentage of participants reporting the events between the MenABCWY and Trumenba combined groups for the analysis intervals will also be presented.

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

6.1.2.6. 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 first 2 analysis intervals defined in Table 6. These summaries will include 95% Clopper-Pearson CIs.

6.1.2.7. 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 total number of days a participant missed school and/or work will be descriptively summarized.

6.2. Secondary Endpoints

6.2.1. Secondary Immunogenicity Endpoints

Hypothesis testing for the first secondary objective will be performed only if the primary objectives are successfully achieved.

6.2.1.1. hSBA Titer for Each of the MenACWY Test Strains for ACWY-Naïve Participants

6.2.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: ACWY-naïve participants: Post–Vaccination 1 evaluable populations for Group 1 and Group 2.
- Analysis methodology: 95% CI for the difference in the percentage of seroresponders (defined as participants achieving a 4-fold rise from baseline for each MenACWY test strain) calculated by the Miettinen and Nurminen procedure.
- 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 95% CIs for the difference in the percentage of seroresponders, defined as participants achieving a 4-fold rise from baseline for each MenACWY test strain, 1 month after Vaccination 1 in Group 1 compared to 1 month after Vaccination 1 in Group 2 will be calculated using the Miettinen and Nurminen method. The lower limit of the CI will be used in the hypothesis test for noninferiority as detailed in Section 5.1. Exact 2-sided 95% CIs for the percentages of seroresponders will be provided using the Clopper-Pearson method.

6.2.1.1.2. Sensitivity/Supplementary Analysis

The main analysis will also be performed on the mITT population.

6.2.1.2. hSBA Titer for Each of the MenACWY Test Strains for ACWY-Experienced Participants

6.2.1.2.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: ACWY-experienced participants: Post–Vaccination 1 evaluable populations for Group 3 and Group 4.
- Analysis methodology: 95% CI for difference in percentage of seroresponders calculated by the Miettinen and Nurminen procedure.
- 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 95% CIs for the difference in the percentage of seroresponders, defined as participants achieving a 4-fold rise from baseline for each MenACWY test strain, 1 month after Vaccination 1 in Group 3 compared to 1 month after Vaccination 1 in Group 4 will be calculated using the Miettinen and Nurminen method. The lower limit of the CI will be used in the hypothesis test for noninferiority as detailed in Section 5.1. Exact 2-sided 95% CIs for the percentages of seroresponders will be provided using the Clopper-Pearson method.

6.2.1.2.2. Sensitivity/Supplementary Analysis

The main analysis will also be performed on the mITT population.

6.3. Other Endpoints

6.3.1. Tertiary/Exploratory Endpoints

6.3.1.1. hSBA Titer for Each of the MenACWY Test Strains

6.3.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.

- Analysis set: Post–Vaccination 1 evaluable population for Groups 2 and 4, and post–Vaccination 2 evaluable population for Groups 1 and 3.

- Analysis methodology: In ACWY-naïve and ACWY-experienced participants separately, descriptive summary statistics for MenACWY strains for participants who received at least 1 dose (Groups 2 and 4) of MenACWY-CRM or 2 doses (Groups 1 and 3) of MenABCWY.

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

For each group (ACWY-naïve and ACWY-experienced participants separately) in the analysis set, the following analysis will be described:

- The percentage of participants achieving an hSBA titer ≥1:8 for each MenACWY test strain, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3.

- hSBA GMTs for each of the MenACWY test strains, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3.

6.3.1.1.2. Sensitivity/Supplementary Analysis

The main analysis will also be performed on the mITT population.

6.3.1.1.3. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: mITT population for Groups 2 and 4.
- Analysis methodology: Descriptive summary statistics for MenACWY strains for participants who received at least 1 dose (Groups 2 and 4) of MenACWY-CRM.
- Intercurrent events and missing data: Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

For each group (ACWY-naïve and ACWY-experienced participants separately) in the analysis set, the following analysis will be described:

- The percentage of participants achieving an hSBA titer ≥1:8 for each MenACWY test strain, at baseline and 7 months after Vaccination 1 in Groups 2 and 4.
- hSBA GMTs for each of the MenACWY test strains, at baseline and 7 months after Vaccination 1 in Groups 2 and 4.
- The percentage of participants achieving at least a 4-fold rise in hSBA titers for each of the MenACWY test strains, at baseline and 7 months after Vaccination 1 in Groups 2 and 4.

