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

Study Intervention Number:	PF-06886992
Study Intervention Name:	*Neisseria meningitidis* Group A, B, C, W, and Y Vaccine (MenABCWY)
US IND Number:	N/A
EudraCT Number:	CCI [redacted]
ClinicalTrials.gov ID:	NCT04645966
Protocol Number:	C3511002
Phase:	2b

Short Title: A Phase 2b Study to Describe the Safety and Immunogenicity of MenABCWY in Healthy Infants 2 and 6 Months of Age

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 2	13 September 2021	• Protocol amendment 2 implemented EDMC recommendations that resulted from an analysis of available fever and safety data and a review of paracetamol regimens following completion of enrollment to sentinel Group 5 (Trumenba 120 µg + Nimenrix + PLP). This resulted in: • A data-driven adjustment to the paracetamol regimens aimed at mitigation of unnecessary medical interventions occurring due to fever. Added SLP and TLP in Section 8.2.1.2. • Updates to the open-label sentinel-cohort stage, the open-label expanded-enrollment stage, and the blinded expanded-enrollment stage to progress sequentially as follows: o 2-Month-old participants receiving MenABCWY + SLP in the sentinel stage, followed by o 2-Month-old participants receiving MenABCWY + TLP in the open-label expanded-enrollment stage, followed by o 2-Month-old participants receiving MenABCWY + SLP or TLP or Bexsero + Nimenrix + PLP or TLP in the blinded expanded-enrollment stage.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Elimination of Group 6 for receiving 120 µg rLP2086 + Nimenrix without PLP and Group 9 for receiving MenABCWY without PLP in the open-label sentinel-cohort stage based on the EDMC's recommendation. • Elimination of Group 12 for receiving Bexsero + Nimenrix ± PLP in the open-label expanded-enrollment stage. • Updated Section 3 to reflect group changes and the paracetamol regimen changes. • Specified the vaccine volumes for injection at the vaccination visits in Section 8.11. • Increased the number of participants to 37 in Group 3 and up to 100 in both Group 7 and Group 11. • Updated the numbers of participants to be enrolled for each stage of the study and the total participant number for the study. • Updated Section 9 Statistical Considerations to reflect the changes made in Section 3. • Incorporated changes per PACL dated 05 March 2021. • Replaced the term SRM with ISF throughout the protocol as the term SRM is no longer used.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added Appendix 7: Alternative Measures During Public Emergencies per new template.

Amendment 1	28 January 2021	• Addition of observer-blind expanded-enrollment stage to allow further safety evaluation while minimizing potential bias. Addition of corresponding safety/immunogenicity objectives and analysis triggering enrollment into this stage.
		
		• Addition of a planned analysis 1 month after the booster vaccination in the open-label expanded-enrollment stage in lieu of the prior final analysis.
		
		• Separated Bexsero randomization groups (Groups 8 and 10) from sentinel-cohort stepdown structure to allow enrollment into these groups at any time during the sentinel stage as vaccine assigned in these groups represents standard of care. Removed enrollment restrictions from these groups and applied fewer stopping rules.
		
		• In order to allow for sufficient numbers of participants for the planned analysis preceding the observer-blind expanded-enrollment stage, adjustments were made to:
		
		  • Increase the number of participants from 25 to 50 in Groups 5, 7, 8, 9, and 10.
		
		  • Decrease the number of participants in Group 11 from 150 to 50 and in Group 12 from 150 to 100.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Added confirmation that serum obtained from participants enrolled in the open-label stages may be used for exploratory analysis and meningococcal assay development as a priority over the analysis shown in the study estimands, based on availability of serum volume. • Removal of defined titers from all exploratory estimands. • Inclusion of flowchart in Section 1.2 showing study progression and decision points. • Inclusion of edits from administrative letter dated 16 November 2020.
Original protocol	19 June 2020	N/A

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

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1. PROTOCOL SUMMARY

1.1. Synopsis

The purpose of the study is to describe the safety, tolerability, and immunogenicity of MenABCWY in healthy infants, beginning with infants 6 months of age and progressing to infants 2 months of age. The investigational pentavalent MenABCWY is composed of licensed vaccines Trumenba® (serogroup B; bivalent rLP2086) and Nimenrix® (groups A, C, W-135, and Y; MenACWY-TT).

Cumulatively, 12,411 pediatric participants have been exposed to Nimenrix in clinical trials (4525 of whom received Nimenrix coadministered with other vaccines), with an acceptable safety profile in participants from 6 weeks of age.

Bivalent rLP2086 has been evaluated in participants 1 through 25 years of age, where 120 µg of bivalent rLP2086 was shown to be safe and well tolerated and elicited a robust immune response. Bivalent rLP2086 was initially evaluated in the infant population in Study B1971008 where infants 2 months of age were to receive the final formulation at 20-, 60-, 120-, or 200-µg dose levels coadministered with other routine vaccines. An initial sentinel cohort of 22 infants 2 months of age received 20 µg of bivalent rLP2086 and 64% of the infants experienced mild to moderate fever. Thereafter, the study progressed to the next sentinel cohort, in which infants 2 months of age received 60 µg of bivalent rLP2086. This study was prematurely terminated after 10 infants had received a first dose of 60 µg of bivalent rLP2086, as 9 of the 10 infants experienced mild to moderate fever. The design of this study did not include the administration of paracetamol prophylaxis and, at the time, a 90% rate of fever was judged to be unacceptably high. Because of the current better understanding and acceptance of the higher incidence of fever seen with MenB vaccines and the impact of prophylactic paracetamol in reducing the occurrence of fever in infants, along with the acceptable safety profile of 120 µg of bivalent rLP2086 seen in toddlers 12 months of age, Pfizer has reconsidered the benefit/risk of evaluating bivalent rLP2086 in infants. As 120 µg of bivalent rLP2086 is considered safe in toddlers 12 months of age, yet high rates of fever were observed in infants 2 months of age, this study will evaluate 120 µg of bivalent rLP2086 as part of MenABCWY (concomitantly with Prevenar 13® [13-valent pneumococcal conjugate vaccine] and Vaxelis [a hexavalent DTPa-HBV-IPV-Hib]) in an initial sentinel cohort of infants 6 months of age, after which a stepwise progression to infants 2 months of age will occur if supported by the safety findings in preceding cohorts. In infants 2 months of age, an initial sentinel cohort will receive 60 µg of bivalent rLP2086 and Nimenrix (concomitantly with Prevenar 13 and Vaxelis), after which, if supported by the safety findings, this age group will receive 120 µg of bivalent rLP2086 and Nimenrix (concomitantly with Prevenar 13 and Vaxelis), and then 120 µg of bivalent rLP2086 as part of MenABCWY (concomitantly with Prevenar 13 and Vaxelis). Study progression will be dictated by safety data assessed by participant age, bivalent rLP2086 dose level, and protocol-assigned paracetamol regimen.

During the conduct of the open-label sentinel stage, a stopping rule event triggered an evaluation of the protocol-assigned paracetamol regimen. This evaluation was reviewed by the IRC and EDMC, and the result was a data-driven adjustment to the paracetamol regimens based on fevers observed in the study at the time. This adjustment was aimed at mitigating unnecessary medical interventions occurring due to fever and has been implemented with protocol amendment 2.

In this study, the protocol-assigned paracetamol regimens will be used only in the primary series of vaccinations, which include the prophylactic liquid paracetamol regimen (PLP) with 3 required doses of paracetamol administered with the first dose starting 30 minutes before vaccination, the scheduled liquid paracetamol regimen (SLP) with an initial dosing schedule of 4 or 5 paracetamol doses starting no later than 8 hours after vaccination, and the therapeutic liquid paracetamol regimen (TLP) with an initial dosing schedule of 4 or 5 paracetamol doses given as treatment only when fever or other reactogenicity symptoms arise within 48 hours after the primary series vaccinations and require treatment (if no symptoms are experienced, no paracetamol will be given). These paracetamol dosing schedules can be modified at the discretion of the IRC based upon data obtained in the study. The exact schedules of the different protocol-assigned paracetamol regimens will be provided in the paracetamol dosing instructions.

The inclusion of a licensed comparator is essential in a development program. Bexsero is a MenB vaccine currently approved for use in infants in Europe. It is standard of care in some countries and will be used as the MenB component comparator in this study.

The study will be conducted in 3 stages as follows:

- An open-label sentinel-cohort stage, aimed at demonstrating that 120 μg of bivalent rLP2086 as a separate injection or as part of MenABCWY is safe and immunogenic when administered to infants 2 months of age;
- An open-label expanded-enrollment stage, aimed at obtaining additional safety and immunogenicity data when open-label MenABCWY is administered to infants 2 months of age;
- A blinded expanded-enrollment stage, aimed at obtaining additional safety and immunogenicity data when MenABCWY is administered to infants 2 months of age in a blinded manner.

Objectives

Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Primary Immunogenicity Objectives

- 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.

- 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.

- 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.

Primary Safety Objective

- To describe the safety profile of MenABCWY after primary vaccinations, by protocol-assigned paracetamol regimen, and after a booster dose.

Secondary Immunogenicity Objective

- 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.

Secondary Safety Objective

- To describe the safety profile of 60 µg and 120 µg of bivalent rLP2086 after primary vaccinations, with and without a protocol-assigned paracetamol regimen, and after a booster dose.

Blinded Expanded-Enrollment Stage

Primary Immunogenicity Objectives

- 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.

- 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.

Primary Safety Objective

- To describe the safety profile of MenABCWY after primary vaccinations, by protocol-assigned paracetamol regimen, and after a booster dose.

Overall Design

This is a Phase 2b multicenter trial that will enroll up to 1272 healthy infants, beginning with infants 6 months of age, then on to infants 2 months of age. 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 up to 472 participants will be enrolled in the open-label stages and up to 800 participants will be enrolled in the blinded expanded-enrollment stage of the study. Participants will be randomized to receive 1 of the following:

- MenABCWY,
- Bivalent rLP2086 (60-µg or 120-µg dose level) and Nimenrix, or
- Bexsero and Nimenrix.

The safety, tolerability, and immunogenicity of MenABCWY will be evaluated in comparison with the licensed vaccines Bexsero and Nimenrix.

The open-label sentinel-cohort stage will comprise 5 cohorts (Cohorts 1 to 4 and a sentinel-control cohort) and 8 groups based on age, protocol-assigned paracetamol use, and vaccine(s) to be administered. During the open-label sentinel-cohort stage, for the primary vaccination series starting at 2 months of age, PLP will be used for all participants receiving 120 µg rLP2086, whereas SLP will be used for all 2-month-old participants receiving MenABCWY following the recommendations from the EDMC. PLP or SLP will be used only in the primary series of vaccinations. These paracetamol dosing schedules can be modified at the discretion of the IRC based upon data obtained in the study. During this stage, approximately 50 participants 6 months of age and up to 322 participants 2 months of age will be randomized. MenABCWY, 60 µg of bivalent rLP2086, 120 µg of bivalent rLP2086, Bexsero, and Nimenrix will be administered on a 2 (primary doses) +1 (booster dose) schedule. Prevenar 13 and Vaxelis will be concomitantly administered to all sentinel-cohort participants during primary vaccinations. See Section 1.2 for each group's vaccination and blood collection schedule.

For sentinel Cohorts 1 to 4, enrollment will be initiated in each cohort sequentially, starting with Cohort 1 (see Figure 1). Enrollment in each of these cohorts will be restricted to 3 participants per day until the first 9 participants have been enrolled. A Pfizer IRC will review and evaluate the 7-day post–primary vaccination 1 safety data of each cohort and will control the study enrollment and progression. Stopping rules will apply to participants in sentinel Cohorts 1 to 4 for the 7-day safety period following primary vaccination 1 only. The study will progress to the open-label expanded-enrollment stage following IRC review of post–primary vaccination 1 safety data from Cohort 4.

Enrollment into the sentinel-control cohort, which will comprise randomization groups of participants receiving Bexsero and Nimenrix (with or without PLP), may occur at any time during the sentinel-cohort stage without IRC review of data from Cohorts 1 to 4.

In the open-label expanded-enrollment stage, approximately 50 to 100 participants 2 months of age will be enrolled into 1 group (Group 11). The participants will receive MenABCWY with TLP as treatment only if fever or reactogenicity symptoms arise within 48 hours after primary series vaccinations and require treatment (if no symptoms are experienced, no paracetamol will be given). Enrollment of participants receiving MenABCWY with TLP will be restricted to 3 participants per day until 9 participants have been enrolled. Seven days after the first 25 participants have received primary vaccination 1, e-diary and AE data from this group will be summarized, as well as e-diary and AE data from prior cohort(s) in the sentinel-cohort stage, for review by the sponsor's IRC. Continuation with the enrollment of participants receiving MenABCWY with TLP into Group 11 and primary vaccination 2 for the participants already enrolled in Group 11 will not be permitted until IRC review of these safety data are complete and these data are found acceptable. With the IRC's approval, enrollment will be continued, such that up to approximately 50 to 100 participants 2 months of age will be enrolled. At any point during the study conduct of Group 11, the IRC may determine that the remaining participants will be enrolled to receive MenABCWY with SLP, based on the safety data gathered. TLP or SLP administration in this group will be associated only with primary series vaccinations. These paracetamol dosing schedules can be modified at the discretion of the IRC based upon data obtained in the study.

MenABCWY, Bexsero, and Nimenrix will be administered on a 2+1 schedule. Prevenar 13 and Vaxelis will be concomitantly administered to all expanded-enrollment stage participants during primary vaccinations. See Section 1.2 for each group's vaccination and blood collection schedule.

In the blinded expanded-enrollment stage, up to 800 participants will be enrolled and will receive the same study vaccinations as in the open-label expanded-enrollment stage, with participants randomized to receive MenABCWY additionally receiving placebo at each vaccination visit to maintain the study blind (Section 1.2.2). Enrollment will be stratified by protocol-assigned paracetamol use, either SLP or TLP for MenABCWY-receiving participants and PLP or TLP for Bexsero-receiving participants. The proportion of participants receiving each regimen being set by the sponsor is based on safety data gathered during the study. The protocol-assigned paracetamol use is only applicable to primary series vaccinations. The exact schedules of protocol assigned paracetamol regimens will be at the discretion of the IRC, may be adjusted as safety data become available, and will be described in the protocol-assigned paracetamol dosing instructions.

Data Monitoring Committee or Other Independent Oversight Committee

A Pfizer IRC will review and evaluate post–primary vaccination 1 safety data of each cohort in the open-label sentinel-cohort stage and the post–primary vaccination 1 safety data from the first 25 participants enrolled to the open-label expanded-enrollment stage and will also perform other ad-hoc reviews of data as required for the purpose of study enrollment and progression. In both the open-label and blinded expanded-enrollment stages, the exact schedules of protocol-assigned paracetamol regimens will be at the discretion of the IRC and may be adjusted as safety data become available. An 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 open-label sentinel-cohort stage participants have completed primary vaccination 2, and when all open-label 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. Recommendations made by the EDMC will be forwarded to Pfizer for final decision making.

