Protocol C3511002

A PHASE 2b TRIAL TO ASSESS THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MenABCWY IN HEALTHY INFANTS 2 AND 6 MONTHS OF AGE

Statistical Analysis Plan
(SAP)

Version: 1

Date: 30 Nov 2021

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 30 Nov 2021	Amendment 2 13 Sep 2021	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3511002. 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, 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, Table 3, and Table 4 show the study design. The impacts of COVID-19 will be assessed prior to the first planned analysis, and the SAP will be amended accordingly to account for these impacts, if needed.

Table 2. Open-Label Sentinel-Cohort Stage

Visit Description		Primary Vaccination 1	Safety Telephone Contact	Primary Vaccination 2	Follow-up After Primary Vaccination 2	Booster Vaccination	Follow-up After Booster Vaccination	Final Telephone Contact
Visit Identifier		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Approximate Month of Age[a]		**6**	**7**	**8**	**9**	**12**	**13**	**18**
Cohort 1	**Group 1 (n ~ 25)**	MenABCWY + PLP		MenABCWY + PLP		MenABCWY		
Cohort 2	**Group 2 (n ~ 25)**	MenABCWY		MenABCWY		MenABCWY		
	Approximate Months of Age	**2**	**3**	**4**	**5**	**12**	**13**	**18**
	Group 3 (n ~ 37)	60 µg rLP2086 + Nimenrix + PLP[b]		60 µg rLP2086 + Nimenrix + PLP		60 µg rLP2086 + Nimenrix		
Cohort 3	**Group 4 (n ~ 25)**	60 µg rLP2086 + Nimenrix		60 µg rLP2086 + Nimenrix		60 µg rLP2086 + Nimenrix		
	Group 5 (n ~ 50)	120 µg rLP2086 + Nimenrix + PLP		120 µg rLP2086 + Nimenrix + PLP		120 µg rLP2086 + Nimenrix		
Cohort 4	**Group 7 (n ~ 50-100)**	MenABCWY + SLP[c]		MenABCWY + SLP		MenABCWY		
Sentinel-Control Cohort[d]	**Group 8 (n ~ 55)**	Bexsero + Nimenrix + PLP		Bexsero + Nimenrix + PLP		Bexsero + Nimenrix		
	Group 10 (n ~ 55)	Bexsero + Nimenrix		Bexsero + Nimenrix		Bexsero + Nimenrix		
Blood Draw					5 mL		5 mL	

Abbreviations: bivalent rLP2086 = bivalent recombinant lipoprotein 2086 vaccine; EDMC = external data monitoring committee; IRC = institutional review board; PLP = prophylactic liquid paracetamol regimen; SLP = scheduled liquid paracetamol regimen.

Note: "rLP2086" refers to bivalent rLP2086.

Note: Groups 6 and 9 were removed in protocol amendment 2 based on the EDMC's recommendation.

a. Participants 6 months of age (Groups 1 and 2) will receive Prevenar 13 and Vaxelis at 6 months of age (Visit 1). Participants 2 months of age (Groups 3-5, 7, 8, and 10) will receive Prevenar 13 and Vaxelis at 2 and 4 months of age (Visits 1 and 3).

b. Protocol amendment 2 added 12 additional participants to Group 3 that will receive SLP for primary vaccinations.

c. Group 7 will receive SLP.

d. Enrollment into the sentinel-control cohort may occur at any time during the sentinel-cohort stage without IRC review of data from Cohorts 14.

Table 3. Open-Label Expanded-Enrollment Stage

Visit Description	Primary Vaccination 1	Safety Telephone Contact	Primary Vaccination 2	Follow-up After Primary Vaccination 2	Booster Vaccination	Follow-up After Booster Vaccination	Final Telephone Contact
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Approximate Months of Age[a]	**2**	**3**	**4**	**5**	**12**	**13**	**18**
Group 11 (n ~ 50 to 100)	MenABCWY + TLP[b]		MenABCWY + TLP		MenABCWY		
Blood Draw				5 mL		5 mL	

Abbreviations: IRC = institutional review board; SLP = scheduled liquid paracetamol regimen; TLP = therapeutic liquid paracetamol regimen.

a. Participants will receive Prevenar 13 and Vaxelis at 2 and 4 months of age (Visits 1 and 3).

b. The protocol-assigned paracetamol regimen for Group 11 may be subject to change at the discretion of the IRC, and instead of TLP, some participants may receive SLP.

Table 4. Blinded Expanded-Enrollment Stage

Visit Description	Primary Vaccination 1	Safety Telephone Contact	Primary Vaccination 2	Follow-up After Primary Vaccination 2	Booster Vaccination	Follow-up After Booster Vaccination	Final Telephone Contact
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Approximate Month of Age[a]	**2**	**3**	**4**	**5**	**12**	**13**	**18**
Group 13 (n = up to 400)[b]	MenABCWY + placebo + SLP or TLP		MenABCWY + placebo + SLP or TLP		MenABCWY + placebo		
Group 14 (n = up to 400)[b]	Bexsero + Nimenrix + PLP or TLP		Bexsero + Nimenrix + PLP or TLP		Bexsero + Nimenrix		
Blood Draw				5 mL		5 mL	

Abbreviations: SLP = scheduled liquid paracetamol regimen; TLP = therapeutic liquid paracetamol regimen.

a. Participants will receive Prevenar 13 and Vaxelis at 2 and 4 months of age (Visits 1 and 3).

b. Up to 400 participants will be enrolled in Groups 13 and 14.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, and exploratory objective are described in Table 5 and Table 6 for open-label and blinded stages, respectively.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To describe the immune response for MenA, MenC, MenW, and MenY induced by MenABCWY compared to the immune response induced by Nimenrix after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combinations: Groups 7+11 (MenABCWY recipients) Groups 8+10 (Nimenrix recipients) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combinations as above: • The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination.	hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints
To describe the immune response for MenB induced by MenABCWY compared to the immune response induced by Bexsero after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combinations: Groups 7+11 (MenABCWY recipients) Groups 8+10 (Bexsero recipients) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combinations as above: • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after the booster vaccination.	hSBA titer for each of the MenB test strains.
To describe the immune response for MenB induced by 60 µg and 120 µg of bivalent rLP2086 after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group or combination: Groups 3+4 (60 µg bivalent rLP2086 recipients) Group 5 (120 µg bivalent rLP2086 recipients) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combinations as above: • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after the booster vaccination.	hSBA titer for each of the MenB test strains.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints
Primary Safety:	**Primary Safety:**	**Primary Safety:**

To describe the safety profile of MenABCWY after primary vaccinations, by protocol-assigned paracetamol regimen, and after a booster dose.	In participants receiving at least 1 dose of investigational product, expressed by protocol-assigned paracetamol regimen and irrespective of protocol-assigned paracetamol regimen receipt, in the following group combinations:
	Groups 7+11 (MenABCWY recipients with SLP or TLP)
	Groups 8+10 (Bexsero + Nimenrix recipients with or without PLP)
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each primary 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 primary vaccination.
	  • 30 Days after any primary vaccination.
	  • During the primary series vaccination phase (from Visits 1-4).
	  • During the primary series follow-up phase (from Visits 4-5).
	  • Throughout the primary series stage (from Visits 1-5).
	• The percentage of participants reporting at least 1 AE during the following time periods:
	  • 30 Days after each primary vaccination.
	  • 30 Days after any primary vaccination.
	  • During the primary series vaccination phase (from Visits 1-4).
	• The percentage of participants reporting at least 1 immediate AE after each primary vaccination.
	
	In participants who completed primary vaccinations and received a booster dose, expressed in the same group combinations as above, regardless of protocol-assigned paracetamol regimen receipt during the primary vaccination series:
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after the booster vaccination.
		• Local reactions (tenderness, redness, and swelling).
		• Systemic events (fever, increased sleep, decreased appetite, and irritability).
		• Use of antipyretic medication.
		• AEs, SAEs, MAEs, NDCMCs, and immediate AEs.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints

	• The percentage of participants reporting at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods:
	  • During the booster vaccination phase (from Visits 5-6).
	  • During the booster follow-up phase (from Visits 6-7).
	  • Throughout the booster stage (from Visits 5-7).
	• The percentage of participants reporting at least 1 AE during the following time period:
	  • During the booster vaccination phase (from Visits 5-6).
	• The percentage of participants reporting at least 1 immediate AE after the booster vaccination.	

Secondary Immunogenicity:	**Secondary Immunogenicity:**	**Secondary Immunogenicity:**
To further describe the immune response for MenB induced by 60 µg and 120 µg of bivalent rLP2086 after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group or combination: Groups 3+4 (60 µg bivalent rLP2086 recipients) Group 5 (120 µg bivalent rLP2086 recipients) • hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combinations as above: • hSBA GMTs for each of the MenB test strains 1 month after the booster vaccination.	hSBA titer for each of the MenB test strains.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints
Secondary Safety:	**Secondary Safety:**	**Secondary Safety:**

To describe the safety profile of 60 µg and 120 µg of bivalent rLP2086 after primary vaccinations, by protocol-assigned paracetamol regimen, and after a booster dose.	In participants receiving at least 1 dose of investigational product, expressed by protocol-assigned paracetamol regimen and irrespective of protocol-assigned paracetamol regimen receipt, in the following groups:
	Group 3 (60 µg bivalent rLP2086 + Nimenrix + PLP recipients)
	Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients)
	Group 5 (120 µg bivalent rLP2086 + Nimenrix + PLP recipients)
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each primary 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 primary vaccination.
	  • 30 Days after any primary vaccination.
	  • During the primary series vaccination phase (from Visits 1-4).
	  • During the primary series follow-up phase (from Visits 4-5).
	  • Throughout the primary series stage (from Visits 1-5).
	• The percentage of participants reporting at least 1 AE during the following time periods:
	  • 30 Days after each primary vaccination.
	  • 30 Days after any primary vaccination.
	  • During the primary series vaccination phase (from Visits 1-4).
	• The percentage of participants reporting at least 1 immediate AE after each primary vaccination.
	