6.3.1.1.4. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 1 evaluable population.
- Analysis methodology: Descriptive summary statistics for MenACWY strains for participants who received at least 1 dose of investigational product.
- Intercurrent events and missing data: Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

For each group in the analysis set, the following analysis will be described:

- The percentage of participants achieving an hSBA titer ≥1:8 for each MenACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4.
- hSBA GMTs for each of the MenACWY test strains, at baseline and 1 month after Vaccination 1 in Groups 1 through 4.

6.3.1.1.5. Sensitivity/Supplementary Analysis

The main analysis will also be performed on the mITT population.

6.3.1.2. Primary MenB Test Strain Evaluations (A22, A56, B24, and B44)

6.3.1.2.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 2 evaluable population.
- Analysis methodology: Descriptive summary statistics and Clopper-Pearson CIs for primary MenB strains for participants who received 2 doses of the investigational product. Summarized by Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2.
- Intercurrent events and missing data: Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
- The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for each primary MenB test strain.
- The percentage of participants with hSBA titers ≥1:4 for each of the 4 primary MenB test strains.
- hSBA GMTs for each of the 4 primary MenB test strains.

6.3.1.2.2. Sensitivity/Supplementary Analysis

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

6.3.1.3. Secondary MenB Test Strain Evaluation

The evaluation of the secondary MenB test strains induced by 2 doses of MenABCWY will be reported if requested/required.

6.3.1.3.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Post–Vaccination 2 evaluable population.
- Analysis methodology: Descriptive summary statistics and Clopper-Pearson CIs for each secondary MenB test strain in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2.

- 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 group in the analysis set, the following analysis will be described:

- The percentage of participants achieving an hSBA titer ≥ LLOQ for each secondary MenB test strain in Groups 1 + 3 combined, at baseline and 1 month after Vaccination 2.

- The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the secondary MenB test strains in Groups 1 + 3 combined, at baseline and 1 month after Vaccination 2.

- hSBA GMTs for each of the secondary MenB test strains in Groups 1 + 3 combined, at baseline and 1 month after Vaccination 2.

6.3.1.3.2. Sensitivity/Supplementary Analysis

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

6.3.1.4. Positive Predictive Value Analyses

PPV analyses of secondary strain response for a given primary strain response within the primary strain subfamily will be performed at 1 month after the second vaccination using the post–Vaccination 2 evaluable immunogenicity population.

For a given time point, the PPV between a primary and secondary strain will be defined as follows: for the participants who had titers ≥ LLOQ for the primary strain, the percentage of participants who have titers ≥ LLOQ for the secondary strain. The calculation will require available assay results for both the primary and secondary strains.

PPV analyses will be reported if the analysis of the secondary MenB test strains induced by 2 doses of MenABCWY is requested/required.

6.3.1.5. Exploratory Analyses for the Relationship Between Pre– and Post–Vaccination 2 hSBA Titers

Additional exploratory analyses may be performed to investigate the relationship between pre– and post–Vaccination 2 hSBA titers for each of the MenACWY test strains in the ACWY-naïve and ACWY-experienced groups. Scatterplots (with Pearson correlation coefficients) of pre–Vaccination 2 hSBA titers versus fold rises from pre–Vaccination 2 to post–Vaccination 2 using the post–Vaccination 2 evaluable immunogenicity population will be provided. Similar analyses may also be done for pre– and post–Vaccination 1 time points.

6.4. Subset Analyses

Subgroup analyses may be performed on the primary and secondary immunogenicity and safety endpoints described in Section 6.1.1, Section 6.1.2, and Section 6.2. No subgroup analysis is planned for rare events (endpoints with less than 1% of participants in any group). Subgroups can include age strata (10 to <18 years; 18 to <26 years), sex, race, and ethnicity.