Statistical Methods

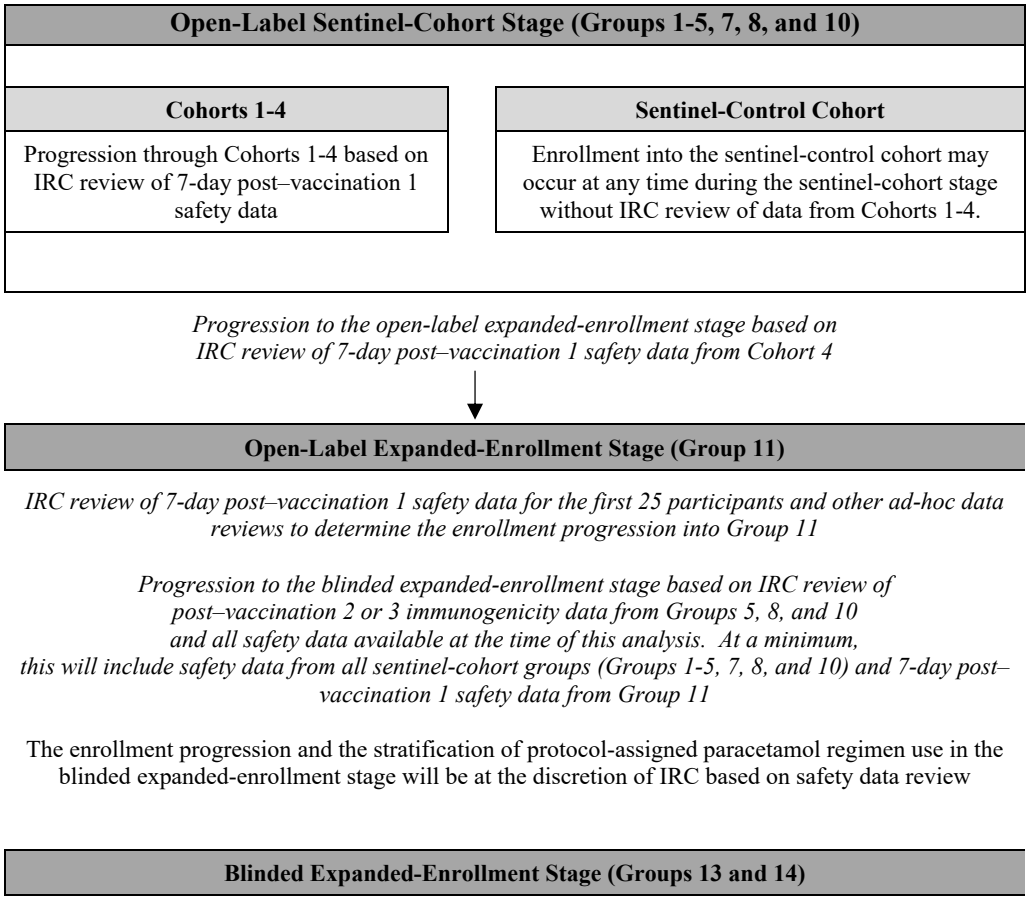
This is not a hypothesis-testing study; an estimation approach will be used to assess the immunogenicity and safety objectives in this study. All immunogenicity data will be summarized descriptively. For all binary endpoints (including primary endpoints), counts, percentages, and 2-sided 95% CIs using the Clopper-Pearson method will be calculated. For hSBA titer results, geometric means and 2-sided 95% CIs based on the t-distribution will be computed. Statistical analyses will be carried out when the final data for the specified analyses are available (see Section 9.5.1).

The primary immunogenicity objectives will be evaluated by descriptive summary statistics for the percentages of participants achieving hSBA titers ≥ LLOQ 1 month after primary vaccination 2 and 1 month after the booster vaccination. Additionally, hSBA GMTs and the RCDCs of the hSBA titers will be provided for the specified time points to provide further characterization of the immune response.

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

1.2. Schema

1.2.1. Study Progression Flowchart



1.2.2. Study Intervention Overview

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.
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 as described in Section 8.2.1.2.
d. 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.

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. See details in Section 8.2.1.2.

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. See details in Section 4.1.3.

1.3. Schedule of Activities

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

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

	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	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Approximate Months of the Study	**0**	**1**	**2**	**3**	**6[a]/10[b]**	**7[a]/11[b]**	**12[a]/16[b]**
Approximate Months of Age:							
Participants 6 Months of Age at Randomization	**6**	**7**	**8**	**9**	**12**	**13**	**18**
Participants 2 Months of Age at Randomization	**2**	**3**	**4**	**5**	**12**	**13**	**18**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**63 to 77 Days After Visit 1**	**28 to 42 Days After Visit 3**	**365 to 386 Days of Age**	**28 to 42 Days After Visit 5**	**168 to 196 Days After Last Study Vaccination**
Informed consent	X						
Review eligibility criteria	X						
Demography	X						
Confirm continued eligibility		X	X	X	X	X	
Medical history and physical examination	X						
Record previous PRP-OMP vaccinations	X						

	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	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Approximate Months of the Study	**0**	**1**	**2**	**3**	**6[a]/10[b]**	**7[a]/11[b]**	**12[a]/16[b]**
Approximate Months of Age:							
Participants 6 Months of Age at Randomization	**6**	**7**	**8**	**9**	**12**	**13**	**18**
Participants 2 Months of Age at Randomization	**2**	**3**	**4**	**5**	**12**	**13**	**18**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**63 to 77 Days After Visit 1**	**28 to 42 Days After Visit 3**	**365 to 386 Days of Age**	**28 to 42 Days After Visit 5**	**168 to 196 Days After Last Study Vaccination**
Brief physical examination			X		X		
Axillary temperature	X		X		X		
Randomization	X						
Obtain blood sample				5 mL		5 mL	
Administer PLP before vaccination (PLP participants only)[c]	X		X				
Dispense protocol-assigned paracetamol to parent(s)/legal guardian (PLP, SLP, and TLP participants only)	X		X				
Investigational product administration and observation[d]	X		X		X		
Record nonstudy vaccinations		X	X	X	X	X	

	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	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Approximate Months of the Study	**0**	**1**	**2**	**3**	**6[a]/10[b]**	**7[a]/11[b]**	**12[a]/16[b]**
Approximate Months of Age:							
Participants 6 Months of Age at Randomization	**6**	**7**	**8**	**9**	**12**	**13**	**18**
Participants 2 Months of Age at Randomization	**2**	**3**	**4**	**5**	**12**	**13**	**18**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**63 to 77 Days After Visit 1**	**28 to 42 Days After Visit 3**	**365 to 386 Days of Age**	**28 to 42 Days After Visit 5**	**168 to 196 Days After Last Study Vaccination**
Provide provisioned e-diary or ensure diary app downloaded[c]	X		X		X		
Provide caliper, measuring tape/ruler, and thermometer, if necessary	X		X		X		
Assess reactogenicity and record use of antipyretic medication	Days 1 to 7		Days 1 to 7		Days 1 to 7		
Collect e-diary (if device provided)				X		X	
Collect protocol-assigned paracetamol from parent(s)/legal guardian for accountability (PLP, SLP, and TLP participants only)			X	X			
Provide parent(s)/legal guardian a contact card	X						
Provide parent(s)/legal guardian a memory aid				X		X	
Complete Study Visit/Telephone Contact AE Checklist		X	X	X	X	X	X

	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	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Approximate Months of the Study	**0**	**1**	**2**	**3**	**6[a]/10[b]**	**7[a]/11[b]**	**12[a]/16[b]**
Approximate Months of Age:							
Participants 6 Months of Age at Randomization	**6**	**7**	**8**	**9**	**12**	**13**	**18**
Participants 2 Months of Age at Randomization	**2**	**3**	**4**	**5**	**12**	**13**	**18**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**63 to 77 Days After Visit 1**	**28 to 42 Days After Visit 3**	**365 to 386 Days of Age**	**28 to 42 Days After Visit 5**	**168 to 196 Days After Last Study Vaccination**
Record concomitant medications used to treat AEs	X	X	X	X	X	X	X
(S)AE collection appropriate for the visit	X	X	X	X	X	X	X

Abbreviations: e-diary = electronic diary; PLP = prophylactic liquid paracetamol regimen; PRP-OMP = polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein; SLP = scheduled liquid paracetamol regimen; TLP = therapeutic liquid paracetamol regimen.

a. Approximate months of the study for participants in Groups 1 and 2.
b. Approximate months of the study for participants in Groups 3 through 14.
c. Record the first dose of PLP administration in the PLP participant's e-diary.
d. During blinded expanded-enrollment stage, study vaccines to be administered by unblinded administrator only.
e. Ensure functionality of the provisioned e-diary device or the downloaded diary application.

2. INTRODUCTION

Pfizer is developing a pentavalent meningococcal vaccine (MenABCWY) by combining Trumenba® (serogroup B; bivalent rLP2086) and Nimenrix® (groups A, C, W-135, and Y; MenACWY-TT), 2 commercially available vaccines, into a single vaccine to prevent invasive disease caused by the 5 major meningococcal serogroups: A, B, C, W, and Y.

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

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

MenABCWY is a pentavalent meningococcal vaccine composed of bivalent rLP2086 (120 µg of meningococcal group B vaccine) and Nimenrix (5 µg of each of the 4 meningococcal polysaccharides from groups A, C, W-135, and Y conjugated to 44 µg of tetanus toxoid).

Bexsero is another MenB vaccine that is approved for active immunization of individuals 10 through 25 years of age in the United States and individuals 2 months of age and older in Europe to prevent invasive disease caused by *N meningitidis* group B and is included as a comparator in this study.

2.1. Study Rationale

MenABCWY is composed of bivalent rLP2086 (120 µg of meningococcal group B vaccine) and Nimenrix (5 µg of each of the 4 meningococcal polysaccharides A, C, W-135, and Y conjugated to 44 µg of tetanus toxoid).

Nimenrix is a licensed vaccine currently approved in a 2+1 schedule for infants 6 weeks to less than 6 months of age, in a 1+1 schedule for infants 6 to 12 months of age, and as a single dose thereafter. Cumulatively, 12,411 pediatric participants have been exposed to Nimenrix in clinical trials (4525 of whom received Nimenrix coadministered with other vaccines), with an acceptable safety profile.

Trumenba was initially evaluated in the infant population in Study B1971008 where infants 2 months of age were to receive the final formulation of bivalent rLP2086 at 20-, 60-, 120-, or 200-µg dose levels coadministered with other routine vaccines. An initial sentinel cohort of 22 infants 2 months of age received 20 µg of bivalent rLP2086, and 64% of the infants experienced mild to moderate fever. Thereafter, the study progressed to the next sentinel cohort, in which infants 2 months of age received 60 µg of bivalent rLP2086. This study was prematurely terminated after 10 infants had received a first dose of 60 µg of bivalent

rLP2086, as 9 of the 10 infants experienced mild to moderate fever. The design of this study did not include the administration of paracetamol prophylaxis and, at the time, a 90% rate of fever was judged to be unacceptably high.

The bivalent rLP2086 clinical development program also evaluated adolescents where bivalent rLP2086 at a dose of 120 µg was shown to be safe and well tolerated and elicited a robust immune response. Bivalent rLP2086 at a dose of 60 µg was also evaluated in adolescents, showing a safety profile comparable to the 120-µg dose; however, the 120-µg dose exhibited higher immunogenicity for more MenB test strains, maximizing the breadth of coverage. Following evaluation in adolescents and young adults, 120 µg of bivalent rLP2086 was evaluated in toddlers and children 1 to <10 years of age, where it was shown to be safe and well tolerated and elicited a robust immune response.

Several years after the termination of Study B1971008, Bexsero (another MenB vaccine) was licensed in Europe for use in infants. High rates of mild to moderate fever (up to 70%) were also reported in clinical trials evaluating Bexsero when administered alone and even higher rates when coadministered with routine vaccination. However, rates of fever were shown to be reduced with the administration of prophylactic paracetamol, particularly fever ≥39.0°C.[1] After the approval of Bexsero in the EU, some European countries instituted MenB routine vaccination programs as standard of care where the primary series is initiated in infants 2 or 3 months of age. The use of prophylactic paracetamol was also introduced as standard of care in some European countries as a measure to reduce rates of fever experienced in infants receiving Bexsero.

Because of the better understanding and acceptance of the higher incidence of fever seen with MenB vaccines and the impact of prophylactic paracetamol in reducing the occurrence of fever in infants, along with the acceptable safety profile of 120 µg of bivalent rLP2086 seen in toddlers 12 months of age, Pfizer decided to reconsider the evaluation of bivalent rLP2086 in infants. As 120 µg of bivalent rLP2086 is considered safe in toddlers 12 months of age, yet high rates of fever were observed in infants 2 months of age, it was determined appropriate to initiate this study evaluating 120 µg of bivalent rLP2086 as part of MenABCWY (concomitantly with Prevenar 13® [13-valent pneumococcal conjugate vaccine] and Vaxelis [a hexavalent DTPa-HBV-IPV-Hib]) in an initial sentinel cohort of infants 6 months of age, after which progression would occur stepping down to infants 2 months of age. In infants 2 months of age, an initial sentinel cohort will receive 60 µg of bivalent rLP2086 and Nimenrix (concomitantly with Prevenar 13 and Vaxelis), after which, if supported by the safety findings, this age group will receive 120 µg of bivalent rLP2086 and Nimenrix (concomitantly with Prevenar 13 and Vaxelis), and then 120 µg of bivalent rLP2086 as part of MenABCWY (concomitantly with Prevenar 13 and Vaxelis). Study progression will be dictated by safety and immunogenicity data assessed by participant age, bivalent rLP2086 dose level, and protocol-assigned paracetamol use.

During the conduct of the open-label sentinel stage, a stopping rule event triggered an evaluation of the paracetamol regimen. This evaluation was reviewed by the IRC and EDMC, and the result was a data-driven adjustment to paracetamol regimens based on fevers observed in the study at the time. This adjustment aimed to mitigate unnecessary medical interventions occurring due to fever and has been implemented with protocol amendment 2.

In this study, the protocol-assigned paracetamol regimens will be used only in the primary series of vaccinations, which include the prophylactic liquid paracetamol regimen (PLP) with 3 required doses of paracetamol administered with the first dose starting 30 minutes before vaccination, the scheduled liquid paracetamol regimen (SLP) with an initial dosing schedule of 4 or 5 paracetamol doses starting no later than 8 hours after vaccination, and the therapeutic liquid paracetamol regimen (TLP) with an initial dosing schedule of 4 or 5 paracetamol doses given as treatment only when fever or other reactogenicity symptoms arise within 48 hours after the primary series vaccinations and require treatment (if no symptoms are experienced, no paracetamol will be given). These paracetamol dosing schedules can be modified at the discretion of the IRC based upon data obtained in the study. The exact schedules of the different protocol-assigned paracetamol regimens will be provided in the paracetamol dosing instructions.

The inclusion of a licensed comparator is essential in a development program. Bexsero is another MenB vaccine currently approved for use in infants in Europe and will be used as the MenB component comparator. Bexsero is licensed in infants 2 months of age and is standard of care in some EU countries as a 2- or 3-dose primary series plus a booster dose administered between 12 and 15 months of age (2+1 or 3+1). This study will evaluate MenABCWY in infants 2 months of age using a 2+1 dosing schedule and will be conducted in 3 stages as follows:

- An open-label sentinel-cohort stage, aimed at demonstrating that 120 μg of bivalent rLP2086 as a separate injection or as part of MenABCWY is safe and immunogenic when administered to infants 2 months of age;

- An open-label expanded-enrollment stage, aimed at obtaining additional safety and immunogenicity data when open-label MenABCWY is administered to infants 2 months of age;

- An blinded expanded-enrollment stage, aimed at obtaining additional safety and immunogenicity data when MenABCWY is administered to infants 2 months of age in a blinded manner.