	In participants who completed primary vaccinations and received a booster dose, expressed in the same groups as above, regardless of protocol-assigned paracetamol regimen receipt during primary vaccinations:
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after the booster vaccination.
		• Local reactions (tenderness, redness, and swelling).
		• Systemic events (fever, increased sleep, decreased appetite, and irritability).
		• Use of antipyretic medication.
		• AEs, SAEs, MAEs, NDCMCs, and immediate AEs.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints

	• The percentage of participants reporting at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods:
	  • During the booster vaccination phase (from Visits 5-6).
	  • During the booster follow-up phase (from Visits 6-7).
	  • Throughout the booster stage (from Visits 5-7).
	• The percentage of participants reporting at least 1 AE during the following time period:
	  • During the booster vaccination phase (from Visits 5-6).
	• The percentage of participants reporting at least 1 immediate AE after the booster vaccination.	

Tertiary/Exploratory Immunogenicity:	**Tertiary/Exploratory Immunogenicity:**	**Tertiary/Exploratory Immunogenicity:**
To further describe the immune response for MenA, MenC, MenW, and MenY induced by MenABCWY compared to the immune response induced by Nimenrix after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combinations: Groups 7+11 (MenABCWY recipients) Groups 8+10 (Nimenrix recipients) • hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combinations as above: • hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after the booster vaccination.	• hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.
To further describe the immune response for MenB induced by MenABCWY compared to the immune response induced by Bexsero after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combinations: Groups 7+11 (MenABCWY recipients) Groups 8+10 (Bexsero recipients)	• hSBA titer for each of the MenB test strains.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints
	• hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combinations as above: • hSBA GMTs for each of the MenB test strains 1 month after the booster vaccination.	
To describe the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY compared to the immune response induced by 2 doses of Nimenrix, by protocol-assigned paracetamol regimen.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed by protocol-assigned paracetamol regimen and irrespective of protocol-assigned paracetamol regimen receipt, in the following group combinations: Groups 7+11 (MenABCWY recipients with SLP or TLP) Groups 8+10 (Nimenrix recipients with or without PLP) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2.	• hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.
To describe the immune response for MenB induced by 2 doses of MenABCWY compared to the immune response induced by 2 doses of Bexsero, by protocol-assigned paracetamol regimen.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed by protocol-assigned paracetamol regimen and irrespective of protocol-assigned paracetamol regimen receipt, in the following group combinations: Groups 7+11 (MenABCWY recipients with SLP or TLP) Groups 8+10 (Bexsero recipients with or without PLP) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after primary vaccination 2.	• hSBA titer for each of the MenB test strains.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints
To describe the immune response for MenA, MenC, MenW, and MenY induced by MenABCWY after 2 primary vaccinations and after a booster dose in healthy infants 6 months of age at study entry.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combination: Groups 1+2 (MenABCWY recipients) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2. • hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combination as above: • The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination. • hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after the booster vaccination.	• hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.
To describe the immune response for MenB induced by MenABCWY after 2 primary vaccinations and after a booster dose in healthy infants 6 months of age at study entry.	In participants receiving primary vaccinations 1 and 2, who are in compliance with the key protocol criteria (evaluable participants), expressed in the following group combination: Groups 1+2 (MenABCWY recipients) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after primary vaccination 2. • hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2.	• hSBA titer for each of the MenB test strains (TBD).

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints
	In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same group combination as above: • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after the booster vaccination. • hSBA GMTs for each of the MenB test strains 1 month after the booster vaccination.	
Tertiary/Exploratory Safety:	**Tertiary/Exploratory Safety:**	**Tertiary/Exploratory Safety:**

To describe the safety profile of MenABCWY after primary vaccinations with and without PLP, and after a booster dose in participants 6 months of age.	In participants receiving at least 1 dose of investigational product, expressed with, without, and irrespective of PLP receipt during primary vaccinations, in Groups 1 and 2:
	Group 1 (MenABCWY + PLP recipients)
	Group 2 (MenABCWY recipients)
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each primary 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 primary vaccination.
	  • 30 Days after any primary vaccination.
	  • During the primary series vaccination phase (from Visits 1-4).
	  • Throughout the primary series stage (from Visits 1-5).
	• The percentage of participants reporting at least 1 AE during the following time periods:
	  • 30 Days after each primary vaccination.
	  • 30 Days after any primary vaccination.
	  • During the primary series vaccination phase (from Visits 1-4).
	• The percentage of participants reporting at least 1 immediate AE after each primary vaccination.
		• Local reactions (tenderness, redness, and swelling).
		• Systemic events (fever, increased sleep, decreased appetite, and irritability).
		• Use of antipyretic medication.
		• AEs, SAEs, MAEs, NDCMCs, and immediate AEs.

Table 5. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Objectives	Estimands	Endpoints

	In participants who completed primary vaccinations and received a booster dose, expressed in Groups 1 and 2 as above, regardless of PLP receipt during primary vaccinations:
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after the booster vaccination.
	• The percentage of participants reporting at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods:
	  • During the booster vaccination phase (from Visits 5-6).
	  • During the booster follow-up phase (from Visits 6-7).
	  • Throughout the booster stage (from Visits 5-7).
	• The percentage of participants reporting at least 1 AE during the following time period:
	  • During the booster vaccination phase (from Visits 5-6).
	• The percentage of participants reporting at least 1 immediate AE after the booster vaccination.	

Table 6. Blinded Expanded-Enrollment Stage

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To describe the immune response for MenA, MenC, MenW, and MenY induced by MenABCWY compared to the immune response induced by Nimenrix after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2 who are in compliance with the key protocol criteria (evaluable participants) expressed in the following groups: Group 13 (MenABCWY recipients) Group 14 (Nimenrix recipients) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2. • hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2. In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same groups as above: • The percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination. • hSBA GMTs for each of the MenA, MenC, MenW, and MenY test strains after the booster vaccination.	hSBA titer for each of the MenA, MenC, MenW, and MenY test strains.
To describe the immune response for MenB induced by MenABCWY compared to the immune response induced by Bexsero after 2 primary vaccinations and after a booster dose.	In participants receiving primary vaccinations 1 and 2 who are in compliance with the key protocol criteria (evaluable participants) expressed in the following groups: Group 13 (MenABCWY recipients) Group 14 (Bexsero recipients) • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after primary vaccination 2. • hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2.	hSBA titer for each of the MenB test strains (TBD).

Table 6. Blinded Expanded-Enrollment Stage

Objectives	Estimands	Endpoints
	In participants who completed primary vaccinations and received a booster dose, and who are in compliance with the key protocol criteria (evaluable participants), expressed in the same groups as above: • The percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after the booster vaccination. • hSBA GMTs for each of the MenB test strains after the booster vaccination.	
Primary Safety:	**Primary Safety:**	**Primary Safety:**

To describe the safety profile of MenABCWY after primary vaccinations, by protocol-assigned paracetamol regimen, and after a booster dose.	In participants receiving at least 1 dose of investigational product, expressed by protocol-assigned paracetamol regimen receipt in the following groups:
	Group 13 (MenABCWY recipients with SLP or TLP)
	Group 14 (Bexsero + Nimenrix recipients with PLP or TLP)
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each primary 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 primary vaccination.
	  • 30 Days after any primary vaccination.
	  • During the primary series vaccination phase (from Visits 1-4).
	  • During the primary series follow-up phase (from Visits 4-5).
	  • Throughout the primary series stage (from Visits 1-5).
	• The percentage of participants reporting at least 1 AE during the following time periods:
	  • 30 Days after each primary vaccination.
	  • 30 Days after any primary vaccination.
	  • During the primary series vaccination phase (from Visits 1-4).
	• The percentage of participants reporting at least 1 immediate AE after each primary vaccination.
		• Local reactions (tenderness, redness, and swelling).
		• Systemic events (fever, increased sleep, decreased appetite, and irritability).
		• Use of antipyretic medication.
		• AEs, SAEs, MAEs, NDCMCs, and immediate AEs.

Table 6. Blinded Expanded-Enrollment Stage

Objectives	Estimands	Endpoints

	In participants who completed primary vaccinations and received a booster dose, expressed by protocol-assigned paracetamol regimen receipt in the same groups as above, during the primary vaccination series:
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after the booster vaccination.
	• The percentage of participants reporting at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods:
	  • During the booster vaccination phase (from Visits 5-6).
	  • During the booster follow-up phase (from Visits 6-7).
	  • Throughout the booster stage (from Visits 5-7).
	• The percentage of participants reporting at least 1 AE during the following time period:
	  • During the booster vaccination phase (from Visits 5-6).
	• The percentage of participants reporting at least 1 immediate AE after the booster vaccination.	

2.2. Study Design

This is a Phase 2b multicenter trial that will enroll at least 1272 healthy infants, beginning with infants 6 months of age and progressing to infants 2 months of age. All participants will be naive to any meningococcal vaccines prior to enrollment. The study will be conducted in 3 stages: an open-label sentinel-cohort stage, an open-label expanded-enrollment stage, and a blinded expanded-enrollment stage. Approximately 472 participants will be enrolled in the open-label stages and up to 800 will be enrolled in the blinded expanded-enrollment stage of this study. An overview of study progression through these stages is shown in Table 7.

During each stage, participants will receive coadminstered Prevenar 13® and Vaxelis per the national immunization schedule for a primary series. Local reactions, systemic events, and use of antipyretic/pain medications will be collected by e-diary for 7 days following primary vaccinations 1 and 2 and the booster vaccination.

The protocol-assigned paracetamol regimen for Group 11 (open-label expanded-enrollment stage) may be subject to change at the discretion of the IRC, and instead of TLP, some participants may receive SLP.

At the discretion of the IRC, for Groups 13 and 14 (blinded expanded-enrollment stage), the split between the double-blind (TLP) and single-blind (PLP/SLP) groups can vary from 50/50 (which corresponds to 200 per group contributing to the double-blind analyses) and 100/0 (which corresponds to 400 per group contributing to the double-blind analyses). After the IRC decision, and prior to the analysis of the blinded expanded-enrollment stage data, the SAP will be updated to reflect the appropriate analyses of the data from this stage of the study.