If a subgroup variable (eg, race) does not have more than 1 group with greater than 5% 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, MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined).

Disposition summaries include:

- N and % of participants included in each study population (ITT, mITT, post–Vaccination 1 evaluable immunogenicity, and post–Vaccination 2 evaluable immunogenicity).
- N and % of participants receiving each vaccination.
- N and % of participants completing the vaccination phase and follow-up phase.
- N and % of participants who withdrew during the vaccination phase (Visits 1-4) and reason for withdrawal.
- N and % of participants who withdrew during the follow-up phase (After Visit 4 to Visit 5) and reason for withdrawal.

For each blood draw, the number and percentage of participants randomized, vaccinated at each visit (Visits 1 and 3), and providing blood samples within the protocol-specified time frame, as well as before and after the specified time frame, 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 reason for exclusion may be provided by randomized vaccine group. A listing of protocol deviations may also be provided.

6.5.2. Vaccine Exposure

Study vaccination data, temporary delays and reasons for vaccination delays, and noncompliant vaccine administration and reasons may be listed by vaccine group as administered. Participants not receiving vaccination as randomized, or randomized to the wrong MenACWY stratum, 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 summaries.

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. E-Diary Completion

E-diary compliance as defined in Section 3.6 will be summarized for each dose (Vaccination 1, Vaccination 2) by vaccine group, MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined), and total compliance using descriptive statistics. The safety population will be used to generate the summary reports. The denominator for the e-diary compliance rates will be the total number of participants who received the specific vaccination.

6.5.5. Concomitant Medications and Nondrug Treatments

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 an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

Analyses and summaries of primary AE endpoints using the 3-tier approach are described in detail in Section 6.1.2.5.

Tier 3 events will be summarized as part of the overall AE summary.

6.6.1.1. Related Events

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

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

6.6.1.2. Severe Events

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

6.6.1.3. 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. 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. Reactogenicity Data

Local reactions and systemic events will be summarized according to Section 6.1.2.1 and Section 6.1.2.2.

Reactogenicity data may also be summarized by dose graphically for local reactions and systemic events, for combined groups of MenABCWY and combined groups of MenACWY-CRM, separately. In addition, for the MenABCWY data, the summary may also be shown by ACWY status (naïve and experienced).

6.6.3. Physical Examination

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

7. INTERIM ANALYSES

7.1. Introduction

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

7.2. 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, and no adjustments to the type I error for the noninferiority assessments will be made for these periodic safety reviews.

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. Chapter 1. In: Categorical data analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc; 2002:18-20.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

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

9. APPENDICES

Appendix 1. Objectives, Estimands, and Endpoints

Study objectives, estimands, and endpoints as described in Section 3 of the protocol. For the tertiary/exploratory objective to further describe the immune response, the endpoints related to the percentage of participants with hSBA titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the MenACWY test strains and the primary MenB test strains will not be reported. The endpoints of percentage of participants achieving an hSBA titer ≥ LLOQ and ≥1:4 (MenB) are not affected. The tertiary/exploratory objective related to secondary MenB test strains induced by 2 doses of MenABCWY will be reported if requested/required.

Objectives	Estimands	Endpoints
Primary Immunogenicity:	Primary Immunogenicity:	Primary Immunogenicity:

To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve participants receiving at least 1 dose (Group 2) of MenACWY-CRM or 2 doses (Group 1) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants):
	• Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 2 in Group 1 compared to 1 month after Vaccination 1 in Group 2.
	  • 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 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.
		hSBA titer for each of the ACWY test strains.