2.2. Background

2.2.1. Background of the Disease and Medical Need

N meningitidis is an obligate human pathogen that colonizes the upper respiratory tract, which, in some individuals, can cause serious, life-threatening IMD, which clinically presents as septicemia, meningitis, or both.[2] IMD is rare in EU/EEA countries, but is a severe and life-threatening disease. The greatest burden is in infants and young children, with a relatively high case fatality and up to one-fifth of all survivors suffering from long-term sequelae.[3] *N meningitidis* groups A, B, C, W-135, and Y are 5 of the 6 meningococcal serogroups that cause the vast majority of meningococcal disease globally,[4] and disease incidence is highest in infants and young children.[3] In Europe, meningococcal disease is primarily caused by group B, followed by groups W and C.[3]

In Europe, the peak of disease in infants occurs around 5 to 6 months of age.[5,6] Current preventive vaccination strategies require separate immunizations at different times for a MenACWY conjugate vaccine as well as a separate group B vaccine. In Europe, MenB has become the most common cause of IMD over the past several years and MenB now exceeds all other serogroups in incidence, accounting for 70% of IMD among children under the age of 1 year, with groups C, W, Y, and other serogroups, including A, accounting for the other 30%.[3] These data show that all 5 serogroups causing the majority of meningococcal disease globally also contribute to disease in infants and that a multivalent vaccine incorporating group B would have significant public health utility. These data also show that initiating immunization at 2 months of age would provide protection to the age groups with the highest disease burden.

Given that meningococcal groups B, C, W, and Y cause disease in infants through early adolescence and young adulthood, with unacceptable mortality and morbidity outcomes with a high contribution of group B to IMD in this age group, a safe and effective pentavalent vaccine, which is currently not available, would fulfill an unmet need for broad protection against IMD that is more durable in the setting of the disease's changing epidemiology.

2.2.2. Clinical Overview

Cumulatively, 12,411 pediatric participants from 6 weeks of age and older have received Nimenrix in clinical trials (4525 of whom received Nimenrix coadministered with other vaccines), with an acceptable safety profile.

The Trumenba clinical development program evaluated adolescents and adults for whom Trumenba at a dose of 120 µg was shown to be safe and well tolerated and elicited a robust immune response. Trumenba at a dose of 60 µg was also evaluated in adolescents, showing a safety profile comparable to the 120-µg dose; however, the 120-µg dose exhibited higher immunogenicity for more MenB test strains, maximizing the breadth of coverage. Following evaluation in adolescents and young adults, 120 µg of bivalent rLP2086 was evaluated in toddlers and children 1 to <10 years of age, where it was shown to be safe and well tolerated and elicited a robust immune response. In Study B1971008, infants 2 months of age were to receive the final formulation of Trumenba at 20-, 60-, 120-, or 200-µg dose levels coadministered with other routine vaccines.

An initial sentinel cohort of 22 infants 2 months of age received 20 µg of bivalent rLP2086, and 64% of infants experienced mild to moderate fever. Thereafter, the study progressed to the next sentinel cohort of infants 2 months of age, who received 60 µg of bivalent rLP2086. This study was prematurely terminated after 10 infants had received a first dose of 60 µg of bivalent rLP2086, as 9 of the 10 infants experienced mild to moderate fever.

In Study B1971057, an FIH and POC study for MenABCWY, 543 participants between 10 and 25 years of age received MenABCWY on a 0- and 6-month schedule. Results from Study B1971057 indicated that in adolescents and adults, MenABCWY is well tolerated, with an acceptable safety profile, and also provides a high degree of protective immune responses without interference among all 5 serogroup components.

2.3. Benefit/Risk Assessment

As previously described, the greatest burden of IMD is in infants and young children, with a relatively high case fatality and up to one-fifth of all survivors suffering from long-term sequelae. Current preventive vaccination strategies require separate immunizations at different times for vaccines against the different serogroups. A safe and effective pentavalent vaccine, which is currently not available, would fulfill an unmet need for broad protection against 5 serogroups causing IMD in these populations.

Trumenba and Nimenrix were proven to be immunogenic and to have an acceptable safety profile in children above 1 year of age, adolescents, and adults. Nimenrix was also proven to be immunogenic and safe in infants above the age of 6 weeks. Consequently, Bexsero and Nimenrix are standards of care in some EU countries. Study B1971008, which evaluated Trumenba in infants 2 months of age, was prematurely terminated after 10 infants had received a first dose of 60 µg of bivalent rLP2086, as 9 of the 10 infants experienced mild to moderate fever. The design of this study did not include the administration of paracetamol prophylaxis and, at the time, a 90% rate of fever was judged to be unacceptably high. This initial perception of unacceptable fever rates has changed over time after the evidence of Bexsero's showing high rates of fever (up to 70%) that were reduced with the use of prophylactic paracetamol.[1]

In the FIH Study B1971057, MenABCWY provided a high degree of immunologic protection against IMD caused by *N meningitidis* groups A, B, C, W, and Y in adolescents and young adults. MenABCWY was statistically noninferior to Trumenba for the MenB component and to MenACWY-CRM for the MenA, MenC, MenW, and MenY components in participants who had received a prior vaccination with a MenACWY-containing vaccine as well as those naïve to a MenACWY vaccine. No new safety events were identified in this study.

This Phase 2b study is one of several studies in the MenABCWY development program, which, if successful, could provide a broadly protective, safe, comprehensive, and first-in-class meningococcal vaccine that could contribute significantly to a simplified vaccination program for the prevention of IMD.

Trumenba and Nimenrix are licensed vaccines. Common AEs noted after vaccination are primarily related to reactogenicity, including local reactions and systemic events. See more details in Section 2.3.1.

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

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

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

More detailed information about the known and expected benefits and risks and reasonable expected AEs of MenABCWY may be found in the MenABCWY IB, which is the SRSD for MenABCWY for this study. Detailed safety information for Nimenrix, Bexsero, Prevenar 13, Vaxelis, and paracetamol can be found in their SmPCs, and detailed safety information for bivalent rLP2086 (60-µg and 120-µg doses) can be found in the Trumenba IB (Table 1). The SmPC of paracetamol is the Lithuanian SmPC for Panadol (120 mg/5 mL).

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Vaccinations With MenABCWY, Trumenba, Nimenrix, Bexsero, Prevenar 13, Vaxelis, and Paracetamol		
Potential risks that may be associated with MenABCWY in adolescents and young adults based on clinical trial experience with bivalent rLP2086, Nimenrix, and MenABCWY include the following: headache, nausea, diarrhea, vomiting, myalgia, arthralgia, injection site pain, fatigue, chills, injection site swelling, injection site redness, fever, loss of/decreased appetite, irritability, insomnia, crying, drowsiness, hypoesthesia, dizziness, rash, pruritus, pain in extremity, injection site hematoma, malaise, and injection site reaction (including induration, pruritus, warmth, and anesthesia). Potential risk of medical evaluations and/or diagnostic procedures due to reactogenicity fever in infants. Potential risks that may be associated with MenABCWY in infants based on clinical trial experience with Nimenrix include the following: loss of/decreased appetite, irritability/fussiness, insomnia, crying, drowsiness, diarrhea, nausea, vomiting, rash, injection site pain, injection site swelling, injection site redness, fever, injection site hematoma, malaise, and injection site reaction (including induration, pruritus, warmth, and anesthesia). Potential risks that may be associated with MenABCWY based on postmarketing experience with bivalent rLP2086 and	The potential risks that may be reported with MenABCWY are based on the known safety profiles of the component vaccines, bivalent rLP2086 and Nimenrix, as presented in the MenABCWY IB (based on the bivalent rLP2086 CDS and Nimenrix CDS).	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Enrollment will be initiated in each numbered cohort sequentially in the sentinel-cohort stage. Enrollment in Cohorts 1 to 4 will be restricted to 3 participants per day until the first 9 participants have been enrolled. In the sentinel stage, the vaccine will be initially given to infants 6 months of age, and then to infants 2 months of age, along with protocol-assigned paracetamol administration during primary vaccinations. E-diary and AE data will be monitored daily by the investigator (or designee) and the sponsor during the first 7 days (including nonbusiness days) after primary vaccination 1 (Section 8.2.1). The IRC determines the study enrollment and progression upon review and evaluation of the 7-day safety data. Fever management procedures will be followed as described (Section 8.2.1.2.2). Stopping rules are clearly defined for safety management and study progression control (Section 8.2.4.1). Protocol amendment 2 implemented EDMC recommendations based on the evaluation of the paracetamol regimens and resulted in a data-driven adjustment to the paracetamol regimen based on fevers observed in the study at the time. This adjustment aimed at mitigating unnecessary medical interventions occurring due to fever.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Nimenrix are as follows: extensive limb swelling at the injection site, frequently associated with erythema, sometimes involving the adjacent joint or swelling of the entire injected limb; lymphadenopathy[a]; allergic reactions; and syncope.		
The risks associated with Trumenba observed in adolescents and young adults 10 years of age and older based on clinical trial experience with bivalent rLP2086 are as follows: headache, nausea, diarrhea, vomiting, myalgia, arthralgia, injection site pain, fatigue, chills, injection site swelling, injection site redness, and fever. The risks associated with Trumenba in toddlers 12 to <24 months of age based on clinical trial experience with bivalent rLP2086 are as follows: drowsiness, irritability (fussiness), loss of/decreased appetite, injection site pain, injection site swelling, injection site redness, and fever. In clinical studies, fever occurred more frequently as participant age decreased. The risks associated with Trumenba based on postmarketing experience are as follows: allergic reactions and syncope. Potential risk of medical evaluations and/or diagnostic procedures due to reactogenicity fever in infants.	The potential risks are based on the known safety profile of Trumenba as presented in the Trumenba IB (based on the bivalent rLP2086 CDS).	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Enrollment will be initiated in each cohort sequentially in the sentinel-cohort stage. Enrollment in Cohorts 1 to 4 will be restricted to 3 participants per day until the first 9 participants have been enrolled. In the sentinel stage, the vaccine will be initially given to participants at half of the full dose (60 µg), and then the full dose (120 µg), with or without protocol-assigned paracetamol administration during primary vaccinations. E-diary and AE data will be monitored daily by the investigator (or designee) and the sponsor during the first 7 days (including nonbusiness days) after primary vaccination 1 (Section 8.2.1). The IRC determines the study enrollment and progression upon review and evaluation of the 7-day safety data. Fever management procedures will be followed as described (Section 8.2.1.2.2). Stopping rules are clearly defined for safety management and study progression control (Section 8.2.4.1). Protocol amendment 2 implemented EDMC recommendations based on the evaluation of the paracetamol regimen and resulted in a data-driven adjustment to the paracetamol regimen based on fevers observed in the study at the time.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		This adjustment aimed at mitigating unnecessary medical interventions occurring due to fever.
The risks associated with Nimenrix in individuals 6 weeks up to 55 years of age based on clinical trial experience include the following: loss of/decreased appetite, irritability, insomnia, crying, drowsiness, headache, hypoesthesia, dizziness, diarrhea, vomiting, nausea, pruritus, rash, myalgia, pain in extremity, fever, injection site pain, injection site swelling, injection site redness, fatigue, injection site hematoma, malaise, and injection site reaction (including induration, pruritus, warmth, and anesthesia). The risks associated with Nimenrix based on postmarketing experience are as follows: extensive limb swelling at the injection site, frequently associated with erythema, sometimes involving the adjacent joint or swelling of the entire injected limb; lymphadenopathy.	The risks are based on the known safety profile of Nimenrix in infants as presented in the product labeling Nimenrix SmPC.	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Individuals with significant reactions after the first vaccination or AEs considered by the investigator to present increased risk to the participant if rechallenged with the second vaccination, or who develop exclusionary conditions during the conduct of the study, will be excluded from further vaccinations.
The risks associated with Bexsero observed in infants and children up to 10 years of age based on clinical trial experience include the following: Very common and common: eating disorders, sleepiness, unusual crying, headache, diarrhea, vomiting, rash, arthralgia, fever (≥38°C), injection site tenderness, injection site erythema, injection site swelling, injection site induration, and irritability. Uncommon: seizure (including febrile seizure), pallor, eczema, and fever (≥40°C). Rare: Kawasaki syndrome and urticaria.	The risks are based on the known safety profile of Bexsero in infants and children up to 10 years of age as presented in the Bexsero SmPC.	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). In the sentinel stage, the vaccine will be given to participants initially with PLP administration during primary vaccinations. E-diary and AE data will be monitored daily by the investigator (or designee) and the sponsor during the first 7 days (including nonbusiness days) after primary vaccination 1 (Section 8.2.1). The IRC determines the study enrollment and progression upon review and evaluation of the 7-day safety data.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
The risks associated with Bexsero in infants and children up to 10 years of age based on postmarketing experience include the following: allergic reactions (including anaphylactic reactions), hypotonic-hyporesponsive episode, meningeal irritation (signs of meningeal irritation, such as neck stiffness or photophobia), and injection site reactions (including extensive swelling of the vaccinated limb, blisters at or around the injection site, and injection site nodule, which may persist for more than 1 month). Potential risk of medical evaluations and/or diagnostic procedures due to reactogenicity fever in infants.		Fever management procedures will be followed as described (Section 8.2.1.2.2). Stopping rules are clearly defined for safety management and study progression control (Section 8.2.4.1).
The risks associated with Prevenar 13 observed in infants and children 6 weeks to 5 years of age based on clinical trial experience include the following: hypersensitivity reaction including facial edema, dyspnea, and bronchospasm; convulsions (including febrile convulsions); hypotonic-hyporesponsive episode; decreased appetite; vomiting; diarrhea; rash; urticaria or urticaria-like rash; pyrexia, irritability, injection site tenderness, erythema, and swelling; somnolence, poor-quality sleep; pyrexia >39°C; and vaccination site movement impairment (due to pain). The risks associated with Prevenar 13 in infants and children 6 weeks to 5 years of age based on postmarketing experience are as follows: lymphadenopathy (localized to the region of the vaccination site);	The risks are based on the known safety profile of Prevenar 13 in infants and children 6 weeks to 5 years of age as presented in the product labeling (SmPC).	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Individuals with significant reactions after the first vaccination or AEs considered by the investigator to present increased risk to the participant if rechallenged with the second vaccination, or who develop exclusionary conditions during the conduct of the study, will be excluded from further vaccinations.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
anaphylactic/anaphylactoid reaction including shock; angioedema; erythema multiforme; vaccination site urticaria; vaccination site dermatitis; vaccination site pruritus; flushing; and apnea in very premature infants (≤28 weeks of gestation).		
The common and very common risks associated with Vaxelis in infants from 6 weeks of age based on clinical trial experience include the following: decreased appetite, somnolence, vomiting, diarrhea, crying, irritability, injection site erythema, injection site pain, injection site swelling, pyrexia, injection site bruising, injection site induration, and injection site nodule. The risks associated with Vaxelis in infants from 6 weeks of age based on postmarketing experience are as follows: hypotonic-hyporesponsive episode.	The risks are based on the known safety profile of Vaxelis (diphtheria, tetanus, pertussis [acellular, component], hepatitis B (rDNA), poliomyelitis [inactivated], and *Haemophilus influenzae* type b conjugate vaccine [adsorbed]) in infants and toddlers as presented in the product labeling (SmPC).	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). Individuals with significant reactions after the first vaccination or AEs considered by the investigator to present increased risk to the participant if rechallenged with the second vaccination or who develop exclusionary conditions during the conduct of the study will be excluded from further vaccinations.
The risks associated with paracetamol 120-mg/5-mL oral suspension based on postmarketing experience include the following: Very rare: thrombocytopenia, anaphylaxis, increased skin sensitivity reactions (including skin rash, angioedema, Stevens-Johnson syndrome, and toxic epidermal necrolysis), hepatic impairment, and bronchospasm in patients with hypersensitivity to acetylsalicylic acid and other NSAIDs. Cases of hepatic impairment (failure) have been reported in patients with glutathione deficiency. Paracetamol should be	The risks are based on the known safety profile as presented in the product labeling of paracetamol 120-mg/5-mL oral suspension (Lithuanian SmPC for Panadol).	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study. In addition, individuals with prior adverse reactions to paracetamol use, including allergic reactions, will be excluded (see Section 5). Individuals with significant reactions after oral administration of paracetamol or AEs considered by the investigator to present increased risk to the participant will be excluded from the study. Parent(s)/legal guardian will be instructed to administer protocol-assigned paracetamol according to the protocol. Parent(s)/legal guardian will be instructed not to coadminister other paracetamol-containing medications during the period of protocol-assigned paracetamol use.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
administered with caution to patients with renal and hepatic impairment. Paracetamol usage with other medicines containing paracetamol may cause an overdose. Paracetamol overdose may lead to liver failure, which may require a liver transplantation, or may cause death. Paracetamol oral suspension containing maltitol and sorbitol should not be used in patients with hereditary fructose intolerance.		E-diary and AE data will be monitored daily by the investigator (or designee) and the sponsor during the first 7 days (including nonbusiness days) after primary vaccination 1 (Section 8.2.1). The IRC determines the study enrollment and progression upon review and evaluation of the 7-day safety data. Fever management procedures will be followed as described (Section 8.2.1.2.2). Stopping rules are clearly defined for safety management and study progression control (Section 8.2.4.1).
Study Procedures: Venipuncture		
There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Venipuncture is required to collect immunogenicity data from participants.	Only qualified nurses, physicians, nurse practitioners, physician's assistants, phlebotomists, or medical assistants certified or otherwise authorized to draw blood per the standards and procedures of the investigative site as allowed by institutional, local, and country guidance will be allowed to draw blood, to minimize local complications.