Table 7. Study Progression Flowchart

Open-Label Sentinel-Cohort Stage (Groups 1-5, 7, 8, and 10)	
Cohorts 1-4	**Sentinel-Control Cohort**
Progression through Cohorts 1-4 based on IRC review of 7-day post–Vaccination 1 safety data	Enrollment into the sentinel-control cohort may occur at any time during the sentinel-cohort stage without IRC review of data from Cohorts 1-4.

Progression to the open-label expanded-enrollment stage based on IRC review of 7-day post–Vaccination 1 safety data from Cohort 4

↓

Open-Label Expanded-Enrollment Stage (Group 11)

IRC review of 7-day post–Vaccination 1 safety data for the first 25 participants and other ad hoc data reviews to determine the enrollment progression into Group 11

Progression to the blinded expanded-enrollment stage based on IRC review of post–Vaccination 2 or 3 immunogenicity data from Groups 5, 8, and 10 and all safety data available at the time of this analysis. At a minimum, this will include safety data from all sentinel-cohort groups (Groups 1-5, 7, 8, and 10) and 7-day post–Vaccination 1 safety data from Group 11

The enrollment progression and the stratification of protocol-assigned paracetamol regimen use in the blinded expanded-enrollment stage will be at the discretion of the IRC based on safety data review

Blinded Expanded-Enrollment Stage (Groups 13 and 14)

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary Endpoints for Open-Label Stage

3.1.1.1. Primary Immunogenicity Endpoints

- hSBA titer for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2 and 1 month after the booster vaccination in Groups 7, 8, 10, and 11.
    - Classification of titer as ≥ LLOQ

- hSBA titer for each of the MenB test strains (A22 and B44 [PMB2707], which are tested together, and A12, A29, B16, B24, and B44 [PMB3042]) at 1 month after primary vaccination 2 and 1 month after the booster vaccination in Groups 3, 4, 5, 7, 8, 10, and 11.
    - Classification of titer as ≥ LLOQ

Where assay titers are available, 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.

3.1.1.2. Primary Safety Endpoints

- Local reactions (tenderness, redness, and swelling) within 7 days after each primary vaccination and the booster vaccination in Groups 7, 8, 10, and 11.
- Systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after each primary vaccination and the booster vaccination in Groups 7, 8, 10, and 11.
- Use of antipyretic medications within 7 days after each primary vaccination and the booster vaccination in Groups 7, 8, 10, and 11.
- AEs, SAEs, MAEs, NDCMCs, and immediate AEs in Groups 7, 8, 10, and 11.

3.1.2. Primary Endpoints for Blinded Expanded-Enrollment Stage

3.1.2.1. Primary Immunogenicity Endpoints

- hSBA titer for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2 and 1 month after the booster vaccination in Groups 13 and 14.
    - Classification of titer as ≥ LLOQ
- hSBA titer for each of the MenB test strains 1 month after primary vaccination 2 and 1 month after the booster vaccination in Groups 13 and 14.
    - Classification of titer as ≥ LLOQ

Where assay titers are available, participants with hSBA titers ≥ LLOQ will be derived similarly to Section 3.1.1.1.

3.1.2.2. Primary Safety Endpoints

- Local reactions (tenderness, redness, and swelling) within 7 days after each primary vaccination and the booster vaccination in Groups 13 and 14.
- Systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after each primary vaccination and the booster vaccination in Groups 13 and 14.
- Use of antipyretic medications within 7 days after each primary vaccination and the booster vaccination in Groups 13 and 14.
- AEs, SAEs, MAEs, NDCMCs, and immediate AEs in Groups 13 and 14.

3.2. Secondary Endpoint(s)

3.2.1. Secondary Endpoints for Open-Label Stage

3.2.1.1. Secondary Immunogenicity Endpoints

- hSBA titer for each of the MenB test strains 1 month after primary vaccination 2 and 1 month after the booster vaccination in Groups 3, 4, and 5.

3.2.1.2. Secondary Safety Endpoints

For local reactions (tenderness, redness, and swelling), systemic events (fever, increased sleep, decreased appetite, and irritability), and use of antipyretic medications within 7 days; and AEs, SAEs, MAEs, NDCMCs, and immediate AEs in Groups 3, 4, and 5.

3.3. Tertiary/Exploratory Endpoint(s)

3.3.1. Tertiary/Exploratory Endpoints for Open-Label Stage

3.3.1.1. Tertiary/Exploratory Immunogenicity Endpoints

- hSBA titer for each of the MenA, MenC, MenW, and MenY test strains 1 month after primary vaccination 2 and 1 month after the booster vaccination in Groups 1, 2, 7, 8, 10, and 11.
- hSBA titer for each of the MenB test strains 1 month after primary vaccination 2 and 1 month after the booster vaccination in Groups 1, 2, 7, 8, 10, and 11.

Where assay titers are available, participants with hSBA titers ≥ LLOQ will be derived similarly to Section 3.1.1.1.

3.3.1.2. Tertiary/Exploratory Safety Endpoints

For local reactions (tenderness, redness, and swelling), systemic events (fever, increased sleep, decreased appetite, and irritability), and use of antipyretic medications within 7 days; and AEs, SAEs, MAEs, NDCMCs, and immediate AEs in Groups 1 and 2 will be handled similarly to Section 3.1.1.2.

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
- Asian
- White
- Multiracial
- Not reported

Ethnicity collected includes:

- Hispanic or Latino
- Not Hispanic or not Latino
- Not reported

For countries where full date of birth is collected, age at time of first vaccination will be derived based on birthday.

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. PRP-OMP–containing vaccines that are or have been commercially available include Comvax, Procomvax, and PedvaxHIB.

3.4.3. E-Diary Completion

For any given day, an e-diary will be transmitted and considered complete if all expected data (the 3 local reactions and the 4 systemic events, including fever, and 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 in the first 24 hours and per day: completed (transmitted) the e-diary on a given day (Day 1 through Day 7).

2. At least X day(s): completed (transmitted) the e-diary on any X number of days (X = 1 through 7; compliance will be computed for each value of X).

3. All 7 days: completed (transmitted) the e-diary on all 7 days.

3.5. Safety Endpoints

3.5.1. Adverse Events

The relationship between SAEs/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, or severe.

The time period for actively eliciting and collecting SAEs, AEs, MAEs, and NDCMCs for each participant is outlined in Table 8.

Table 8. Summary of Adverse Event Collection

Visit Description	Primary Vaccination 1	Safety Telephone Contact	Primary Vaccination 2	Follow-up After Primary Vaccination 2	Booster Vaccination	Follow-up After Booster Vaccination	Final Telephone Contact
Visit Identifier	1	2	3	4	5	6	7
AEs							
SAEs, MAEs, NDCMCs							

Abbreviations: 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. Participants' missed days of school or work due to an AE will be captured via the AE checklist. 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 begins from the time the participant's parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention). This duration of this active collection period is defined below:

- Through and including Visit 4.
- From Visit 5 through and including Visit 6.

The time period for actively eliciting and collecting SAEs, MAEs, and NDCMCs ("active collection period") for each participant begins from the time the parent(s)/legal guardian provides informed consent through Visit 7 (final telephone contact) for all groups.

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

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

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 9 analysis intervals for the AE data collected via the CRF (Table 9). The analysis populations used for these intervals are described in detail in Section 4.

Table 9. Analysis Intervals for AEs, SAEs, MAEs, and NDCMCs

#	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)	Safety Data
1	Within 30 days after primary vaccination 1	Vaccination 1 safety	Vaccination 1 date	Vaccination 1 date + 30 days	AEs, SAEs, MAEs, NDCMCs
2	Within 30 days after primary vaccination 2	Vaccination 2 safety	Vaccination 2 date	Vaccination 2 date + 30 days	AEs, SAEs, MAEs, NDCMCs

Table 9. Analysis Intervals for AEs, SAEs, MAEs, and NDCMCs

#	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)	Safety Data
3	Within 30 days after any primary vaccination	Safety	Vaccination 1 date or Vaccination 2 date	Vaccination 1 date + 30 days or Vaccination 2 date + 30 days	AEs, SAEs, MAEs, NDCMCs
4	During primary vaccination phase	Safety	Visit 1 date	Visit 4 date - 1 (or end of primary vaccination day)	AEs, SAEs, MAEs, NDCMCs
5	During primary follow-up phase	Follow-up	Visit 4 date, or end of primary vaccination date + 1 for early-withdrawal participants	Visit 5 date - 1	SAEs, MAEs, NDCMCs
6	Throughout primary stage	Safety	Visit 1 date	Visit 5 date - 1	SAEs, MAEs, NDCMCs
7	During booster vaccination phase	Booster safety	Visit 5 date	Visit 6 date (or end of booster vaccination day)	AEs, SAEs, MAEs, NDCMCs
8	During booster follow-up phase	Booster Follow-up	Visit 6 date + 1, or end of booster vaccination date + 1 for early-withdrawal participants	Visit 7 date	SAEs, MAEs, NDCMCs
9	Throughout booster stage	Booster safety	Visit 5 date	Visit 7 date	SAEs, MAEs, NDCMCs

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition.
Note: Visit 1 is the date of primary vaccination 1; Visit 4 is the date of follow-up after primary vaccination 2; Visit 5 is the date of booster vaccination; Visit 6 is the date of follow-up after booster vaccination; and Visit 7 is the date of final telephone contact.

Three analysis intervals will be applied to immediate AEs (Table 10).

Table 10. Analysis Intervals for Immediate AEs

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

3.5.2. Laboratory Data

Laboratory assessments will not be collected for this study.

3.5.3. Reactogenicity Data

Reactogenicity data are solicited AEs. The reactogenicity data collected from the study e-diary will include local reactions (tenderness, redness, and swelling), systemic events (fever, increased sleep, decreased appetite, and irritability), and use of antipyretic medication.

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

Four analysis intervals will be applied to reactogenicity data (Table 11).

Table 11. Analysis Intervals for Reactogenicity Date

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

3.5.3.1. 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 12.