Objectives	Estimands	Endpoints

	In ACWY-experienced participants receiving at least 1 dose (Group 4) of MenACWY-CRM or 2 doses (Group 3) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants):
	• Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 2 in Group 3 compared to 1 month after Vaccination 1 in Group 4.
	  • 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 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 demonstrate that the immune response for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba.	In participants receiving at least 2 doses of investigational product and who are in compliance with the key protocol criteria (evaluable participants): • Differences in 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), in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2. • Difference in 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, in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2. • 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.	hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

Objectives	Estimands	Endpoints
	• For participants with a baseline hSBA titer of ≥ 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.	
Primary Safety:	Primary Safety:	Primary Safety:

To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs.	In participants receiving at least 1 dose of investigational product, expressed in MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined):
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each vaccination.
	• The percentage of participants reporting 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 vaccination.
	  • During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]).
	  • During the follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5]).
	  • Throughout the study (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5]).
	• The percentage of participants reporting at least 1 AE during the following time periods:
	  • 30 Days after each vaccination.
		• Local reactions (pain, redness, and swelling).
		• Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain).
		• Use of antipyretic medication.
		• AEs, SAEs, MAEs, NDCMCs, and immediate AEs.
		• Days missing from school or work because of AEs.

Objectives	Estimands	Endpoints
	• 30 Days after any vaccination. • During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]). • The percentage of participants reporting at least 1 immediate AE. • The percentage of participants who missed days of school or work because of AEs.	
Secondary Immunogenicity:	Secondary Immunogenicity:	Secondary Immunogenicity:
To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants): • Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 1 in Group 1 compared to Group 2. • 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 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.	hSBA titer for each of the ACWY test strains.

Objectives	Estimands	Endpoints

	In ACWY-experienced participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants):
	• Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 1 in Group 3 compared to Group 4.
	  • 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 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.	

Objectives	Estimands	Endpoints
Tertiary/Exploratory:	Tertiary/Exploratory:	Tertiary/Exploratory:
To describe the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve and ACWY-experienced participants separately who have received at least 1 dose (Groups 2 and 4) of MenACWY-CRM or 2 doses (Groups 1 and 3) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥1:8 for each ACWY test strain, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3. • The percentage of participants achieving hSBA titers of ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each ACWY test strain, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3. • hSBA GMTs for each of the ACWY test strains, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3.	hSBA titer for each of the ACWY test strains.
To describe the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve and ACWY-experienced participants separately who have received at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥1:8 for each ACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4. • The percentage of participants achieving hSBA titers of ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each ACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4. • hSBA GMTs for each of the ACWY test strains, at baseline and 1 month after Vaccination 1 in Groups 1 through 4.	hSBA titer for each of the ACWY test strains.

Objectives	Estimands	Endpoints
To describe the immune response for MenB, as measured by hSBA performed with primary MenB test strains, induced by 2 doses of MenABCWY compared to the immune response induced by 2 doses of Trumenba.	In participants receiving at least 2 doses of investigational product who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for each primary MenB test strain in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2. • 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 in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2. • hSBA GMTs for each of the 4 primary MenB test strains in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2.	hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
To describe the immune response for MenB, as measured by hSBA performed with secondary MenB test strains, induced by 2 doses of MenABCWY.	In participants receiving at least 2 doses of investigational product who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each secondary MenB test strain in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2. • The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each secondary MenB test strain in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2. hSBA GMTs for the secondary MenB test strains in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2.	hSBA titer for each secondary MenB test strain.

Appendix 2. List of Abbreviations

Abbreviation	Term
ACWY	meningococcal group A, C, W, and Y
AE	adverse event
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
CRF	case report form
e-diary	electronic diary
E-DMC	external data monitoring committee
FDA	Food and Drug Administration (United States)
GLIMMIX	generalized linear mixed-effects model with repeated measures
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
ID	identification
IRT	interactive response technology
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LOD	limit of detection
MAE	medically attended adverse event
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* group A
MenABCWY	*Neisseria meningitidis* group A, B, C, W, and Y vaccine
MenACWY	*Neisseria meningitidis* group A, C, W, and Y
MenACWY-CRM	meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria 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
MMRM	mixed-effects model with repeated measures
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
PPV	positive predictive value
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SoA	schedule of activities
SOC	system organ class
TLF	tables, listings, and figures
US	United States
WHO	World Health Organization