a. Lymphadenopathy is included in the SmPC for Nimenrix but is not listed in the CDS as its causality is not clear.

2.3.2. Benefit Assessment

Based on the known degree of protective immunogenicity afforded by the licensed vaccines Trumenba, Nimenrix, and Bexsero, as well as data for the investigational vaccine MenABCWY from the FIH Study B1971057, the potential benefits of participation in this study and receipt of all vaccination doses include protection against IMD caused by *N meningitidis* groups A, B, C, W, and Y after receipt of all scheduled vaccinations.

The potential benefits of participation in this study also include protective immunity afforded by licensed vaccines Prevenar 13 and Vaxelis for prevention of invasive disease caused by 13 *S pneumoniae* serotypes, and diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and Hib, respectively.

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

2.3.3. Overall Benefit/Risk Conclusion

Taking into account that Bexsero and Nimenrix are standards of care in some EU countries and the measures implemented to minimize risk to participants in this study, the potential risks of vaccination with MenABCWY, Trumenba, Nimenrix, and Bexsero (which primarily include transient, mild to moderate local reactions and systemic events and the potential risks for minor complications from intramuscular injections or venipuncture) are justified by the anticipated benefits (protective immunity against IMD) that participants may receive.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

Sera obtained from participants enrolled in the open-label stages may be used for exploratory analysis and meningococcal assay development as a priority over the analysis as shown in the estimands below, based on availability of serum volume.

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.
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 (TBD).

Objectives	Estimands	Endpoints
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 (TBD).
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).	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.

Objectives	Estimands	Endpoints
	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. 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 (TBD).

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. 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).	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.

Objectives	Estimands	Endpoints
	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 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.	hSBA titer for each of the MenB test strains (TBD).

Objectives	Estimands	Endpoints
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 (TBD).
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.

Objectives	Estimands	Endpoints
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. 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.	hSBA titer for each of the MenB test strains (TBD).
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).	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.

Objectives	Estimands	Endpoints
	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 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.	

3.2. 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 group combinations: 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 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 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 group combinations: 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. 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 GMTs for each of the MenB test strains after the booster vaccination.	hSBA titer for each of the MenB test strains (TBD).

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 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. 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).	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.

Objectives	Estimands	Endpoints
	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.	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b multicenter trial that will enroll up to 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 up to 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 Section 1.2.1.

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 (Section 8.2.1).

During the conduct of the open-label sentinel stage, a stopping rule event triggered an evaluation of the protocol-assigned paracetamol regimen. This evaluation was reviewed by the IRC and EDMC, and the result was a data-driven adjustment to the paracetamol timing based on fevers observed in the study at the time. This adjustment aimed to mitigate unnecessary medical interventions occurring due to fever and has been implemented with protocol amendment 2.

4.1.1. Open-Label Sentinel-Cohort Stage

The sentinel-cohort stage will comprise 5 cohorts (Cohorts 1 to 4 and a sentinel-control cohort) and 8 groups based on age, protocol-assigned paracetamol use, and vaccine(s) to be administered (see Section 1.2). Protocol-assigned paracetamol will be applicable only to vaccinations in the primary series. Approximately 50 participants 6 months of age and up to 322 participants 2 months of age will be randomized into the following cohorts/groups, with randomization groups containing Bexsero and Nimenrix being enrolled at any time (Groups 8 and 10):

- **Cohort 1**
    - Group 1 (n~25): infants 6 months of age will receive MenABCWY with PLP
- **Cohort 2**
    - Group 2 (n~25): infants 6 months of age will receive MenABCWY without PLP
    - Group 3 (n~37): infants 2 months of age will receive 60 µg of bivalent rLP2086 and Nimenrix with PLP or SLP

- **Cohort 3**
    - Group 4 (n~25): infants 2 months of age will receive 60 µg of bivalent rLP2086 and Nimenrix without PLP
    - Group 5 (n~50): infants 2 months of age will receive 120 µg of bivalent rLP2086 and Nimenrix with PLP
- **Cohort 4**
    - Group 7 (n~50-100): infants 2 months of age will receive MenABCWY with SLP (the exact schedule of the protocol-assigned paracetamol regimen will be at the discretion of the IRC, may be subject to change on an ongoing basis as data become available, and will be described in the protocol-assigned paracetamol dosing instructions).
- **Sentinel-control cohort**
    - Group 8 (n~55): infants 2 months of age will receive Bexsero and Nimenrix with PLP
    - Group 10 (n~55): infants 2 months of age will receive Bexsero and Nimenrix without PLP

MenABCWY, 60 µg bivalent rLP2086, 120 µg bivalent rLP2086, Bexsero, and Nimenrix will be administered on a 2 (primary doses) + 1 (booster dose) schedule.

Prevenar 13 and Vaxelis will be concomitantly administered to all sentinel-cohort participants during primary vaccinations. 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 3-10) will receive Prevenar 13 and Vaxelis at 2 and 4 months of age (Visits 1 and 3).

4.1.1.1. Cohorts 1 to 4

For Cohorts 1 to 4, enrollment will be initiated in each cohort sequentially, starting with Cohort 1. Enrollment in each of these cohorts will be restricted to 3 participants per day until 9 participants have been enrolled. Seven days after the last participant in each cohort has received primary vaccination 1, e-diary and AE data from that cohort will be summarized, as well as e-diary and AE data from prior cohort(s) (if applicable), for review by the sponsor's IRC. Primary vaccination 2 in the corresponding cohort and enrollment into the subsequent cohort will not be permitted until IRC review of these safety data are complete and these data are found acceptable (see Figure 1). Stopping rules will apply to participants in Cohorts 1 to 4 for the 7-day safety period following primary vaccination 1 only (Section 8.2.4.1). The number of participants in a specific group may be increased by up to 25% by the sponsor, as needed, if more safety data for that group is deemed beneficial.

The study will progress to the open-label expanded-enrollment stage following IRC review of post–primary vaccination 1 safety data from Cohort 4. A summary of study progression through the sentinel-cohort stage is shown in Figure 1.

In order to provide ongoing oversight of participant safety, 7 days after all the sentinel-cohort stage participants have completed primary vaccination 2, reactogenicity and AE data from all participants available at the time will be summarized for review by the IRC.

4.1.1.2. Sentinel-Control Cohort

Enrollment into the sentinel-control cohort may occur at any time during the sentinel-cohort stage without IRC review of data from Cohorts 1 to 4. Enrollment into the sentinel-control cohort will not be subject to enrollment restrictions imposed on Cohorts 1 to 4, and fewer stopping rules will apply to participants in this cohort (Section 8.2.4.1).

During the IRC review of reactogenicity and AE data from participants in Cohorts 1 to 4 (post-vaccination 1 and 2), available reactogenicity and AE data from participants in the sentinel-control cohort will also be reviewed.

A planned analysis will be conducted after Groups 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). See Section 9.5.1. The study will progress to the blinded stage if the safety and immunogenicity data from this analysis are deemed acceptable by the sponsor, or if safety and immunogenicity data from the equivalent analysis 1 month after the booster vaccination are deemed acceptable.

4.1.2. Open-Label Expanded-Enrollment Stage

The open-label expanded-enrollment stage will include 1 additional treatment group (Group 11) with approximately 50 to 100 participants (see Section 1.2) that will receive MenABCWY and TLP as treatment only if fever or other reactogenicity symptoms arise within 48 hours after primary series vaccinations (if no symptoms are experienced, no paracetamol will be given). Enrollment of participants receiving MenABCWY with TLP will be restricted to 3 participants per day until 9 participants have been enrolled. Seven days after the first 25 participants have received primary vaccination 1, e-diary and AE data from this group will be summarized, as well as e-diary and AE data from prior cohort(s) in the sentinel-cohort stage, for review by the sponsor's IRC. Continuation with the enrollment of participants receiving MenABCWY with TLP into Group 11 and primary vaccination 2 for the participants already enrolled in Group 11 will not be permitted until IRC review of these safety data are complete and these data are found acceptable. With the IRC's approval, enrollment will be continued such that up to approximately 50 to 100 participants 2 months of age will be enrolled as below. At any point during the study conduct of Group 11, the IRC may determine that the remaining participants will be enrolled to receive MenABCWY with SLP, based on the safety data gathered. TLP or SLP administration in this group will be associated only with primary series vaccinations. Group 11 (n~50 to 100): infants 2 months

of age will receive MenABCWY with TLP (the exact schedule of the protocol-assigned paracetamol regimen will be at the discretion of the IRC, may be subject to change on an ongoing basis as data become available, and will be described in the protocol-assigned paracetamol dosing instructions).

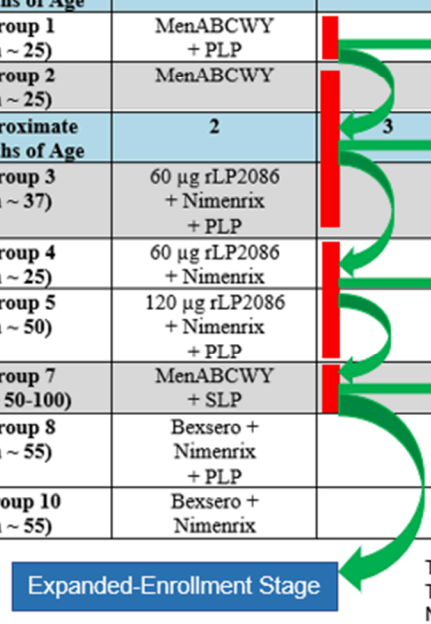
MenABCWY will be administered on a 2+1 schedule. Prevenar 13 and Vaxelis will be concomitantly administered to all expanded-enrollment stage participants during primary series vaccinations. Participants 2 months of age will receive Prevenar 13 and Vaxelis at 2 and 4 months of age (Visits 1 and 3).

In order to provide ongoing oversight of participant safety, 7 days after all expanded-enrollment stage participants have completed primary vaccination 2, reactogenicity and AE data from all participants available at the time will be summarized for review by the IRC.

A planned analysis of safety and immunogenicity data will be conducted after all expanded-enrollment stage participants have completed Visit 4, 1 month after primary vaccination 2. A further planned analysis of safety and immunogenicity data will be conducted after all open-label stage participants have completed Visit 6, 1 month after the booster vaccination (see Section 9.5.1).

Figure 1. Enrollment Strategy and Study Progression in Sentinel-Cohort Stage

Sentinel Cohort	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	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		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		MenABCWY + SLP		MenABCWY		
Sentinel-Control Cohort	Group 8 (n ~ 55)	Bexsero + Nimenrix + PLP		Bexsero + Nimenrix + PLP		Bexsero + Nimenrix		
	Group 10 (n ~ 55)	Bexsero + Nimenrix		Bexsero + Nimenrix		Bexsero + Nimenrix		



The red bar represents IRC review on 7-day safety data after primary vaccination 1.
The expanded-cohort enrollment will start if IRC finds Cohort 4 safety acceptable.
Note: "rLP2086" refers to bivalent rLP2086.

4.1.3. Blinded Expanded-Enrollment Stage

The following groups will be included in the blinded phase (see Section 1.2):

- Group 13 (n = up to 400): infants 2 months of age will receive MenABCWY + placebo with SLP or TLP

- Group 14 (n = up to 400): infants 2 months of age will receive Bexsero + Nimenrix with PLP or TLP

The study vaccination schedule, including that for Prevenar 13 and Vaxelis, will be the same as for the expanded-enrollment stage, but participants in Group 13 will receive both MenABCWY and placebo, rather than MenABCWY alone, in order to maintain the study blind.

In the blinded stage, enrollment will be stratified by protocol-assigned paracetamol use, with the proportion of participants receiving each regimen being set by the sponsor based on safety data gathered during the study. The protocol-assigned paracetamol use is only applicable to primary series vaccinations. Participants enrolled in Groups 13 and 14 and assigned TLP will follow a double-blind design. Participants in Groups 13 and 14 who are assigned SLP and PLP, respectively, will follow a single-blind design due to the differences in the paracetamol regimens. The exact number of participants to be enrolled into each group and each stratum for protocol-assigned paracetamol use, enrollment speed, and exact schedules of protocol-assigned paracetamol regimens will be at the discretion of the IRC, may be subject to change as safety data become available, and will be described in the protocol-assigned paracetamol dosing instructions.

Planned safety analysis based on the numbers of participants enrolled per protocol-assigned paracetamol regimen following the double-blind and single-blind design will be detailed in the SAP.

4.1.4. Approximate Duration of Participation for Each Participant

Participants enrolled at 6 months of age will be in the study for approximately 12 months. Participants enrolled at 2 months of age will be in the study for approximately 16 months.

4.1.5. Approximate Number of Participants

Up to 1272 participants will be enrolled, with approximately up to 472 participants in the open-label stages and up to 800 in the blinded expanded-enrollment stage.