Table 12. Derived Variables for Local Reactions

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

a. For redness and swelling, mild, moderate, and severe categories were based on the caliper size reported from the e-diary and defined in Table 13.
b. For redness and swelling, "none" means 0 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 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 13. Tenderness will be assessed by the participant/parent/legal guardian according to the grading scale in Table 14.

Table 13. Grading of Redness and Swelling

Mild	0.5 to 2.0 cm (1 to 4 caliper units)
Moderate	>2.0 to 7.0 cm (5 to 14 caliper units)
Severe	>7.0 cm (>14 caliper units)

Table 14. Grading of Tenderness

Mild	Hurts if gently touched (eg, participant whimpers, winces, protests, or withdraws)
Moderate	Hurts if gently touched, with crying
Severe	Causes limitation of limb movement

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

- = ., if values are missing for all days (Days 1-7);
- = 0, if the 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 12), 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.

For local reactions, the following variables will be derived for local reactions:

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

3.5.3.2. Systemic Events Endpoints

Participants will be asked to assess severity of each event according to Table 15.

Table 15. Grading of Other Systemic Events

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Decreased appetite (loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to feed
Drowsiness (increased sleep)	Increased or prolonged sleeping bouts	Slightly subdued interfering with daily activity	Disabling; not interested in usual daily activity
Irritability (fussiness) (synonymous with restless sleep; decreased sleep)	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted

Axillary temperature will be collected in the e-diary for Day 1 at 4, 8, 12, and 24 hours, and daily for Days 2 through 7 after each primary series vaccination and booster vaccination 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. Fever will be scaled as shown in Table 16.

Table 16. 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°C
Temperature >40.0°C

For each systemic event, the following variables will be available:

1. Each systemic event on each day (Days 1-7) after each primary series vaccination and booster vaccination.

2. Each systemic event on any day (Days 1-7) after each primary series vaccination, any primary series vaccination, and booster vaccination.

3. Any systemic event on any day (Days 1-7) after each primary series vaccination, any primary series vaccination, and booster vaccination.

4. Maximum severity of each systemic event on any day (Days 1-7) after each primary series vaccination, any primary series vaccination, and booster vaccination.

5. Duration of each systemic event after each primary series vaccination and booster vaccination.

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 3.5.3.1).

3.5.3.3. Use of Antipyretic Medication

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

The following variables will be derived:

1. Use of antipyretic medication on each day (Days 1-7) after each primary series vaccination and booster vaccination.

2. Use of antipyretic medication on any day (Days 1-7) after each primary series vaccination, any primary series vaccination, and booster vaccination.

3. Use of antipyretic medication during the first 24 hours after each primary series vaccination and booster vaccination.

4. Number of antipyretic medication doses during the first 24 hours after each primary series vaccination and booster vaccination.

Duration of use of antipyretic medication after each primary series vaccination and booster vaccination.

3.5.4. Medical Device Errors

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

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 SOPs. In the population and defined population for analysis tables below, investigational product is referring to MenABCWY, bivalent rLP2086, Nimenrix, or Bexsero, not the paracetamol regimen.

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product (as-randomized)	All participants who are assigned a randomization number in the IRT system.
Evaluable	Defined according to post–primary vaccination 2 evaluable and post–booster vaccination evaluable criteria.
mITT	Defined according to post–primary vaccination 2 mITT and post–booster vaccination mITT criteria.
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–primary 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 Visits 1 and 3 as randomized. 4. Had blood drawn for assay testing within the required time frames at Visit 4 (1 month after primary vaccination 2 [window 28-42 days]). 5. Had at least 1 valid and determinate MenA, MenC, MenW, MenY, 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.
Post–booster vaccination evaluable immunogenicity population	1. Were randomized to the study group of interest. 2. Were eligible through Visit 6, 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 Visits 1, 3, and 5 as randomized. 4. Had blood drawn for assay testing within the required time frames at Visit 6 (1 month after the booster vaccination [window 28-42 days]). 5. Had at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result at Visit 6. 6. Had received no prohibited vaccines or treatment through Visit 6. 7. Had no important protocol deviations through Visit 6.
Post–primary vaccination 2 mITT	All participants who received at least 1 primary series study vaccination and had at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result available at Visit 4.
Post–booster vaccination mITT	All participants who received the booster study vaccination and had at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result available at Visit 6.
Primary vaccination 1 safety population	This population will include participants who received the first dose of investigational product at Visit 1 and who had safety follow-up between Visit 1 and prior to Visit 3.

Defined Population for Analysis	Description
Primary vaccination 2 safety population	This population will include participants who received the second dose of investigational product at Visit 3 and who had safety follow-up between Visit 3 and prior to Visit 4.
Primary vaccination 2 follow-up safety population	This population will include participants who received at least 1 dose of investigational product and who had safety follow-up between Visit 4 and prior to Visit 5.
Booster vaccination safety population	This population will include participants who received the booster dose of investigational product and who had safety follow-up between Visit 5 and prior to Visit 6.
Booster vaccination follow-up safety population	This population will include participants who received the booster dose of investigational product and who had safety follow-up between Visit 6 and up to and including Visit 7.

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. An important protocol deviation 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 for the open-label stage prior to each immunogenicity analysis involving those populations being done and for the blinded expanded-enrollment stage prior to unblinding of the study.

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 randomly assigned population and excluded from any safety analyses.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no hypotheses for this study.

5.2. General Methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the percentage (%) 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 (2002).[1] The 95% CI will be presented in terms of percentages.

5.2.1.1. Immunogenicity Data

Each MenB test strain has a qualified LLOQ value defined in Table 17.

Table 17. Qualified hSBA LLOQ for MenB Test Strains

Strain Variant	LLOQ
PMB80 (A22)	1:16
PMB2707 (B44)	1:8
PMB824 (A12)	1:16
PMB3175 (A29)	1:8
PMB451 (B16)	1:8
PMB2948 (B24)	1:8
PMB3042 (B44)	1:8

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

Each MenACWY serogroup has a qualified LLOQ value defined in Table 18.

Table 18. Qualified hSBA LLOQ for MenACWY Serogroups

Serogroup	LLOQ
A	1:8
C	1:8
W	1:8
Y	1:8

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

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.

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Geometric Mean Titers

GMTs will be computed for each hSBA titer for MenB and MenACWY strains. If the hSBA result is below LLOQ, it will be set to 0.5 × LLOQ for the GMT calculation. The assay results at each blood sampling time point will be (natural-log) logarithmically transformed for analysis. GMTs are obtained by 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 will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with data points on the right side of the step.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms on handling missing AE dates will be applied according to the following: A partial AE start date (missing day or missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the vaccination date(s) from the same participant, following the Pfizer standard of handling incomplete AE start date. A completely missing start date for an AE is not allowed in the data collection.

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).[2] No sensitivity analysis is planned for reactogenicity data.

5.3.2. Immunogenicity Data

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

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

6. ANALYSES AND SUMMARIES

Section 2.1 describes the estimands for each of the study objectives. Below are the planned analyses by endpoints.

6.1. Primary Endpoint(s)

6.1.1. Primary Endpoints for Open-Label Stage

6.1.1.1. hSBA Titer for Each of the MenA, MenC, MenW, and MenY Test Strains

6.1.1.1.1. Main Analysis

For the primary vaccinations:

- Planned analysis: Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2 for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Nimenrix recipients).
- Analysis set: Post–primary vaccination 2 evaluable immunogenicity population.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each strain, the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided.

For the booster vaccination:

- Planned analysis: Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Nimenrix recipients).
- Analysis set: Post–booster vaccination evaluable immunogenicity population.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each strain, the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided.

6.1.1.1.2. Sensitivity/Supplementary Analyses

For the primary vaccination, the main analysis will also be performed on the post–primary vaccination 2 mITT population if there is a difference of more than 10% between the post–primary vaccination 2 evaluable immunogenicity and post–primary vaccination 2 mITT populations. Similarly, for the booster vaccination, the main analysis will also be performed on the post–booster vaccination mITT population if there is a difference of more than 10% between the post–booster vaccination evaluable immunogenicity and post–booster vaccination mITT populations.

6.1.1.2. hSBA Titer for Each of the MenB Test Strains

6.1.1.2.1. Main Analysis

For the primary vaccinations:

- Planned analysis:
    1. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenB test strain 1 month after primary vaccination 2 for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).
    2. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenB test strain 1 month after primary vaccination 2 for the following group combinations: Groups 3+4 (60 µg bivalent rLP2086 recipients) and Group 5 (120 µg bivalent rLP2086 recipients).
- Analysis set: Post–primary vaccination 2 evaluable immunogenicity population.

- Analysis methodology: Descriptive statistics.
- Reporting results: For each MenB test strain, the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided.

For the booster vaccination:

- Planned analysis:
    1. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenB test strain 1 month after the booster vaccination for the following group and group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).
    2. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenB test strain 1 month after the booster vaccination for the following group combination: Groups 3+4 (60 µg bivalent rLP2086 recipients) and Group 5 (120 µg bivalent rLP2086 recipients).
- Analysis set: Post–booster vaccination evaluable immunogenicity population.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each MenB test strain, the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided.

6.1.1.2.2. Sensitivity/Supplementary Analyses

For the primary vaccination, the main analysis will also be performed on the post–primary vaccination 2 mITT population if there is a difference of more than 10% between the post–primary vaccination 2 evaluable immunogenicity and post–primary vaccination 2 mITT populations. Similarly, for the booster vaccination, the main analysis will also be performed on the post–booster vaccination mITT population if there is a difference of more than 10% between the post–booster vaccination evaluable immunogenicity and post–booster vaccination mITT populations.

6.1.1.3. Local Reactions Within 7 Days

6.1.1.3.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted local reactions (redness, swelling, and tenderness) within 7 days after each primary vaccination for the following groups or group combinations: Groups 7+11 (MenABCWY recipients with SLP), Group 8 (Bexsero recipients with PLP), Group 11 (MenABCWY recipients with TLP), Group 10 (Bexsero recipients without PLP), Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and Groups 8+10 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each local reaction on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
  - Presence or absence of any local reaction on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
  - Maximum severity of each local reaction on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted local reactions (redness, swelling, and tenderness) within 7 days after the booster vaccination for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each local reaction on "any day (Day 1-7)" after the booster vaccination.