4.2. Scientific Rationale for Study Design

The aim of the study is to assess the safety, tolerability, and immunogenicity of MenABCWY in healthy infants, initially 6 months of age, and then going down in age to infants 2 months of age. MenABCWY is composed of 2 vaccines already licensed in Europe, Trumenba (120 µg bivalent rLP2086) and Nimenrix (MenACWY-TT).

The MenACWY component of MenABCWY, Nimenrix (MenACWY-TT), is a licensed vaccine currently approved in a 2+1 schedule for infants 6 weeks to less than 6 months of age, in a 1+1 schedule for infants 6 to 12 months of age, and as a single dose thereafter. Clinical studies of Nimenrix in the pediatric population have demonstrated an acceptable safety profile.

The MenB component of MenABCWY, bivalent rLP2086, was initially evaluated in the infant population in Study B1971008 where infants 2 months of age were to receive the final formulation of bivalent rLP2086 at 20-, 60-, 120-, or 200-µg dose levels coadministered with other routine vaccines. An initial sentinel cohort of 22 infants 2 months of age received 20 µg of bivalent rLP2086, and 64% of the infants experienced mild to moderate fever. Thereafter, the study progressed to the next sentinel cohort of infants 2 months of age, who received 60 µg of bivalent rLP2086. This study was prematurely terminated after 10 infants had received a first dose of 60 µg of bivalent rLP2086, as 9 of the 10 infants experienced mild to moderate fever. The design of this study did not include the administration of paracetamol prophylaxis and, at the time, a 90% rate of fever was judged to be unacceptably high.

The bivalent rLP2086 clinical development program also evaluated adolescents where bivalent rLP2086 at a dose of 120 µg was shown to be safe and well tolerated and elicited a robust immune response. Bivalent rLP2086 at a dose of 60 µg was also evaluated in adolescents showing a safety profile comparable to the 120-µg dose; however, the 120-µg dose exhibited higher immunogenicity for more MenB test strains, maximizing the breadth of coverage. Following evaluation in adolescents and young adults, 120 µg of bivalent rLP2086 was evaluated in toddlers and children 1 to <10 years of age, where it was shown to be safe and well tolerated and elicited a robust immune response.

Several years after the termination of Study B1971008, Bexsero (another MenB vaccine) was licensed in Europe in infants. High rates of mild to moderate fever (up to 70%) were also reported in clinical trials evaluating Bexsero when administered alone with higher rates when coadministered with routine vaccination. However, rates of fever were shown to be reduced with the administration of prophylactic paracetamol, particularly fever ≥39.0°C.[1] After the approval of Bexsero in the EU, some European countries instituted MenB routine vaccination programs where the primary series is initiated in infants 2 or 3 months of age. The use of prophylactic paracetamol was also introduced as standard of care in some European countries as a measure to reduce rates of fever experienced in infants receiving Bexsero.

Because of the better understanding and acceptance of the higher incidence of fever seen with MenB vaccines and the impact of prophylactic paracetamol in reducing the occurrence of fever in infants, along with the acceptable safety profile of 120 µg of bivalent rLP2086 seen in toddlers 12 months of age, Pfizer has reconsidered the benefit and risk of evaluating bivalent rLP2086 in infants. As 120 µg of bivalent rLP2086 is considered safe in toddlers 12 months of age, yet high rates of fever were observed in infants 2 months of age, this study will evaluate 120 µg of bivalent rLP2086 as part of MenABCWY (concomitantly with Prevenar 13 and Vaxelis) in an initial sentinel cohort of infants 6 months of age, after which a stepwise progression to infants 2 months of age will occur if supported by the safety

findings. In infants 2 months of age, an initial sentinel cohort will receive 60 µg of bivalent rLP2086 and Nimenrix (concomitantly with Prevenar 13 and Vaxelis), after which, if supported by the safety findings, this age group will receive 120 µg of bivalent rLP2086 with Nimenrix (concomitantly with Prevenar 13 and Vaxelis), and then 120 µg of bivalent rLP2086 as part of MenABCWY. Throughout the sentinel stage, the study progression will be dictated by safety data assessed by participant age, bivalent rLP2086 dose level, and protocol-assigned paracetamol use.

The inclusion of a licensed comparator is essential in a development program. Bexsero is a MenB vaccine currently approved in infants in Europe and will be used as the MenB component comparator. Bexsero is licensed in infants 2 months of age as a 2- or 3-dose primary series plus a booster dose administered between 12 and 15 months of age (2+1 or 3+1). This study will evaluate MenABCWY in infants 2 months of age using a 2+1 dosing schedule.

4.3. Justification for Dose

Trumenba (120 µg of bivalent rLP2086) is supplied as a 0.5-mL dose PFS, while Nimenrix is supplied as a lyophilized powder in a single-dose vial and a solvent in a PFS to be reconstituted for injection.

MenABCWY consists of 120 µg of bivalent rLP2086, supplied as a high-fill-volume PFS, which is used to reconstitute Nimenrix, and 0.5 mL of the resultant MenABCWY is administered via intramuscular injection.

Trumenba (120 µg of bivalent rLP2086) is considered safe in toddlers 12 months of age, yet high rates of fever were observed in infants 2 months of age; therefore, it was determined appropriate to initiate this study evaluating 120 µg of bivalent rLP2086 as part of MenABCWY (concomitantly with Prevenar 13 and Vaxelis) in an initial sentinel cohort of infants 6 months of age, after which progression would occur stepping down in age to infants 2 months of age. In infants 2 months of age, an initial sentinel cohort will receive 60 µg of bivalent rLP2086 and Nimenrix (concomitantly with Prevenar 13 and Vaxelis), after which this age group will receive 120 µg of bivalent rLP2086 and Nimenrix (concomitantly with Prevenar 13 and Vaxelis), and then 120 µg of bivalent rLP2086 as part of MenABCWY (concomitantly with Prevenar 13 and Vaxelis). Study progression will be dictated by safety data assessed by participant age, bivalent rLP2086 dose level, and protocol-assigned paracetamol use.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the trial globally.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants:

   - Open-label sentinel-cohort stage: 2 months of age (≥60 to ≤98 days) or 6 months of age (≥150 to ≤210 days) at the time of randomization.

   - Open-label expanded-enrollment stage and blinded expanded-enrollment stage: 2 months of age (≥60 to ≤98 days) at the time of randomization.

Type of Participant and Disease Characteristics:

2. Participant's parent(s)/legal guardian who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Participant is available for the entire study period and the participant's parent(s)/legal guardian can be reached by telephone.

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

Weight

5. Body weight ≥4 kg for participants 2 months of age at the time of randomization.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Prior adverse reaction to paracetamol use, including allergic reactions.

2. Participant was born prematurely (<37 weeks of gestation).

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

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

5. A known or suspected defect of the immune system that would prevent an immune response to the vaccine, such as participants with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, intravenous, or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy. Please refer to the ISF for additional details.

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

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

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

9. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

10. Previous vaccination with any meningococcal vaccine. Written vaccination history must be obtained prior to randomization.

11. For participants 2 months of age, prior vaccination with any of the following licensed or investigational vaccines: pneumococcal vaccine and hexavalent DTPa-HBV-IPV-Hib or its component, except for the birth dose of hepatitis B vaccine.

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

13. Receipt of any blood products, including immunoglobulin, before the first study vaccination.

14. Current chronic use of systemic antibiotics.

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

Not applicable.

Other Exclusions:

16. Children or grandchildren of investigator site staff or Pfizer employees directly involved in the conduct of the study.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants whose parent(s)/legal guardian consent to allow their participation in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

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

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

5.5.1. Criteria for Temporarily Delaying Vaccine Administration

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

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

2. Participant has received any nonlive vaccine (or intramuscular/sublingual allergen immunotherapy) or rotavirus vaccine within 14 days, or any live vaccine (other than a rotavirus vaccine) within 28 days, before investigational product administration.

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

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

5. Participant has received antipyretic medications and/or other pain medications on the day prior to planned vaccination other than that assigned per the study protocol.

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

5.5.2. Criteria for Temporarily Delaying Immunogenicity Blood Draw

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

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to the investigational products listed in Section 6.1.

6.1. Study Intervention(s) Administered

Vaccine or Drug Name	MenABCWY	Bivalent rLP2086 (60-µg Dose)	Bivalent rLP2086 (120-µg Dose)	Nimenrix	Bexsero	Prevenar 13	Vaxelis	Paracetamol[a]	Placebo (Normal Saline)
Group(s)	1, 2, 7, 11, and 13	3 and 4	5	3, 4, 5, 8, 10, and 14	8, 10, and 14	1, 2, 3-5, 7, 8, 10, 11, 13, and 14	1, 2, 3-5, 7, 8, 10, 11, 13, and 14	1, 3, 5, 7, 8, 11, 13, and 14	13
Dose Formulation	Nimenrix will be reconstituted with bivalent rLP2086, supplied as a high-fill-volume PFS.	0.5-mL PFS; appropriate volume to be withdrawn from 0.5-mL PFS to administer a dose of 0.25 mL	0.5-mL PFS	Nimenrix is supplied as a lyophilized powder in a single-dose vial and a solvent in a PFS to be reconstituted for injection.	0.5-mL PFS	0.5-mL PFS	0.5-mL PFS	120-mg/5-mL suspension	0.5-mL PFS
Dosage Level(s)	0.5-mL dose at Visits 1, 3, and 5	0.25-mL dose at Visits 1, 3, and 5	0.5-mL dose at Visits 1, 3, and 5	0.5-mL dose at Visits 1, 3, and 5	0.5-mL dose at Visits 1, 3, and 5	0.5-mL dose at Visit 1 for Groups 1 and 2; Visits 1 and 3 for Groups 3-5, 7, 8, 10, 11, 13, and 14	0.5-mL dose at Visit 1 for Groups 1 and 2; Visits 1 and 3 for Groups 3-5, 7, 8, 10, 11, 13, and 14	5-mL dose for Group 1; 2.5-mL dose for Groups 3, 5, 7, 8, 11, 13, and 14	0.5-mL dose at Visits 1, 3, and 5
Route of Administration	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Oral	Intramuscular
IMP or NIMP	IMP	IMP	IMP	IMP	IMP	NIMP	NIMP	IMP	IMP
Sourcing	Pfizer	Pfizer	Pfizer	Pfizer	Pfizer	Pfizer	Pfizer	Pfizer	Pfizer
Packaging and Labeling	Each MenABCWY kit will consist of a vial of Nimenrix, bivalent rLP2086 high-fill-volume PFS, and vial adaptor. Kits will be packaged in a carton and labeled as required per country requirement.	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton and labeled as required per country requirement.	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton and labeled as required per country requirement.	Study intervention will be provided as a lyophilized powder in a single-dose vial and a solvent in a PFS. The vial and PFS will be packaged in a carton and labeled as required per country requirement.	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton and labeled as required per country requirement. Kits provided for the blinded phase will include a blinded label	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton and labeled as required per country requirement.	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton and labeled as required per country requirement.	Study intervention will be provided in a bottle. Each bottle will be packaged in a carton and labeled as required per country requirement.	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton and labeled as required per country requirement. Kits provided will include a blinded label and a tamper-evident seal. .

Vaccine or Drug Name	MenABCWY	Bivalent rLP2086 (60-µg Dose)	Bivalent rLP2086 (120-µg Dose)	Nimenrix	Bexsero	Prevenar 13	Vaxelis	Paracetamol[a]	Placebo (Normal Saline)
	Kits provided for the blinded phase will include a blinded label and a tamper-evident seal.			Kits provided for the blinded phase will include a blinded label and a tamper-evident seal.	and a tamper-evident seal.				

a. See details of protocol-assigned paracetamol dosages and schedules in Table 5.

The sentinel-cohort stage and the expanded-cohort stage will be open-label. The blinded phase will use blinded labels for MenABCWY, Nimenrix, Bexsero, and placebo.

6.1.1. Administration

Participants will receive the investigational products in accordance with the study's SoA. See Table 1.

Table 1. Study Intervention Administration Schedule and SRSDs

Investigational Product	Group(s)	Visit(s)	Injection Location	SRSD
MenABCWY	1, 2, 7, 11, and 13	Visits 1, 3, and 5	Left thigh	MenABCWY IB
Trumenba (60-µg dose)	3 and 4	Visits 1, 3, and 5	Left thigh	Trumenba IB
Trumenba (120-µg dose)	5	Visits 1, 3, and 5	Left thigh	Trumenba IB
Nimenrix	3, 4, 5, 8, 10, and 14	Visits 1, 3, and 5	Right thigh	SmPC
Bexsero	8, 10, and 14	Visits 1, 3, and 5	Left thigh	SmPC
Placebo	13	Visits 1, 3, and 5	Right thigh	N/A
Prevenar 13	1 and 2	Visit 1	Right thigh	SmPC
	3-5, 7, 8, 10, 11, 13, and 14	Visits 1 and 3	Right thigh	
Vaxelis	1 and 2	Visit 1	Right thigh	SmPC
	3-5, 7, 8, 10, 11, 13, and 14	Visits 1 and 3	Right thigh	
Paracetamol[a]	1, 3, 5, 7, 8, 11, 13, and 14	Visits 1 and 3	N/A	Lithuanian SmPC for Panadol (120 mg/5 mL)

Abbreviations: IB = investigator's brochure; N/A = not applicable; SmPC = summary of product characteristics; SRSD = single reference safety document.
a. See details of protocol-assigned paracetamol dosages and schedules in Table 5.

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

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

Study intervention administration details will be recorded on the CRF.

6.1.2. Medical Devices

1. The Pfizer-manufactured medical devices (or devices manufactured for Pfizer by a third party) provided for use in this study are the vial adaptor and PFS for MenABCWY, and the PFS for Trumenba, Nimenrix, placebo, and Prevenar 13.

2. Other medical devices (not manufactured by or for Pfizer) provided for use in this study are the PFS for Bexsero and Vaxelis.

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

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

6.2. Preparation/Handling/Storage/Accountability

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

2. Study intervention will be shipped to the study site after required regulatory and legal documents have been received by the sponsor. The investigational vaccines/placebo will be shipped at +2°C to +8°C. Upon receipt at the study site, the investigational vaccines/placebo should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage. Liquid paracetamol will be shipped and stored per the product leaflet.

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

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

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

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

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

8. Site staff will instruct participants on the proper storage requirements for take-home study intervention, eg, liquid paracetamol.

9. See the IP manual, package insert, or equivalent for storage conditions of the study intervention once reconstituted.

10. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. Used needles and syringes should be disposed of according to local practice. Empty outer study intervention containers must be retained until reviewed by the sponsor's representative and then may be destroyed after the sponsor's representative has performed accountability. Study intervention return/destruction must be documented on the accountability log. Protocol-assigned paracetamol will be accounted for as outlined in the IP manual. The protocol-assigned paracetamol bottle that is taken home by the participant's parent/legal guardian needs to be returned to the investigator by the participant's parent(s)/legal guardian on the following study site visit.

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

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

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

6.2.1. Preparation and Dispensing

See the IP manual, package insert, or equivalent for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by appropriately qualified and experienced members of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

In addition to the above, during the blinded expanded-enrollment stage, study staff preparing, dispensing, and administering the study intervention will be unblinded, and all participants will remain blinded to whether they received MenABCWY + placebo or Bexsero + Nimenrix throughout this stage of the study.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

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

During both the open-label and blinded stages, the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required. Study intervention will be dispensed at the study visits summarized in the SoA.

During the open-label stages, the investigator's knowledge of the vaccine assignment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Returned study intervention must not be redispensed to the participants.

6.3.2. Blinding During the Open-Label Stages

All study staff and sponsor personnel will be unblinded during the open-label stages.

6.3.3. Blinding During the Blinded Expanded-Enrollment Stage

6.3.3.1. Blinding of Study Staff

During the blinded expanded-enrollment stage, the study staff dispensing, preparing, and administering study vaccines will be unblinded. For participants assigned to receive TLP, all other study and site staff, including the investigator, investigator staff, participants, and participants' parent(s)/legal guardian, will be blinded to whether these participants have received MenABCWY + placebo or Bexsero + Nimenrix throughout the blinded expanded-enrollment stage. In particular, the individuals who evaluate participant safety will be blinded. Because these study interventions are different in physical appearance, the MenABCWY, placebo, Bexsero, and Nimenrix study vaccine syringes will be administered in a manner that prevents the study participants' parent(s)/legal guardian from identifying the vaccine type based on its appearance (see Section 6.1). For participants assigned to receive PLP or SLP, participants' parent(s)/legal guardian will be blinded to whether these

participants have received MenABCWY + placebo or Bexsero + Nimenrix throughout the blinded expanded-enrollment stage. All other study and site staff, including the investigator and investigator staff, will not be blinded to whether these participants have received MenABCWY + placebo or Bexsero + Nimenrix throughout the blinded expanded-enrollment stage.

All study staff will be unblinded to the use of protocol-assigned paracetamol regimen, Prevenar 13, and Vaxelis throughout the blinded expanded-enrollment stage. Participants' parent(s)/legal guardian will be blinded to the association of the use of protocol-assigned paracetamol regimens with specific investigational vaccines throughout the blinded expanded-enrollment stage. For participants assigned to receive PLP or SLP, the feasibility of blinding the participants' parent(s)/legal guardian to the association of the use of protocol-assigned paracetamol with specific investigational vaccines will be reassessed by the Sponsor prior to study progression to the blinded expanded-enrollment stage. The participants' parent(s)/legal guardian may not be blinded to the use of protocol-assigned paracetamol for participants assigned to receive PLP or SLP if blinding is deemed not feasible.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum during the blinded expanded-enrollment stage. The remaining study staff must not know whether a participant has been assigned to receive MenABCWY + placebo or Bexsero + Nimenrix.

6.3.3.2. Blinding of the Sponsor

Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). An unblinded clinician who is not a direct member of the study team will review unblinded protocol deviations. For participants assigned to receive TLP, all other study team members will remain blinded to whether participants have been assigned to MenABCWY + placebo or Bexsero + Nimenrix during the blinded expanded-enrollment stage until the study is unblinded. All laboratory testing personnel performing serology assays will remain blinded to vaccine assigned/received and to visit number throughout the study.

All study team members will be unblinded to the use of protocol-assigned paracetamol regimens, Prevenar 13, and Vaxelis throughout the blinded expanded-enrollment stage.

6.3.3.3. Breaking the Blind

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

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

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF, except protocol-assigned paracetamol administration, which is to be recorded in the source documents and in the e-diary. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

For protocol-assigned paracetamol administration at the site, the date and time of the dose administered will be recorded in the participant's e-diary. For protocol-assigned paracetamol administration at home, compliance with the study intervention will be assessed by e-diary entry after each primary vaccination (see Section 8.2.1.2.2).

6.5. Concomitant Therapy

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD up to Visit 6 will be recorded on the CRF.

Sufficient supply of Prevenar 13 and Vaxelis will be provided by Pfizer to sites to ensure participants are able to complete the primary series and receive a booster dose of these vaccines, in accordance with the national immunization schedule. However, in special circumstances and with approval by the sponsor, for doses other than primary vaccinations 1 and 2, a site may independently obtain pneumococcal vaccine or DTPa-HBV-IPV-Hib or its components rather than receive shipment of these vaccines from the sponsor.

The name, start and stop dates, and route of administration for concomitant medications (prescription and nonprescription) used to treat an AE (excluding events recorded only in the e-diary) from the signing of the ICD to Visit 7 will be recorded on the CRF.

6.5.1. Prohibited During the Study

- Other than determined by protocol assignment/randomization group, antipyretic and other pain medications to **prevent** symptoms that might occur as a result of study vaccination are not permitted. Use of antipyretic and other pain medications to **alleviate** symptoms that have occurred following study vaccination is permitted.

- On the day of planned vaccination, if the participant has received antipyretic medications and/or other pain medications outside protocol assignment, vaccination should be temporarily delayed as specified in Section 5.5.1.

- Receipt of blood products, including immunoglobulin, and/or immunosuppressive therapy (including a ≥14-day course of systemic corticosteroids).

- Nonstudy meningococcal vaccines throughout the study.

- Nonstudy pneumococcal vaccines and nonstudy DTPa-HBV-IPV-Hib or its components through Visit 4.

- Nonstudy vaccines, other than nonstudy pneumococcal vaccines or nonstudy DTPa-HBV-IPV-Hib or its components administered after Visit 4, are not permitted 14 days (for nonlive vaccines or rotavirus vaccine) or 28 days (for live vaccine other than a rotavirus vaccine) before or after any study vaccination.

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

6.5.2. Permitted During the Study

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed at any time. In such situations, if needed, administration of study intervention may be rescheduled to allow it to occur >14 days (for nonlive nonstudy vaccines or rotavirus vaccine) or >28 days (for live nonstudy vaccines other than a rotavirus vaccine) after administration of nonstudy vaccines used to manage the disease outbreak or pandemic.

- Nonstudy pneumococcal vaccines and nonstudy DTPa-HBV-IPV-Hib or its components are allowed any time after Visit 4, including the administration of such vaccine(s) concomitantly with the investigational products administered at Visit 5. Other nonstudy vaccines that are part of recommended immunization schedules and not provided through the study are allowed anytime during the study but should not be administered within 14 days (for nonlive vaccines or rotavirus vaccine) or 28 days (for live vaccines other than a rotavirus vaccine) of investigational product administration.

- Should nonstudy vaccines be administered concomitantly with the investigational products administered at Visit 5, the nonstudy vaccines will be administered in a limb other than the left thigh.

- Antipyretic and other pain medication to **treat** symptoms following investigational product administration is permitted.
- A local anesthetic may be used at the site of the blood draw.
- Topical antibiotics are permitted.
- Topical and inhaled corticosteroids are permitted.

6.5.3. Prior Vaccinations and Treatments

If the participant is known to have ever received a PRP-OMP vaccine, the name of the vaccine and date of administration will be recorded on the CRF. PRP-OMP–containing vaccines that are or have been commercially available include Comvax, Procomvax, and PedvaxHIB. These are also listed in the ISF.

6.5.4. Prohibited Prior Treatments

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

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

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

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

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may be withdrawn from the study at any time at the request of his/her parent(s)/legal guardian. Reasons for discontinuation from the study include the following:

- Parent(s)/legal guardian refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Parent(s)/legal guardian request;
- Protocol violation.

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

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

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

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

A final telephone contact (Section 8.11.7) for the collection of safety information should be completed for all participants who withdraw or have been withdrawn within 6 months after administration of study intervention, unless consent for further contact has been withdrawn, or the participant is lost to follow-up. Participant withdrawal should be explained in the source documents, and should include whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or postvaccination study follow-up.

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

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

The total blood sampling volume for individual participants in this study is approximately 10 mL.

8.1. Efficacy Assessments and/or Immunogenicity Assessment

To facilitate immunogenicity analyses, all participants in the study will have approximately 5 mL of blood collected at Visit 4 (1 month after primary vaccination 2) and Visit 6 (1 month after the booster vaccination) during the study, as described in Section 8.11 and the SoA.

Sera obtained will be used in immunogenicity assays. LOD and LLOQ titers for these assays will be detailed in the SAP.

Sera obtained from participants enrolled in the open-label stages may be used for exploratory analysis and meningococcal assay development as a priority over the analysis as shown in the estimands below, based on availability of serum volume.

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

For assessment of the immune response to Nimenrix and the MenACWY components of MenABCWY, test strains specific for each of the MenACWY groups (A [PMB277], C [PMB3204], W [PMB6270], Y [PMB3385]) will be used in the hSBAs for determination of the immunogenicity endpoints in this study.

8.1.2. MenB Serum Bactericidal Assays

For assessment of the immune response to the MenB component of MenABCWY, Trumenba, and Bexsero, 2 MenB test strains (1 expressing an LP2086 subfamily A protein and 1 expressing an LP2086 subfamily B protein) will be used in the hSBAs for determination of the immunogenicity endpoints in this study, which will be identified prior to the commencement of testing. MenB test strains will be detailed in the SAP.

8.1.3. Biological Samples

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

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

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

8.2. Safety Assessments

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

Primary vaccinations for all participants will be conducted in the morning to allow time for daytime temperature monitoring.

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

- Physical examination.
- Reactogenicity: local reactions and systemic events, including fever.
- Use of antipyretic medication to treat symptoms following investigational product administration.
- AEs and SAEs.

A medical history will be obtained and a physical examination will be performed on all participants at Visit 1 to establish a baseline. Weight, length, general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, neurologic status, musculoskeletal, and lymph nodes will be assessed. Significant medical history and observations from the physical examination will be documented on the CRF.

A brief physical examination of general appearance, ears, throat, heart, and lungs will be performed prior to vaccinations at Visits 3 and 5 for all participants.

The safety parameters include reactogenicity, ie, both local reactions and systemic events that occur in the 7 days (Days 1 through 7) after investigational product administration. These prompted e-diary events are:

- Local reactions at the site of investigational product administration on the left thigh (redness, swelling, and tenderness).
- Systemic events (fever, loss of appetite or decrease appetite, drowsiness [synonym: increased sleep], irritability [synonyms: fussiness, restless sleep, and decreased sleep]).

Local reactions, systemic events, and use of antipyretic medication associated with vaccine administration will be collected using an e-diary. For events that resolve after Day 7, the end date will be collected in the CRF. If a participant does not complete the e-diary for 7 days, end dates of local reactions, systemic events, or antipyretic medication use that was ongoing on the last day the e-diary was completed by the participant will be collected on the CRF.

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

MAEs and NDCMCs will also be assessed throughout the study and documented on the appropriate AE CRF. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

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

The participant's parent(s)/legal guardian will be given a memory aid at Visits 4 and 6. The memory aid will be used to remind parent(s)/legal guardian to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The parent(s)/legal guardian may use the memory aid as needed at Visit 5 and during the telephone contact at Visit 7 to prompt recall of events. These may be used to assist in reporting and discussion of events with study staff, but these memory aids will not be considered source documents and will not be collected at study visits. Only information collected by study staff as part of a study visit or telephone contact will be included in the source documents and entered into the CRF.

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

8.2.1. Electronic Diary

Participants will be required to use an e-diary, installed on a provisioned device or an application on a personal device, and will be asked to monitor and record local reactions, systemic events, and antipyretic medication use for 7 days following vaccination.

The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time.

For local reactions and systemic events that resolve after Day 7, the end date will be collected on the CRF. If the e-diary is not completed for 7 days, the end dates of local reactions, systemic events, or antipyretic medication use that occurred during the 7 days will be collected on the CRF. The investigator or designee must contact the parent(s)/legal guardian in order to obtain stop dates for any prompted e-diary events or other AE data ongoing on the last day that the e-diary was completed. The stop dates are to be documented in the source documents and the information entered in the CRF.

Data reported in the e-diary will be transferred electronically to the e-diary vendor (a trusted third party), where they will be available for review by investigators at all times via an internet-based portal. At intervals agreed upon between the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator on the CRF.

Investigators will be required to review the e-diary data online at frequent intervals as part of the ongoing safety review and evaluation of participant compliance. For sentinel-cohort participants, following primary vaccination 1, online review must be performed daily (see Section 8.2.4.1).

8.2.1.1. Local Reactions

Local reactions (redness, swelling, and tenderness) at the site of investigational product administration will be recorded daily for 7 days (Days 1 through 7) following each vaccination. Only local reactions at the site of investigational product administration with MenABCWY, Trumenba, or Bexsero on the left thigh will be recorded.

8.2.1.1.1. Injection Site Redness and Swelling

Redness and swelling will be measured and recorded in caliper units (range: 1 to 14) for the first 7 days following vaccination (Days 1 through 7), and then categorized using the scale shown in Table 2. The measurements will then be recorded in the e-diary.

A caliper will be given to the participant's parent(s)/legal guardian with instructions for measuring both redness and swelling at the left thigh injection site. Each caliper unit is equivalent to 0.5 cm. The parent(s)/legal guardian will be asked to measure the largest diameters of the local reaction. Where a caliper measurement is between 2 values, the higher value should be reported. At the time of entry into the e-diary, the parent(s)/legal guardian should record the maximum severity of the reaction since the previous entry into the e-diary. In the event the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units), the participant's parent(s)/legal guardian will also measure the maximum diameter of the redness and/or swelling at the left thigh injection site using the measuring tape provided and report this immediately to the investigator. The participant's parent(s)/legal guardian will report the maximum diameter of the redness and/or swelling at the left thigh injection site to the investigator daily until the reaction becomes ≤14 caliper units. These measurements will be recorded in the CRF.

Table 2. 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)

8.2.1.1.2. Injection Site Tenderness

Tenderness at the left thigh injection site will be assessed by the participant's parent(s)/legal guardian as mild, moderate, or severe according to the grading scale in Table 3. The assessment will then be recorded in the e-diary.

Table 3. 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

8.2.1.2. Systemic Events

8.2.1.2.1. Temperature

A digital thermometer will be given to the parent(s)/legal guardian with instructions on how to measure the participant's axillary temperature at home. Axillary temperature will be collected and recorded in the e-diary following each vaccination. Temperature measurements will be taken only when the participant is awake at the following intervals:

- Approximately 4, 8, 12, and 24 hours after vaccination on Day 1 (day of vaccination). The time the measurement is taken is also recorded in the e-diary.
- In the evening daily on Days 2 through 7. The time the measurement is taken is also recorded in the e-diary.
- At any time on Days 1 through 7 when fever is suspected. The time the measurement is taken is also recorded in the e-diary.

In addition to the scheduled temperature measurements on Day 1, the highest daily temperature and the time the measurement was taken on Days 1 through 7 will be recorded in the e-diary. Fever is defined as a temperature of ≥38.0°C. Temperature will be measured and recorded to 1 decimal place and then categorized according to the severity scale in Table 4.

Table 4. Scale for Fever

Temperature 38.0°C to 38.4°C
Temperature 38.5°C to 38.9°C
Temperature 39.0°C to 40°C
Temperature >40.0°C

8.2.1.2.2. Fever Management

- **For Participants Assigned to Receive the Prophylactic Liquid Paracetamol Regimen (PLP) in Groups 1, 3, 5, 8, and 14 with PLP Stratum**

For participants assigned to receive PLP for primary vaccinations, the first dose of PLP will be administered orally within 30 minutes before the administration of MenB vaccines. Two additional doses of PLP will be provided to parent(s)/legal guardian to administer to the participant at 4- to 6-hour intervals on Day 1 following each primary vaccination.