- Presence or absence of any local reaction on "any day (Day 1-7)" after the booster vaccination.
- Maximum severity of each local reaction on "any day (Day 1-7)" after the booster vaccination.

6.1.1.3.2. Supplementary Analysis

As supplementary analyses to support the assessment of local reactions, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction after each primary vaccination for the following groups or group combinations:
  - Groups 7+11 (MenABCWY recipients with SLP),
  - Group 8 (Bexsero recipients with PLP),
  - Group 11 (MenABCWY recipients with TLP),
  - Group 10 (Bexsero recipients without PLP),
  - Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and
  - Groups 8+10 (Bexsero recipients)

  and booster vaccination for the following group combinations:
  - Groups 7+11 (MenABCWY recipients) and
  - Groups 8+10 (Bexsero recipients).
- Onset day of each local reaction after each primary vaccination for the following groups or group combinations:
  - Groups 7+11 (MenABCWY recipients with SLP),
  - Group 8 (Bexsero recipients with PLP),
  - Group 11 (MenABCWY recipients with TLP),
  - Group 10 (Bexsero recipients without PLP),

- Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and
- Groups 8+10 (Bexsero recipients)

and booster vaccination for the following group combinations:

- Groups 7+11 (MenABCWY recipients) and
- Groups 8+10 (Bexsero recipients).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum.

Figures:

Bar charts with the proportions of participants for any day (Day 1 through Day 7) will be plotted for each primary vaccination for the following groups or group combinations:

- Groups 7+11 (MenABCWY recipients with SLP),
- Group 8 (Bexsero recipients with PLP),
- Group 11 (MenABCWY recipients with TLP),
- Group 10 (Bexsero recipients without PLP),
- Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and
- Groups 8+10 (Bexsero recipients)

and booster vaccination for the following group combinations:

- Groups 7+11 (MenABCWY recipients) and
- Groups 8+10 (Bexsero recipients),

with different patterns displayed in the bar charts for different maximum severity levels for any day.

6.1.1.4. Systemic Events Within 7 Days

6.1.1.4.1. Main Analysis

For primary vaccination:

- Planned analysis: The percentage of participants reporting prompted systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after each primary vaccination for the following groups or group combinations:
  Groups 7+11 (MenABCWY recipients with SLP), Group 8 (Bexsero recipients with PLP), Group 11 (MenABCWY recipients with TLP), Group 10 (Bexsero recipients without PLP), Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and Groups 8+10 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
  - Presence or absence of any systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
  - Maximum severity of each systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after the booster vaccination for the following group combinations:
  Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each systemic event on "any day (Day 1-7)" after the booster vaccination.

- Presence or absence of any systemic event on “any day (Day 1-7)” after the booster vaccination.
- Maximum severity of each systemic event on “any day (Day 1-7)” after the booster vaccination.

6.1.1.4.2. Supplementary Analysis

As supplementary analyses to support the assessment of systemic events, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each systemic event after each primary vaccination for the following groups or group combinations:
  - Groups 7+11 (MenABCWY recipients with SLP),
  - Group 8 (Bexsero recipients with PLP),
  - Group 11 (MenABCWY recipients with TLP),
  - Group 10 (Bexsero recipients without PLP),
  - Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and
  - Groups 8+10 (Bexsero recipients)

  and booster vaccination for the following group combinations:
  - Groups 7+11 (MenABCWY recipients) and
  - Groups 8+10 (Bexsero recipients).
- Onset day of each systemic event after each primary vaccination for the following groups or group combinations:
  - Groups 7+11 (MenABCWY recipients with SLP),
  - Group 8 (Bexsero recipients with PLP),
  - Group 11 (MenABCWY recipients with TLP),
  - Group 10 (Bexsero recipients without PLP),

- Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and
- Groups 8+10 (Bexsero recipients)

and booster vaccination for the following group combinations:

- Groups 7+11 (MenABCWY recipients) and
- Groups 8+10 (Bexsero recipients).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum.

Figures:

Bar charts with the proportions of participants for any day (Day 1 through Day 7) will be plotted for each primary vaccination for the following groups or group combinations:

- Groups 7+11 (MenABCWY recipients with SLP),
- Group 8 (Bexsero recipients with PLP),
- Group 11 (MenABCWY recipients with TLP),
- Group 10 (Bexsero recipients without PLP),
- Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and
- Groups 8+10 (Bexsero recipients)

and booster vaccination for the following group combinations:

- Groups 7+11 (MenABCWY recipients) and
- Groups 8+10 (Bexsero recipients),

with different patterns displayed in the bar charts for different maximum severity levels for any day.

6.1.1.5. Use of Antipyretic Medications Within 7 Days

6.1.1.5.1. Main Analysis

For primary vaccination:

- Planned analysis: The percentage of participants reporting prompted use of antipyretic medication within 7 days after each primary vaccination for the following groups or group combinations: Groups 7+11 (MenABCWY recipients with SLP), Group 8 (Bexsero recipients with PLP), Group 11 (MenABCWY recipients with TLP), Group 10 (Bexsero recipients without PLP), Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and Groups 8+10 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variable:
  - Use of antipyretic medication on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted use of antipyretic medication within 7 days after the booster vaccination for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variable:
  - Use of antipyretic medication on "any day (Day 1-7)" after the booster vaccination.

6.1.1.5.2. Supplementary Analysis

As supplementary analyses to support the assessment of protocol-assigned paracetamol use, the following endpoints will be summarized with the same analysis time point and analysis population:

- The percentage of participants reporting prompted use of protocol-assigned paracetamol dosing compliance after each primary vaccination, which is calculated for the following:

- (number of actual SLP doses / number of planned SLP doses) × 100 for the following groups: Groups 7 and 11 (MenABCWY recipients with SLP). If the optional fifth dose of SLP is given, this will be used in the calculation of number of planned SLP doses; else if it is not given, then the number of planned SLP doses will be 4.

- (number of actual PLP doses / number of planned PLP doses) × 100 for the following group: Group 8 (Bexsero recipients with PLP).

- If the first dose of TLP (if required) is given, then the following calculation applies: (number of actual TLP doses / number of planned TLP doses) × 100 for the following group: Group 11 (MenABCWY recipients with TLP). If the optional fifth dose of SLP is given, this will be used in the calculation of number of planned SLP doses; else if it is not given, then the number of planned SLP doses will be 4.

- The percentage of participants reporting prompted use PLP dosing compliance based on protocol-specified timing after each primary vaccination, which is calculated for the following:

  - (number of SLP doses within per-protocol timing window / number of planned SLP doses within per-protocol timing window) × 100 for the following groups: Groups 7 and 11 (MenABCWY recipients with SLP). The first dose of SLP should be given no later than 8 hours from vaccination time. The rest of the SLP doses should be given every 4 to 6 hours. The fifth SLP dose is optional.

  - (number of actual PLP doses within per-protocol timing window / number of planned PLP doses within per-protocol timing window) × 100 for the following group: Group 8 (Bexsero recipients with PLP).

  - (number of actual TLP doses within per-protocol timing window / number of planned TLP doses within per-protocol timing window) × 100 for the following group: Group 11 (MenABCWY recipients with TLP). The first dose of TLP (if required) should be given no later than 48 hours from vaccination time. The rest of the TLP doses should be given every 4 to 6 hours. The fifth TLP dose is optional.

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

For primary vaccination:

- Planned analysis: The numbers and percentages of participants with SAEs, MAEs, and NDCMCs for each of the analysis intervals defined in Table 9 and will be summarized by the following groups or group combinations: Groups 7+11 (MenABCWY recipients with SLP), Group 8 (Bexsero recipients with PLP), Group 11 (MenABCWY recipients with TLP), Group 10 (Bexsero recipients without PLP), Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and Groups 8+10 (Bexsero recipients).

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

- Analysis methodology: Descriptive statistics.

- Reporting results: For the events during the vaccination and follow-up phases, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

For booster vaccination:

- Planned analysis: The numbers and percentages of participants with MAEs, SAEs, and NDCMCs for each of the analysis intervals defined in Table 9 will be summarized by the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).

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

- Analysis methodology: Descriptive statistics.

- Reporting results: For each group, the events during the booster phase, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

6.1.1.7. Adverse Events

For primary vaccination:

- Planned analysis: The numbers of participants with AEs for analysis intervals 1 through 4 and 7 defined in Table 9 will be summarized by the following groups or group combinations: Groups 7+11 (MenABCWY recipients with SLP), Group 8 (Bexsero recipients with PLP), Group 11 (MenABCWY recipients with TLP), Group 10 (Bexsero recipients without PLP), Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and Groups 8+10 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.
    - Nonserious AEs are not required to be reported during the follow-up phase; however, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data may be listed separately.

For booster vaccination:

- Planned analysis: The numbers of participants with AEs for analysis intervals 1 through 4 and 7 defined in Table 9 will be summarized by the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.
    - Nonserious AEs are not required to be reported during the follow-up phase; however, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data may be listed separately.

6.1.1.8. Immediate Adverse Events

For primary vaccination:

- Planned analysis: 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 10 by the following groups or group combinations: Groups 7+11 (MenABCWY recipients with SLP), Group 8 (Bexsero recipients with PLP), Group 11 (MenABCWY recipients with TLP), Group 10 (Bexsero recipients without PLP), Groups 7+11 (MenABCWY recipients [without regard to protocol-assigned paracetamol]), and Groups 8+10 (Bexsero recipients) after each primary vaccination.

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

- Analysis methodology: Descriptive statistics.

- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

For booster vaccination:

- Planned analysis: The number and percentage of participants reporting AEs occurring within the 30-minute observation period immediately after vaccination will be summarized according to the last analysis interval defined in Table 10 by the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients) after the booster vaccination.

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

- Analysis methodology: Descriptive statistics.

Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

6.1.2. Primary Endpoints for Blinded Expanded-Enrollment Stage

6.1.2.1. hSBA Titer for Each of the MenA, MenC, MenW, and MenY Test Strains

6.1.2.1.1. Main Analysis

For the primary vaccinations:

- Planned analysis:

    1. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2 for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Nimenrix recipients).

    2. hSBA GMTs for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2 for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Nimenrix recipients).

- Analysis set: Post–primary vaccination 2 evaluable immunogenicity population.

- Analysis methodology: Descriptive statistics.

- Reporting results:

    1. For each strain, the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided.

    2. For each strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided.

For the booster vaccination:

- Planned analysis:

    1. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Nimenrix recipients).

    2. hSBA GMTs for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Nimenrix recipients).

- Analysis set: Post–booster vaccination evaluable immunogenicity population.

- Analysis methodology: Descriptive statistics.

- Reporting results:

    1. For each strain, the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided.

2. For each strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided.

6.1.2.1.2. Sensitivity/Supplementary Analyses

For the primary vaccination, the main analysis will also be performed on the post–primary vaccination 2 mITT population if there is a difference of more than 10% between the post–primary vaccination 2 evaluable immunogenicity and post–primary vaccination 2 mITT populations. Similarly, for the booster vaccination, the main analysis will also be performed on the post–booster vaccination mITT population if there is a difference of more than 10% between the post–booster vaccination evaluable immunogenicity and post–booster vaccination mITT populations.

6.1.2.2. hSBA Titer for Each of the MenB Test Strains

6.1.2.2.1. Main Analysis

For the primary vaccinations:

- Planned analysis:

  1. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenB test strain 1 month after primary vaccination 2 for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).

  2. hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2 for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).

- Analysis set: Post–primary vaccination 2 evaluable immunogenicity population.

- Analysis methodology: Descriptive statistics.

- Reporting results:

  1. For each MenB test strain, the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided.

  2. For each MenB test strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided.

For the booster vaccination:

- Planned analysis:

    1. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenB test strain 1 month after the booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).

    2. hSBA GMTs for each of the MenB test strains 1 month after the booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).

- Analysis set: Post–booster vaccination evaluable immunogenicity population.

- Analysis methodology: Descriptive statistics.

- Reporting results:

    1. For each MenB test strain, the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided.

    2. For each MenB test strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided.

6.1.2.2.2. Sensitivity/Supplementary Analyses

For the primary vaccination, the main analysis will also be performed on the post–primary vaccination 2 mITT population if there is a difference of more than 10% between the post–primary vaccination 2 evaluable immunogenicity and post–primary vaccination 2 mITT populations. Similarly, for the booster vaccination, the main analysis will also be performed on the post–booster vaccination mITT population if there is a difference of more than 10% between the post–booster vaccination evaluable immunogenicity and post–booster vaccination mITT populations.

6.1.2.3. Local Reactions Within 7 Days

6.1.2.3.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted local reactions (redness, swelling, and tenderness) within 7 days after each primary vaccination for the following groups:

- Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or
- Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups.

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each local reaction on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
  - Presence or absence of any local reaction on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
  - Maximum severity of each local reaction on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted local reactions (redness, swelling, and tenderness) within 7 days after the booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each local reaction on "any day (Day 1-7)" after the booster vaccination.
  - Presence or absence of any local reaction on "any day (Day 1-7)" after the booster vaccination.

- Maximum severity of each local reaction on “any day (Day 1-7)” after the booster vaccination.

6.1.2.3.2. Supplementary Analysis

As supplementary analyses to support the assessment of local reactions, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction after each primary vaccination for the following groups:
  - Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or
  - Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

  this will depend on the proportion of participants to be enrolled in SLP/PLP groups and booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).

- Onset day of each local reaction after each primary vaccination for the following groups:
  - Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or
  - Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

  this will depend on the proportion of participants to be enrolled in SLP/PLP groups and booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum.

Figures:

Bar charts with the proportions of participants for any day (Day 1 through Day 7) will be plotted for each primary vaccination for the following groups:

- Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or

- Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups and booster vaccination for the following groups: Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP), with different patterns displayed in the bar charts for different maximum severity levels for any day.

6.1.2.4. Systemic Events Within 7 Days

6.1.2.4.1. Main Analysis

For primary vaccination:

- Planned analysis: The percentage of participants reporting prompted systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after each primary vaccination for the following groups:

  - Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or

  - Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

  this will depend on the proportion of participants to be enrolled in SLP/PLP groups.

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

- Analysis methodology: Descriptive statistics.

- Reporting results: For each group, n, %, and 95% CI will be for the following variables:

  - Presence or absence of each systemic event on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.

  - Presence or absence of any systemic event on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.

  - Maximum severity of each systemic event on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after the booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
    - Presence or absence of each systemic event on "any day (Day 1-7)" after the booster vaccination.
    - Presence or absence of any systemic event on "any day (Day 1-7)" after the booster vaccination.
    - Maximum severity of each systemic event on "any day (Day 1-7)" after the booster vaccination.

6.1.2.4.2. Supplementary Analysis

As supplementary analyses to support the assessment of systemic events, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each systemic event after each primary vaccination for the following groups:
    - Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or
    - Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

  this will depend on the proportion of participants to be enrolled in SLP/PLP groups and booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).
- Onset day of each systemic event after each primary vaccination for the following groups:

- Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or

- Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups and booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum.

Figures:

Bar charts with the proportions of participants for any day (Day 1 through Day 7) will be plotted for each primary vaccination for the following groups:

- Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or

- Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups and booster vaccination for the following groups: Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP), with different patterns displayed in the bar charts for different maximum severity levels for any day, respectively.

6.1.2.5. Use of Antipyretic Medications Within 7 Days

6.1.2.5.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted use of antipyretic medication within 7 days after each primary vaccination for the following groups:

  - Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or

- Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups.

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variable:
  - Use of antipyretic medication on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted use of antipyretic medication within 7 days after the booster vaccination for the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variable:
  - Use of antipyretic medication on "any day (Day 1-7)" after the booster vaccination.

6.1.2.5.2. Supplementary Analysis

As supplementary analyses to support the assessment of protocol-assigned paracetamol use, the following endpoints will be summarized with the same analysis time point and analysis population:

- The percentage of participants reporting prompted use protocol-assigned paracetamol dosing compliance after each primary vaccination, which is calculated as (number of actual protocol-assigned paracetamol doses / number of planned protocol-assigned paracetamol doses) × 100 for the following groups:
  - Group 13 (MenABCWY recipients with TLP) and
  - Group 14 (Bexsero recipients with TLP)

    or

- Group 13 (MenABCWY recipients with SLP),
- Group 14 (Bexsero recipients with PLP),
- Group 13 (MenABCWY recipients with TLP), and
- Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups.

- The percentage of participants reporting prompted use protocol-assigned paracetamol dosing compliance per-protocol timing after each primary vaccination, which is calculated as (number of protocol-assigned paracetamol doses within per-protocol timing window / number of planned protocol-assigned paracetamol doses within per-protocol timing window) × 100 for the following groups:
  - Group 13 (MenABCWY recipients with TLP) and
  - Group 14 (Bexsero recipients with TLP)

  or

  - Group 13 (MenABCWY recipients with SLP),
  - Group 14 (Bexsero recipients with PLP),
  - Group 13 (MenABCWY recipients with TLP), and
  - Group 14 (Bexsero recipients with TLP);

  this will depend on the proportion of participants to be enrolled in SLP/PLP groups.

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

For primary vaccinations:

- Planned analysis: The numbers and percentages of participants with SAEs, MAEs, and NDCMCs for each of the analysis intervals defined in Table 9 will be summarized by the following groups:
  - Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or

- Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups after each primary vaccination.

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the events during the vaccination and follow-up phases, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

For booster vaccination:

- Planned analysis: The numbers and percentages of participants with MAEs, SAEs, and NDCMCs for each of the analysis intervals defined in Table 9 will be summarized by the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients) after the booster vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the events during the booster phase, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

6.1.2.7. Adverse Events

For primary vaccinations:

- Planned analysis: The numbers of participants with AEs for analysis intervals 1 through 4 and 7 defined in Table 9 will be summarized by the following groups:
  - Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or
  - Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups after each primary vaccination.

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.
    - Nonserious AEs are not required to be reported during the follow-up phase; however, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data may be listed separately.

For booster vaccination:

- Planned analysis: The numbers of participants with AEs for analysis intervals 1 through 4 and 7 defined in Table 9 will be summarized by the following groups:
  Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients) after the booster vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.
    - Nonserious AEs are not required to be reported during the follow-up phase; however, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data may be listed separately.

6.1.2.8. Immediate Adverse Events

For primary vaccinations:

- Planned analysis: 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 10 by the following groups:
    - Group 13 (MenABCWY recipients with TLP) and Group 14 (Bexsero recipients with TLP) or

- Group 13 (MenABCWY recipients with SLP), Group 14 (Bexsero recipients with PLP), Group 13 (MenABCWY recipients with TLP), and Group 14 (Bexsero recipients with TLP);

this will depend on the proportion of participants to be enrolled in SLP/PLP groups after each primary vaccination.

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

For booster vaccination:

- Planned analysis: The number and percentage of participants reporting AEs occurring within the 30-minute observation period immediately after vaccination will be summarized according to the last analysis interval defined in Table 10 by the following groups: Group 13 (MenABCWY recipients) and Group 14 (Bexsero recipients) after the booster vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.

Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

6.2. Secondary Endpoint(s)

6.2.1. Secondary Endpoints for Open-Label Stage

6.2.1.1. hSBA Titer for Each of the MenB Test Strains

6.2.1.2. Main Analysis

For the primary vaccinations:

- Planned analysis: hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2 for the group combination 3+4 (60 µg bivalent rLP2086 recipients) and Group 5 (120 µg bivalent rLP2086 recipients).
- Analysis set: Post–primary vaccination 2 evaluable immunogenicity population.
- Analysis methodology: Descriptive statistics.

- Reporting results: For each MenB test strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided.