For 2-month-old participants receiving rLP2086-containing vaccines in Groups 3 and 5, if fever persists despite the administration of 3 doses of PLP, additional paracetamol doses should be given for up to 48 hours after vaccination.

- **For Participants Assigned to Receive the Scheduled Liquid Paracetamol Regimen (SLP) in Groups 7, 11, and 13**

The first dose of paracetamol will be administered orally by parent(s)/legal guardian no later than 8 hours after each primary vaccination or earlier if fever or other reactogenicity symptoms arise and require treatment. Parent(s)/legal guardian will continue administering paracetamol for a certain number of doses as described in the protocol-assigned paracetamol dosing instructions. The initial regimen will require administration of 4 doses every 4 to 6 hours with an optional fifth dose if symptoms persist, but this regimen may be adjusted at the discretion of the IRC based on ongoing review of the safety data.

- **For Participants Randomized to Receive the Therapeutic Liquid Paracetamol Regimen (TLP) in Groups 11, 13, and 14**

The first dose of paracetamol will be administered orally by parent(s)/legal guardian only when fever or other reactogenicity symptoms arise and require treatment (if no symptoms are experienced, no paracetamol will be given). Parent(s)/legal guardian will continue administering paracetamol for a certain number of doses as described in the protocol-assigned paracetamol dosing instructions. The initial regimen will require administration of 4 doses every 4 to 6 hours with an optional fifth dose if symptoms persist, but this regimen may be adjusted at the discretion of the IRC based on ongoing review of the safety data.

See the protocol-assigned paracetamol dosages and schedules in Table 5.

Table 5. Protocol-Assigned Paracetamol Dosages and Schedules

Group(s)/Stratum	Protocol-Assigned Paracetamol	Vaccinations	Participant Age at Enrollment	Dose
Group 1	PLP	Primary series vaccinations 1 and 2	6 months	120 mg (5 mL)
Groups 3, 5, 8, and 14/PLP	PLP	Primary series vaccinations 1 and 2	2 months	60 mg (2.5 mL)
Groups 7, and 11-13/SLP	SLP	Primary series vaccinations 1 and 2	2 months	60 mg (2.5 mL)
Groups 11, 13, and 14/TLP	TLP	Primary series vaccinations 1 and 2	2 months	60 mg (2.5 mL)

Abbreviations: PLP = prophylactic liquid paracetamol regimen; SLP = scheduled liquid paracetamol regimen; TLP = therapeutic liquid paracetamol regimen.
Note: Protocol amendment 2 added 12 additional participants to Group 3 that will receive SLP for primary vaccinations. 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.

This study will use the above protocol-assigned paracetamol regimens, but these regimens may be adjusted based on safety data observed during the study, and the updated regimens will be detailed in the paracetamol dosing instructions.

Refer to the participant paracetamol dosing instructions to confirm the current protocol-assigned paracetamol dosing schedule to be used per randomization group.

For all participants assigned to receive protocol-assigned paracetamol, if the participant's temperature is ≥38°C after the last dose of protocol-assigned paracetamol and the participant is otherwise well, the parent(s)/legal guardian may continue administering paracetamol-containing antipyretics every 4 to 6 hours and should contact the study site. Parent(s)/legal guardian must always leave at least 4 hours between paracetamol doses, but not exceeding the maximum daily dosing of 4 doses per 24-hour period per the product instructions.

The timing of all doses of protocol-assigned paracetamol, and the timing of all doses of additional antipyretic medication on Day 1, following each vaccination will be recorded in the e-dairy as described in Section 8.2.1.3.

- **For Participants Randomized Not to Receive Protocol-Assigned Paracetamol in Groups 2, 4, and 10**

The parent(s)/legal guardian will be advised to administer a single dose of paracetamol if a participant's temperature is ≥38°C (conditional on no paracetamol having been received in the preceding 4 hours).

If the participant's temperature remains ≥38°C, further doses of paracetamol may be administered every 4 to 6 hours until afebrile, but not exceeding the maximum daily dosing of 4 doses per 24-hour period per product instructions.

The timing of all doses of antipyretic medication on Day 1 following each vaccination will be recorded in the e-diary as described in Section 8.2.1.3.

- **Additional Measures for Fever Management**

Use of additional therapies (eg, NSAIDs) to treat fever will be at the discretion of the parent(s)/legal guardian based on counseling by the participant's physician.

For persistent fevers or for participants otherwise unwell in the opinion of the parent(s)/legal guardian, seeking of medical attention should not be delayed.

8.2.1.2.3. Other Systemic Events

The e-diary will be used to record the presence of other systemic events, including loss of or decreased appetite, drowsiness (increased sleep), and irritability (fussiness) after each vaccination, using the grading scales in Table 6.

Table 6. 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

8.2.1.3. Use of Antipyretic/Pain Medications

The use of antipyretic medication taken to treat fever or pain after vaccination will be recorded in the e-diary daily during the active safety observation periods (Day 1 to Day 7) after each vaccination.

Other than determined by protocol assignment/randomization group, prophylactic use of antipyretics and other pain medications to prevent fever or pain that might occur as a result of study vaccination is not permitted (Section 6.5.1).

On the day prior to vaccination, if the participant has received antipyretics and other pain medications outside the protocol-assigned paracetamol use, vaccination should be temporarily delayed as specified in Section 5.5.1.

Use of antipyretic and other pain medications following investigational product administration to treat symptoms is permitted (Section 6.5.2).

Please refer to the ISF for further details.

8.2.2. Open-Label Safety Assessment

8.2.2.1. Sentinel-Cohort Safety Assessment

After primary vaccination 1, 7-day e-diary and AE data will be collected for each sentinel cohort. These safety data from sentinel Cohorts 1 to 4, as well as the safety data from prior cohort(s) (if applicable), will be summarized and reviewed by the sponsor's IRC. Primary vaccination 2 in the corresponding cohort and enrollment into the subsequent cohort will not be permitted until IRC review of the safety data is complete and these data are found acceptable. Stopping rules will apply to participants in sentinel Cohorts 1 to 4 for the 7-day safety period following primary vaccination 1 only (Section 4.1.1).

The study will progress to the expanded-enrollment stage following IRC review of post–primary vaccination 1 safety data from Cohort 4.

Enrollment into the sentinel-control cohort may occur at any time during the sentinel-cohort stage without IRC review of data from Cohorts 1 to 4. Stopping rules will not apply to participants in this cohort (Section 8.2.4.1).

In order to provide ongoing oversight of participant safety, 7 days after all sentinel-cohort stage participants have completed primary vaccination 2, reactogenicity and AE data from all participants available at the time will be summarized for review by the IRC. The IRC does maintain discretion to adjust details of the paracetamol regimens and number of participants enrolled into each regimen based on review of emerging safety data.

The EDMC will not participate in the decision-making processes for study progression, but will be informed of the IRC's determination. The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. Recommendations made by the EDMC will be forwarded to Pfizer for final decision making.

8.2.2.2. Expanded-Cohort Safety Assessment

In order to provide ongoing oversight of participant safety, 7 days after the first 25 participants in Group 11 have received MenABCWY with TLP for primary vaccination 1, e-diary and AE data will be summarized, as well as e-diary and AE data from prior cohort(s) in the sentinel-cohort stage (if applicable), for review by the sponsor's IRC. Continuation with the enrollment of participants receiving MenABCWY with TLP into Group 11 and primary vaccination 2 for the participants already enrolled in the group will not be permitted until IRC review of these safety data are complete and found to be acceptable. At any point during the study conduct of Group 11, the IRC may determine that the remaining participants will be enrolled to receive MenABCWY with SLP, based on the safety data gathered. TLP or SLP administration in this group will be associated only with primary series vaccinations. In addition, 7 days after all expanded-enrollment stage participants have completed primary vaccination 2, reactogenicity and AE data from all participants available at the time will be summarized for review by the IRC (Section 4.1.2).

8.2.3. Blinded Phase Safety Assessment

During the blinded phase, an independent statistical center will provide unblinded safety reports to the EDMC for review. The exact number of participants to be enrolled into each group and each stratum for protocol-assigned paracetamol use, the enrollment speed and the exact schedules of protocol-assigned paracetamol regimens will be at the discretion of IRC and may be subject to change as safety data become available.

Planned safety analysis based on the numbers of participants enrolled per protocol-assigned paracetamol regimen following the double-blind and single-blind design will be detailed in the SAP.

8.2.4. Study Pause

This study will be paused if stopping rule criteria are met.

8.2.4.1. Stopping Rules

E-diary and AE data will be monitored daily by the investigator (or medically qualified designee) and the sponsor during the first 7 days (including nonbusiness days) after primary vaccination 1 in order to promptly identify and flag any case that potentially contributes to a stopping rule.

In the event of a stopping rule being met, the following criteria will apply:

- For stopping rules that apply to participants in sentinel Cohorts 1 to 4 only:
    - Individual randomization groups within the sentinel cohort affected by the stopping rule will pause enrollment and vaccination.
    - No further study vaccinations will be administered to any participant in the paused individual randomization groups within the sentinel cohort until the investigator is directed to do so by the sponsor.

  - For all sentinel participants affected by a pause, no vaccination visits will be conducted until the investigator is directed to proceed. However, all other routine study-conduct activities, such as ongoing data entry, reporting of AEs, participant e-diary completion, and participant follow-up, will continue during the pause.

- For stopping rules that apply to all participants in the open-label stages of the study:
  - Enrollment and vaccination in the whole study will be paused.
  - No further study vaccinations will be administered to any participant in the study until directed to do so by the sponsor.
  - For all participants, no vaccination visits will be conducted until the investigator is directed to proceed. However, all other routine study-conduct activities, such as ongoing data entry, reporting of AEs, participant e-diary completion, and participant follow-up, will continue during the pause.

- Cases that meet stopping rule criteria will be promptly referred to the IRC for rapid evaluation. The IRC will review the case safety data and determine whether the study may progress. The IRC opinion on study progression will be forwarded to the EDMC.

The following stopping rules are applicable for this study.

1. For participants in sentinel Cohorts 1 to 4 within the 7-day safety period following primary vaccination 1:
   - For individual randomization groups within the sentinel cohort, 2 or more participants reporting MAEs that are similar in nature, **other than fever**, deemed related to investigational product or that cannot be attributed to any other cause.
   - For individual randomization groups within the sentinel cohort, 2 or more participants reporting MAEs of fever that lead to invasive investigations performed at a medical facility.
   - For individual randomization groups within the sentinel cohort, 1 or more participants reporting febrile convulsions that are deemed related or cannot be attributed to any other cause by the investigator.
   - For individual randomization groups within the sentinel cohort, 1 or more participants reporting SAEs of the same type that are deemed related or cannot be attributed to any other cause by the investigator.
2. For all participants at any time during the open-label stages of the study:
   - For the duration of the study, if a death occurs that cannot be attributed to any other cause, or if an investigator determines that the death is related to vaccination.

- For the duration of the study, if any AE occurs that, as judged by the sponsor, warrants a study pause to allow IRC evaluation of the event.

For each participant, any given event may not contribute more than once to a stopping rule.

The investigator should immediately notify the sponsor if any participant under the investigator's care appears to fulfill any of the criteria listed above. Reporting details are described in the ISF.

8.2.4.2. Resuming Enrollment and Vaccination After a Study Pause

Enrollment and vaccination may proceed at the discretion of the IRC before the IRC receives a recommendation from the EDMC. The visit window for primary vaccination 2 may be extended for individual participants by up to 14 days from the receipt of the positive IRC recommendation, at the discretion of the sponsor.

8.3. Adverse Events and Serious Adverse Events

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 6. Device deficiencies are covered in Section 8.3.9.

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

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

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

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

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

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.
See Table 7.

Table 7. Summary of AE Data 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							

Note: The bars represents safety data collection time periods.

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant's parent(s)/legal guardian.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding via Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by needlestick injury or skin contact.

- A male family member or healthcare provider who has been exposed to the study intervention by needlestick injury or skin contact then exposes his female partner prior to or around the time of conception.

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

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

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.3.1 through Section 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

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

The definition of a medical device deficiency can be found in Appendix 6.

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

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

The method of documenting medical device deficiencies is provided in Appendix 6.

8.3.9.2. Follow-up of Medical Device Deficiencies

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

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

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

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

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

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

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

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

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

8.3.10. Medication Errors

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

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

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- Other examples include, but are not limited to:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of investigational vaccine greater than 1 dose within a 24-hour time period will be considered an overdose. Any dose of paracetamol greater than the maximum daily dosing of 4 doses within a 24-hour time period per the product instructions will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

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

8.11. Study Procedures

8.11.1. Visit 1 (Day 1): Primary Vaccination 1

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

Vaccination 1 for all participants should be conducted in the morning to allow time for daytime temperature monitoring.

- Obtain written informed consent from the participant's parent(s)/legal guardian before performing study-specific procedures. The date of informed consent will be recorded on the CRF.
- Record the participant's demographic information (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.
- Record previous PRP-OMP vaccinations as describe in Section 6.5.3.
- Perform a physical examination including body length and weight, evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, neurological, musculoskeletal, and lymph nodes, including worsening of medical history conditions. Results must be recorded on source documents and the CRF. Findings from a physical examination conducted as part of standard routine care and before informed consent may be used for purposes of the study only if the

examination was performed no more than 2 days before vaccination. A brief examination must be performed on the day of vaccination to document that no change in health has occurred in the interim.

- On the day of vaccination, prior to administration of study intervention, measure and record the participant's axillary temperature.
- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- If a participant is eligible for the study, assign a randomization number and investigational product container numbers via the IRT, or an equivalent system.
- For participants assigned to receive PLP in Groups 1, 3, 5, and 8 or in the PLP stratum of Group 14:
  - Administer a dose of PLP orally within 30 minutes before MenB vaccination. The dosage to be administered is detailed in Table 5.
  - Record the time of PLP administration in the participant's e-diary.
- For **all** participants assigned to receive protocol-assigned paracetamol in Groups 1, 3, 5, 7, 8, 11, 13, and 14:
  - Issue a bottle of paracetamol to parent(s)/legal guardian for paracetamol to be administered orally to the participant after vaccination as detailed in the participant paracetamol dosing instructions (Section 8.2.1.2.2). Inform parent(s)/legal guardian to return the bottle at the next study site visit.
- During the open-label sentinel-cohort and open-label expanded-enrollment stages:
  - Administer a single intramuscular injection of **MenABCWY (0.5 mL)** or **bivalent rLP2086 (0.25 mL for the 60-µg dose or 0.5 mL for the 120-µg dose)** or **Bexsero (0.5 mL)** into the **left** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).
  - Administer a single 0.5-mL intramuscular injection of **Nimenrix** (if applicable) into the **right** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).
  - Administer **Prevenar 13** and **Vaxelis** intramuscularly into the **right** thigh. The time of investigational product administration will be recorded on the CRF.

- During the blinded expanded-enrollment stage, the unblinded administrator will administer (Section 6.3.3.1):

  - A single 0.5-mL intramuscular injection of **MenABCWY** or **Bexsero** into the **left** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

  - A single 0.5-mL intramuscular injection of **placebo or Nimenrix** into the **right** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

  - Administer **Prevenar 13** and **Vaxelis** intramuscularly into the **right** thigh. The time of investigational product administration will be recorded on the CRF.

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

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

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

- Assist the participant's parent(s)/legal guardian in downloading the e-diary app onto the participant's own device or issue a provisioned device if required (Section 8.2.1).