For the booster vaccination:

- Planned analysis: hSBA GMTs for each of the MenB test strains 1 month after the booster vaccination for the group combination 3+4 (60 µg bivalent rLP2086 recipients) and Group 5 (120 µg bivalent rLP2086 recipients).
- Analysis set: Post–booster vaccination evaluable immunogenicity population.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each MenB test strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided.

6.2.1.3. Sensitivity/Supplementary Analysis

If the mITT analysis is done for the primary analysis, then the same approach may need to be performed for the secondary analysis.

6.2.2. Local Reactions Within 7 Days

6.2.2.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted local reactions (redness, swelling, and tenderness) within 7 days after each primary vaccination for the following groups: Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP), Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each local reaction on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.
  - Presence or absence of any local reaction on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.

- Maximum severity of each local reaction on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted local reactions (redness, swelling, and tenderness) within 7 days after the booster vaccination for the group combination 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each local reaction on "any day (Day 1-7)" after the booster vaccination.
  - Presence or absence of any local reaction on "any day (Day 1-7)" after the booster vaccination.
  - Maximum severity of each local reaction on "any day (Day 1-7)" after the booster vaccination.

6.2.2.2. Supplementary Analysis

As supplementary analyses to support the assessment of local reactions, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction after each primary vaccination for the following groups:
  - Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP),
  - Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and
  - Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP)

  and booster vaccination for the group or group combination
  - Groups 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and
  - Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients).

- Onset day of each local reaction after each primary and booster vaccination for the following groups:
  - Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP),
  - Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and
  - Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP)

  and booster vaccination for the group or group combination
  - Groups 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and
  - Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum.

Figures:

Bar charts with the proportions of participants for any day (Day 1 through Day 7) will be plotted for each primary vaccination for the following groups:

- Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP),
- Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and
- Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP)

and booster vaccination for the group or group combination

- Group 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and
- Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients),

with different patterns displayed in the bar charts for different maximum severity levels for any day.

6.2.3. Systemic Events Within 7 Days

6.2.3.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after each primary vaccination for the following groups: Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP), Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
    - Presence or absence of each systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
    - Presence or absence of any systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
    - Maximum severity of each systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after the booster vaccination for the group combination 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
    - Presence or absence of each systemic event on "any day (Day 1-7)" after the booster vaccination.

- Presence or absence of any systemic event on "any day (Day 1-7)" after the booster vaccination.
- Maximum severity of each systemic event on "any day (Day 1-7)" after the booster vaccination.

6.2.3.2. Supplementary Analysis

As supplementary analyses to support the assessment of systemic events, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each systemic event after each primary vaccination for the following groups:
  - Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP),
  - Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and
  - Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP)

  and booster vaccination for the group or group combination
  - Groups 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and
  - Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients).
- Onset day of each systemic event after each primary vaccination for the following groups:
  - Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP),
  - Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and
  - Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP)

  and booster vaccination for the group or group combination
  - Groups 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and
  - Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum.

Figures:

Bar charts with the proportions of participants for each systemic event on each day (Day 1 through Day 7) and any day (Day 1 through Day 7) will be plotted for each primary vaccination for the following groups:

- Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP),
- Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and
- Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP)

and booster vaccination for the group or group combination

- Groups 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and
- Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients),

with different patterns displayed in the bar charts for different severity levels (each day) and different maximum severity levels for any day.

6.2.4. Use of Antipyretic Medications Within 7 Days

6.2.4.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted use of antipyretic medication within 7 days after each primary vaccination for the following groups:
  Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP),
  Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and
  Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variable:
  - Use of antipyretic medication on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted use of antipyretic medication within 7 days after the booster vaccination for the group combination 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variable:
  - Use of antipyretic medication on "any day (Day 1-7)" after the booster vaccination.

6.2.4.2. Supplementary Analysis

As supplementary analyses to support the assessment of protocol-assigned paracetamol use, the following endpoints will be summarized with the same analysis time point and analysis population:

- The percentage of participants reporting prompted use protocol-assigned paracetamol dosing compliance after each primary vaccination, which is calculated as (number of actual PLP doses / number of planned PLP doses) × 100 for the following groups: Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP) and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP).
- The percentage of participants reporting prompted use protocol-assigned paracetamol dosing compliance per-protocol timing after each primary vaccination, which is calculated as (number of PLP doses within per-protocol timing window / number of planned PLP doses within per-protocol timing window) × 100 for the following groups: Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP) and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP).

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

For primary vaccinations:

- Planned analysis: The numbers and percentages of participants with MAEs, SAEs, and NDCMCs for each of the analysis intervals defined in Table 9 will be summarized by the following groups: Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP), Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP) after each primary vaccination.

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the events during the vaccination and follow-up phases, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

For booster vaccination:

- Planned analysis: The numbers and percentages of participants with MAEs, SAEs, and NDCMCs for each of the analysis intervals defined in Table 9 will be summarized by the group combination 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients) after the booster vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the events during the vaccination and follow-up phases, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

6.2.6. Adverse Events

For primary vaccinations:

- Planned analysis: The numbers of participants with AEs for analysis intervals 1 through 4 and 7 defined in Table 9 will be summarized by the following groups:
  Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP),
  Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and
  Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP) after each primary vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.
  - Nonserious AEs are not required to be reported during the follow-up phase; however, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data may be listed separately.

For booster vaccination:

- Planned analysis: The numbers of participants with AEs for analysis intervals 1 through 4 and 7 defined in Table 9 will be summarized by the group combination 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients) after the booster vaccination.

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

- Analysis methodology: Descriptive statistics.

- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

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

6.2.7. Immediate Adverse Events

For primary vaccinations:

- Planned analysis: 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 10 by the following groups: Group 3 (60 µg bivalent rLP2086 + Nimenrix recipients with PLP or SLP), Group 4 (60 µg bivalent rLP2086 + Nimenrix recipients without PLP), and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients with PLP) after each primary vaccination.

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

- Analysis methodology: Descriptive statistics.

- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

For booster vaccination:

- Planned analysis: 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 10 by the group combination 3+4 (60 µg bivalent rLP2086 + Nimenrix recipients) and Group 5 (120 µg bivalent rLP2086 + Nimenrix recipients) after the booster vaccination.

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

Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

6.3. Tertiary/Exploratory Endpoints

6.3.1. hSBA Titer for Each of the MenA, MenC, MenW, and MenY Test Strains

6.3.1.1. Main Analysis

For the primary vaccinations:

- Planned analysis:
  1. hSBA GMTs for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2 for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Nimenrix recipients).
  2. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2 for the following group combination and groups: Groups 7+11 (MenABCWY recipients with SLP), Group 8 (Nimenrix with PLP recipients), Group 11 (MenABCWY recipients with PLP), and Group 10 (Nimenrix recipients without PLP).
  3. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2 for the following group combination: Groups 1+2 (MenABCWY recipients).
  4. hSBA GMTs for each MenA, MenC, MenW, and MenY test strain 1 month after primary vaccination 2 for the following group combination: Groups 1+2 (MenABCWY recipients).
- Analysis set: Post–primary vaccination 2 evaluable immunogenicity population.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided for 1 and 4 in the planned analysis (above) and the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided for 2 and 3 in the planned analysis.

For the booster vaccination:

- Planned analysis:

    1. hSBA GMTs for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Nimenrix recipients).

    2. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).

    3. hSBA GMTs for each MenA, MenC, MenW, and MenY test strain 1 month after the booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).

- Analysis set: Post–booster vaccination evaluable immunogenicity population.

- Analysis methodology: Descriptive statistics.

- Reporting results: For each strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided for 1 and 3 in the planned analysis (above) and the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided for 2 in the planned analysis.

6.3.1.2. Sensitivity/Supplementary Analyses

If the mITT analysis is done for the primary analysis, then the same approach may need to be performed for the tertiary analysis.

6.3.2. hSBA Titer for Each of the MenB Test Strains

6.3.2.1. Main Analysis

For the primary vaccinations:

- Planned analysis:

    1. hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2 for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).

2. Percentage of participants achieving an hSBA titer ≥ LLOQ for each MenB test strain 1 month after primary vaccination 2 for the following group combination and groups: Groups 7+11 (MenABCWY recipients with SLP), Group 8 (Nimenrix recipients with PLP), Group 11 (MenABCWY recipients with PLP), and Group 10 (Nimenrix recipients without PLP).

3. Percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after primary vaccination 2 for the following group combination: Groups 1+2 (MenABCWY recipients).

4. hSBA GMTs for each of the MenB test strains 1 month after primary vaccination 2 for the following group combination: Groups 1+2 (MenABCWY recipients).

- Analysis set: Post–primary vaccination 2 evaluable immunogenicity population.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each MenB test strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided for 1 and 4 in the planned analysis (above) and the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided for 2 and 3 in the planned analysis.

For the booster vaccination:

- Planned analysis:

  1. hSBA GMTs for each of the MenB test strains 1 month after the booster vaccination for the following group combinations: Groups 7+11 (MenABCWY recipients) and Groups 8+10 (Bexsero recipients).

  2. Percentage of participants achieving an hSBA titer ≥ LLOQ for each of the MenB test strains 1 month after the booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).

  3. hSBA GMTs for each of the MenB test strains 1 month after the booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).

- Analysis set: Post–booster vaccination evaluable immunogenicity population.
- Analysis methodology: Descriptive statistics.

- Reporting results: For each MenB test strain, the GMT and corresponding 2-sided 95% CI for the GMT will be provided for 1 and 3 in the planned analysis (above) and the numerator (n) and denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CIs for the percentages will be provided for 2 in the planned analysis.

6.3.2.2. Sensitivity/Supplementary Analyses

If the mITT analysis is done for the primary analysis, then the same approach may need to be performed for the secondary analysis.

6.3.3. Local Reactions Within 7 Days

6.3.3.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted local reactions (redness, swelling, and tenderness) within 7 days after each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each local reaction on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.
  - Presence or absence of any local reaction on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.
  - Maximum severity of each local reaction on “any day (Day 1-7)” after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted local reactions (redness, swelling, and tenderness) within 7 days after the booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.

- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each local reaction on "any day (Day 1-7)" after the booster vaccination.
  - Presence or absence of any local reaction on "any day (Day 1-7)" after the booster vaccination.
  - Maximum severity of each local reaction on "any day (Day 1-7)" after the booster vaccination.

6.3.3.2. Supplementary Analysis

As supplementary analyses to support the assessment of local reactions, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction after each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP); and booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).
- Onset day of each local reaction after each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP); and booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum.

Figures:

Bar charts with the proportions of participants for each local reaction on each day (Day 1 through Day 7) and any day (Day 1 through Day 7) will be plotted for each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP); and booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients), with different patterns displayed in the bar charts for different severity levels (each day) and different maximum severity levels for any day.

6.3.4. Systemic Events Within 7 Days

6.3.4.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
  - Presence or absence of any systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.
  - Maximum severity of each systemic event on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted systemic events (fever, increased sleep, decreased appetite, and irritability) within 7 days after the booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variables:
  - Presence or absence of each systemic event on "any day (Day 1-7)" after the booster vaccination.
  - Presence or absence of any systemic event on "any day (Day 1-7)" after the booster vaccination.

- Maximum severity of each systemic event on "any day (Day 1-7)" after the booster vaccination.

6.3.4.2. Supplementary Analysis

As supplementary analyses to support the assessment of systemic events, the following endpoints will be summarized with the same analysis time point and analysis population:

- Duration (days) of each systemic event after each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP); and booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).

- Onset day of each systemic event after each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP); and booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).

These continuous endpoints will be summarized by displaying n, mean, median, standard deviation, minimum, and maximum.

Figures:

Bar charts with the proportions of participants for each systemic event on each day (Day 1 through Day 7) and any day (Day 1 through Day 7) will be plotted for each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP); and booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients), with different patterns displayed in the bar charts for different severity levels (each day) and different maximum severity levels for any day.

6.3.5. Use of Antipyretic Medications Within 7 Days

6.3.5.1. Main Analysis

For primary vaccinations:

- Planned analysis: The percentage of participants reporting prompted use of antipyretic medication within 7 days after each primary vaccination for the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP).

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

- Analysis methodology: Descriptive statistics.

- Reporting results: For each group, n, %, and 95% CI will be for the following variable:
  - Use of antipyretic medication on "any day (Day 1-7)" after each primary vaccination and any primary vaccination.

For booster vaccination:

- Planned analysis: The percentage of participants reporting prompted use of antipyretic medication within 7 days after the booster vaccination for the following group combination: Groups 1+2 (MenABCWY recipients).
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, n, %, and 95% CI will be for the following variable:
  - Use of antipyretic medication on "any day (Day 1-7)" after the booster vaccination.

6.3.5.2. Supplementary Analysis

As supplementary analyses to support the assessment of protocol-assigned paracetamol use, the following endpoints will be summarized with the same analysis time point and analysis population:

- The percentage of participants reporting prompted use protocol-assigned paracetamol dosing compliance after each primary vaccination, which is calculated as (number of actual PLP doses / number of planned PLP doses) × 100 for the following group: Group 1 (MenABCWY recipients with PLP).
- The percentage of participants reporting prompted use protocol-assigned paracetamol dosing compliance per-protocol timing after each primary vaccination, which is calculated as (number of PLP doses within per-protocol timing window / number of planned PLP doses within per-protocol timing window) × 100 for the following group: Group 1 (MenABCWY recipients with PLP).

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

For primary vaccinations:

- Planned analysis: The numbers and percentages of participants with MAEs, SAEs, and NDCMCs for each of the analysis intervals defined in Table 9 will be summarized by the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP) after each primary vaccination.

- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the events during the vaccination and follow-up phases, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

For booster vaccination:

- Planned analysis: The numbers and percentages of participants with MAEs, SAEs, and NDCMCs for each of the analysis intervals defined in Table 9 will be summarized by the following group combination: Groups 1+2 (MenABCWY recipients) after the booster vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the events during the vaccination and follow-up phases, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

6.3.7. Adverse Events

For primary vaccinations:

- Planned analysis: The numbers of participants with AEs for analysis intervals 1 through 4 and 7 defined in Table 9 will be summarized by the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP) after each primary vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.
    - Nonserious AEs are not required to be reported during the follow-up phase; however, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data may be listed separately.

For booster vaccination:

- Planned analysis: The numbers of participants with AEs for analysis intervals 1 through 4 and 7 defined in Table 9 will be summarized by the following group combination: Groups 1+2 (MenABCWY recipients) after the booster vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.
    - Nonserious AEs are not required to be reported during the follow-up phase; however, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data may be listed separately.

6.3.8. Immediate Adverse Events

For primary vaccinations:

- Planned analysis: 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 10 by the following groups: Group 1 (MenABCWY recipients with PLP) and Group 2 (MenABCWY recipients without PLP) after each primary vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

For booster vaccination:

- Planned analysis: The number and percentage of participants reporting AEs occurring within the 30-minute observation period immediately after vaccination will be summarized according to the last analysis interval defined in Table 10 by the following group combination: Groups 1+2 (MenABCWY recipients) after the booster vaccination.
- Analysis set: Safety. Refer to Section 4 for visit-specific populations.
- Analysis methodology: Descriptive statistics.

Reporting results: For each group, the n, %, and 95% CI may be presented for any event, for each SOC, and for each preferred term within each SOC.

6.4. Subset Analyses

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

6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct and Participant Disposition

All participants in the mITT population will be included in the disposition summaries. Summaries will be displayed by vaccine group separately.

Disposition summaries include:

- N and % of participants included in each study population (post–primary vaccination 2 mITT, post–booster vaccination mITT, post–primary vaccination 2 evaluable immunogenicity, and post–booster vaccination evaluable immunogenicity)
- N and % of participants receiving each primary vaccination and booster vaccination
- N and % of participants completing the primary vaccination phase, primary follow-up phase, booster vaccination phase, and booster follow-up phase
- N and % of participants who withdrew during the primary vaccination phase (Visit 1 to before Visit 4) and reason for withdrawal
- N and % of participants who withdrew during the primary follow-up phase (Visit 4 to before Visit 5) and reason for withdrawal
- N and % of participants who withdrew during the booster vaccination phase (Visit 5 to before Visit 6) and reason for withdrawal
- N and % of participants who withdrew during the booster follow-up phase (Visit 6 to Visit 7) and reason for withdrawal

For each blood draw, the number and percentage of participants randomized, primary vaccinated at each visit (Visits 1, 3), booster vaccinated at Visit 5, 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 vaccination group. A listing of protocol deviations may also be provided.

6.5.2. Study Intervention Exposure

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

6.5.3. Demographic, Medical History, and Baseline Characteristics

The safety population will be used to generate these tables. All summaries will be presented for each vaccine group separately and for the total population.

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

Medical history and baseline physical examination will descriptively summarized.

6.5.4. E-Diary Completion

E-diary compliance as defined in Section 3.4.3 will be summarized for each dose (primary vaccination 1, primary vaccination 2, and booster vaccination) by vaccine group 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

Nonstudy vaccines and concomitant medications captured throughout the study will be categorized according to the WHODD and will be descriptively summarized for participants in the safety population.

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

6.6. Safety Summaries and Analyses

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

6.6.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification.

6.6.1.1. Related Events

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

The number and percentage of participants reporting at least 1 related AE or SAE and the total number of related events may be summarized by SOC and preferred term. 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 events will be reported and will be summarized by SOC and preferred term. Associated 95% exact CIs will also be displayed.

6.6.1.3. Neuroinflammatory and Autoimmune Conditions

A list of preferred terms 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 6.1.1.3 and Section 6.1.1.4.

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 in this study. The following statistical analyses will be carried out when the data for the specified analyses are available:

- Analysis 1: conducted after Group 5, 8, and 10 participants have completed Visit 4, 1 month after primary vaccination 2. This analysis will include immunogenicity data from Groups 5, 8, and 10 up to 1 month after Vaccination 2, and all safety data available at that time, which, at a minimum, will include safety data from all sentinel-cohort groups (Groups 1-5, 7, 8, and 10). An equivalent analysis may be conducted after Group 5, 8, and 10 participants have completed Visit 6, 1 month after the booster vaccination.

- Analysis 2: safety and immunogenicity data through 1 month after primary vaccination 2 from participants in the open-label stages;

- Analysis 3: safety and immunogenicity data through 1 month after booster vaccination from participants in the open-label phase;

- Analysis 4: a final analysis will be done after all the available data have been collected.

As the open-label stage is unblinded, the sponsor may conduct unblinded review of the safety and immunogenicity data from this phase at any time during the course of the study.

7.2. Interim Analyses and Summaries

This study will use an IRC and an EDMC. The IRC is independent of the study team and includes only internal members, and the EDMC includes only external members. The IRC/EDMC charter describes the role of the IRC/EDMC in more detail.

A Pfizer IRC will review and evaluate post–primary vaccination 1 safety data of each cohort in the sentinel-cohort stage and control the study enrollment and progression. The EDMC will be informed of the IRC's determinations. Enrollment and vaccination may proceed at the discretion of the IRC. The IRC will also review safety data after all expanded-enrollment stage participants have completed primary vaccination 2.

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the EDMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, 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; 2002:18-20.

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

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DMC	data monitoring committee
e-diary	electronic diary
EDMC	external data monitoring committee
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
IRC	internal review committee
IRT	interactive response technology
ITT	intent-to-treat
LLOQ	lower limit of quantitation
MAE	medically attended adverse event
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
MenB	*Neisseria meningitidis* group B
MenC	*Neisseria meningitidis* group C
MenW	*Neisseria meningitidis* group W
MenY	*Neisseria meningitidis* group Y
mITT	modified intent-to-treat
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
PLP	prophylactic liquid paracetamol
PRP-OMP	polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
rLP2086	recombinant lipoprotein 2086
SAE	serious adverse event
SAP	statistical analysis plan
SLP	scheduled liquid paracetamol
SOC	system organ class

Abbreviation	Term
SOP	standard operating procedure
TBD	to be determined
TLP	therapeutic liquid paracetamol
WHODD	World Health Organization Drug Dictionary