- Provide instruction regarding e-diary completion. Ask the parent(s)/legal guardian to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination. Instructions on daily transfer of data and charging the battery should also be provided.

- Issue a caliper, a measuring tape/ruler, and a digital thermometer and provide verbal and written instructions on their use.

- Measuring tape/ruler data must be collected by the parent(s)/legal guardian. All data must be recorded in the e-diary by the parent(s)/legal guardian.

- Ask the parent(s)/legal guardian to use the caliper to measure the maximum diameter of redness and swelling at the **left** thigh injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 8.2.1.1.1.

- Ask the parent(s)/legal guardian to contact the investigator immediately if the participant experiences severe redness or swelling (>14 caliper units) at the **left** thigh injection site or an axillary temperature ≥39°C, within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.12).

    - If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units, Section 8.2.1.1), the parent(s)/legal guardian should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the **left** thigh injection site, and report this immediately to the investigator.

    - Ask the parent(s)/legal guardian to report the maximum diameter of the redness and/or swelling at the **left** thigh injection site to the investigator daily until the reaction becomes ≤14 caliper units.

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

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

- For sentinel-cohort participants (Groups 1-10):

    - Ask the participant's parent(s)/legal guardian to contact the investigator immediately if the child experiences any MAE or SAE during the active safety period (Day 1 to Day 7) (see Section 8.2.4.1).

    - The investigator must contact the Pfizer study physician immediately in the event of a participant's experiencing an MAE or SAE during the active safety period (Day 1 to Day 7). See Section 8.2.4.1 for further detail on safety reporting requirements for sentinel-cohort participants. All AEs should be promptly captured in the CRF and/or SAE reports as applicable (see Section 8.3 for reporting requirements).

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

- Remind the parent(s)/legal guardian to bring the e-diary to the next study visit.

- Complete the source documents.

- Complete the CRF and update the investigational product accountability records.

Between visits, review the e-diary data online at frequent intervals. For sentinel-cohort participants, following primary vaccination 1, online review of e-diary data must be performed daily (see Section 8.2.4.1). Contact the parent(s)/legal guardian to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered into the CRF at the next study visit of the participant.

8.11.2. Visit 2 (28 to 42 Days After Visit 1): Safety Telephone Contact

- Contact the parent(s)/legal guardian by telephone.
- Ensure that the participant continues to be eligible for the study and does not meet any withdrawal criteria (Section 7.2).
- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, and medication use. Please refer to the ISF for additional details.
    - Record AEs as described in Section 8.3 and the SoA.
    - Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Schedule an appointment for the next study visit, and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.11.3. Visit 3 (63 to 77 Days After Visit 1): Primary Vaccination 2

The visit window for primary vaccination 2 may be extended for individual participants by up to 14 days from the receipt of the positive IRC recommendation, at the discretion of the sponsor.

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

Vaccination 2 for all participants should be conducted in the morning to allow time for daytime temperature monitoring.

- Ensure that the participant continues to be eligible for the study and does not meet any withdrawal criteria (Section 7.2) and any of the temporary delay of vaccination criteria as described in Section 5.5.1.
- Perform a brief physical examination comprising general appearance, ears, throat, heart, and lungs.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
    - Record AEs as described in Section 8.3 and the SoA.
    - Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Collect the provided bottle of paracetamol from parent(s)/legal guardian of participants assigned to receive paracetamol as per protocol for primary vaccination 1.
- On the day of vaccination, prior to administration of study intervention, measure and record the participant's axillary temperature.
- For participants assigned to receive PLP in Groups 1, 3, 5, and 8 or in the PLP stratum of Group 14:
    - Administer a dose of paracetamol orally within 30 minutes before MenB vaccination. The dosage to be administered is detailed in Table 5.

- Record the time of PLP administration in the participant's e-diary.

- For **all** participants assigned to receive protocol-assigned paracetamol in Groups 1, 3, 5, 7, 8, 11, 13, and 14:

  - Issue a bottle of paracetamol to parent(s)/legal guardian for additional doses of paracetamol to be administered orally to the participant after vaccination as detailed in the participant paracetamol dosing instructions (Section 8.2.1.2.2). Inform parent(s)/legal guardian to return the bottle at the next study site visit.

- During the open-label sentinel-cohort and open-label expanded-enrollment stages:

  - Administer a single intramuscular injection of **MenABCWY (0.5 mL)** or **bivalent rLP2086 (0.25 mL for the 60-µg dose or 0.5 mL for the 120-µg dose)** or **Bexsero (0.5 mL)** into the **left** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

  - Administer a single 0.5-mL intramuscular injection of **Nimenrix** (if applicable) into the **right** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

  - For Groups 3 through 12, administer **Prevenar 13** and **Vaxelis** intramuscularly into the **right** thigh. The time of investigational product administration will be recorded on the CRF.

- During the blinded expanded-enrollment stage, the unblinded administrator will administer (Section 6.3.3.1):

  - A single 0.5-mL intramuscular injection of **MenABCWY** or **Bexsero** into the **left** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

  - A single 0.5-mL intramuscular injection of **placebo or Nimenrix** into the **right** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

  - Administer **Prevenar 13** and **Vaxelis** intramuscularly into the **right** thigh. The time of investigational product administration will be recorded on the CRF.

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

- Ensure the participant's parent(s)/legal guardian have access to the e-diary app or a provisioned device (see Section 8.2.1) and are comfortable with use of the e-diary.

- Ask the parent(s)/legal guardian to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination. Instructions on daily transfer of data and charging the battery should also be provided.

- Issue a caliper, a measuring tape/ruler, and a digital thermometer and provide verbal and written instructions on their use.

- Measuring tape/ruler data must be collected by the parent(s)/legal guardian. All data must be recorded in the e-diary by the parent(s)/legal guardian.

- Ask the parent(s)/legal guardian to use the caliper to measure the maximum diameter of redness and swelling at the **left** thigh injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 8.2.1.1.1.

- Ask the parent(s)/legal guardian to contact the investigator immediately if the participant experiences severe redness or swelling (>14 caliper units) at the **left** thigh injection site, or an axillary temperature ≥39°C, within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.12).

    - If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units), the parent(s)/legal guardian should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the **left** thigh injection site, and report this immediately to the investigator.

    - Ask the parent(s)/legal guardian to report the maximum diameter of the redness and/or swelling at the left thigh injection site to the investigator daily until the reaction becomes ≤14 caliper units.

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

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

- Remind the parent(s)/legal guardian to bring the e-diary to the next study visit.

- Complete the source documents.

- Complete the CRF and update the investigational product accountability records.

Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered into the CRF at the next study visit of the participant.

8.11.4. Visit 4 (28 to 42 Days After Visit 3): Follow-up After Primary Vaccination 2

- Ensure that the participant continues to be eligible for the study and does not meet any withdrawal criteria (Section 7.2).
- Collect a blood sample (approximately 5 mL) from the participant. Local/topical anesthetic may be used to numb the skin prior to the blood draw.
- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Collect the provisioned e-diary device, if previously provided to the participant's parent(s)/legal guardian.
- Collect the provided bottle of paracetamol from parent(s)/legal guardian of participants assigned to receive paracetamol as per protocol for primary vaccination 2.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, and medication use. Please refer to the ISF for additional details.
    - Record AEs as described in Section 8.3 and the SoA.
    - Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Provide the parent(s)/legal guardian with a memory aid. Instruct the parent(s)/legal guardian to use the memory aid between Visit 4 and Visit 5 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF for additional details.
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.

- Complete the CRFs.

8.11.5. Visit 5 (365 to 386 Days of Age): Booster Vaccination

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

Booster vaccination for all participants can be conducted anytime during the day.

- Ensure that the participant continues to be eligible for the study and does not meet any withdrawal criteria (Section 7.2) and any of the temporary delay of vaccination criteria as described in Section 5.5.1.
- Perform a brief physical examination comprising general appearance, ears, throat, heart, and lungs.
- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, and medication use. Please refer to the ISF for additional details.
  - Record AEs as described in Section 8.3 and the SoA.
  - Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- On the day of vaccination, prior to administration of study intervention, measure and record the participant's axillary temperature.
- During the open-label sentinel-cohort and open-label expanded-enrollment stages:
  - Administer a single intramuscular injection of **MenABCWY (0.5 mL)** or **bivalent rLP2086 (0.25 mL for the 60-µg dose or 0.5 mL for the 120-µg dose)** or **Bexsero (0.5 mL)** into the **left** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).
  - Administer a single 0.5-mL intramuscular injection of **Nimenrix** (if applicable) into the **right** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

- During the blinded expanded-enrollment stage, the unblinded administrator will administer (Section 6.3.3.1):

  - A single 0.5-mL intramuscular injection of **MenABCWY** or **Bexsero** into the **left** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

  - A single 0.5-mL intramuscular injection of **Placebo or Nimenrix** into the **right** thigh. The time of investigational product administration will be recorded on the CRF (see Table 1).

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

- Ensure the participant's parent(s)/legal guardian have access to the e-diary app or a provisioned device (see Section 8.2.1) and are comfortable with use of the e-diary.

- Ask the parent(s)/legal guardian or participant to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination. Instructions on daily transfer of data and charging the battery should also be provided.

- Issue a caliper, a measuring tape/ruler, and a digital thermometer and provide verbal and written instructions on their use.

- Measuring tape/ruler data must be collected by the parent(s)/legal guardian. All data must be recorded in the e-diary by the parent(s)/legal guardian.

- Ask the parent(s)/legal guardian to use the caliper to measure the maximum diameter of redness and swelling at the **left** thigh injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 8.2.1.1.1.

- Ask the parent(s)/legal guardian to contact the investigator immediately if the participant experiences severe redness or swelling (>14 caliper units) at the **left** thigh injection site, or an axillary temperature ≥39°C, within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.12).

  - If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units), the parent(s)/legal guardian should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the **left** thigh injection site, and report this immediately to the investigator.

  - Ask the parent(s)/legal guardian to report the maximum diameter of the redness and/or swelling at the **left** thigh injection site to the investigator daily until the reaction becomes ≤14 caliper units.

- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Remind the parent(s)/legal guardian to bring the e-diary to the next study visit.
- Complete the source documents.
- Complete the CRF and update the investigational product accountability records.

Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered into the CRF at the next study visit of the participant.

8.11.6. Visit 6 (28 to 42 Days After Visit 5): Follow-up After Booster Vaccination

- Ensure that the participant continues to be eligible for the study and does not meet any withdrawal criteria (Section 7.2).
- Collect a blood sample (approximately 5 mL) from the participant. Local/topical anesthetic may be used to numb the skin prior to the blood draw.
- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Collect the provisioned e-diary device, if previously provided to the participant's parent(s)/legal guardian.
- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the ISF for additional details.
  - Record AEs as described in Section 8.3 and the SoA.
  - Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.

- Provide the parent(s)/legal guardian with a memory aid. Instruct the parent(s)/legal guardian to use the memory aid between Visit 6 and Visit 7 (final telephone contact) to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF for additional details.

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

- Schedule an appointment for the final telephone contact and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.

- Complete the CRFs.

8.11.7. Visit 7 (168 to 196 Days After Last Study Vaccination): Final Telephone Contact

This telephone contact should occur approximately 6 months after the last study vaccination; this contact should be attempted for all participants who have received at least 1 study vaccination, unless they have withdrawn consent or are lost to follow-up.

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

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

  - Inquire about SAEs, NDCMCs, or AEs that resulted in evaluation at a medical facility since the last visit. Please refer to the ISF for additional details.

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

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

- Record concomitant medications used to treat AEs that were ongoing since the previous visit and record their end dates or confirming that they are still continuing as described in Section 6.5.

- Complete the source documents.

- Complete the CRFs.

8.12. Unscheduled Visits

If the participant experiences a severe redness or swelling at the **left** thigh injection site (>14 caliper units) or a temperature ≥39.0°C in the 7 days after vaccination, a study site visit should be arranged as soon as possible to assess the extent of the event. The parent(s)/legal guardian contact will be documented in the CRF.

If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units, Section 8.2.1.1.1), ensure the parent(s)/legal guardian has also measured the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided. Ask the parent(s)/legal guardian to report the maximum diameter of the redness and/or swelling at the injection site daily until the reaction becomes ≤14 caliper units. Record these measurements in the CRF.

At an unscheduled visit, the participant's axillary temperature should be measured and the symptom that prompted the visit should be assessed by a medically qualified member of the study staff. Findings will be recorded on the CRF. If the participant experiences any unsolicited AEs, these should be recorded on the AE CRF.

If the unscheduled visit does not take place following participant report of fever ≥39.0°C or severe redness/swelling, the reason must be documented in the CRF (for example, reaction no longer present or e-diary entry error).

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

9. STATISTICAL CONSIDERATIONS

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

In the following statistical sections when groups are written as "Group x and Group y," this indicates that both groups will appear, separately, in the same summary. When groups are written as "group combination x+y," this indicates that the groups will appear combined in a single row or column in the indicated summary. Table 8 presents the individual group numbers along with their descriptions.

Table 8. Vaccine Groups and Descriptions

Group	Description	Sample Size
Open-Label Sentinel-Cohort Stage		
6 Months of age		
1	MenABCWY + PLP	25
2	MenABCWY	25
2 Months of age		
3	60 µg bivalent rLP2086 + Nimenrix + PLP	37
4	60 µg bivalent rLP2086 + Nimenrix	25
5	120 µg bivalent rLP2086 + Nimenrix + PLP	50
7	MenABCWY + SLP	50-100
8	Bexsero + Nimenrix + PLP	55
10	Bexsero + Nimenrix	55
Open-Label Expanded-Enrollment Stage		
2 Months of age		
11	MenABCWY (with TLP or SLP)	50-100
Blinded Expanded-Enrollment Stage		
2 Months of age		
Double-blind only[a]		
13	MenABCWY + placebo (with TLP)	Up to 400
14	Bexsero + Nimenrix (with TLP)	Up to 400
Double-blind and single-blind[a]		
Double-blind		
13	MenABCWY + placebo (with TLP)	Up to 200
14	Bexsero + Nimenrix (with TLP)	Up to 200
Single-blind		
13	MenABCWY + placebo (with SLP)	Up to 200
14	Bexsero + Nimenrix (with PLP)	Up to 200

Abbreviation: PLP = prophylactic liquid paracetamol; SLP = scheduled liquid paracetamol regimen; TLP = therapeutic liquid paracetamol regimen.

a. Based on the safety data from Groups 7 and 11, the blinded expanded-enrollment stage of the study will either be conducted as a completely double-blind stage where both treatment groups use TLP regardless of their group assignment or it will be conducted as partially double-blind with some proportion of the participants receiving TLP regardless of their group assignment and partially single-blind with the remaining participants receiving either SLP or PLP depending on their group assignment.

9.1. Estimands and Statistical Hypotheses

There are no hypotheses for this study.

9.1.1. Estimands

The estimand(s) corresponding to each primary, secondary, and exploratory objective are described in the table in Section 3. These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed and are estimating the maximum potential difference between the groups, since the impact of noncompliance is likely to diminish the observed difference between the groups. The missing serology results will not be imputed.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules.

9.2. Sample Size Determination

9.2.1. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

The sample size for this component of the study is not based on any hypothesis-testing criteria. The study aims to have a sufficient number of participants in order to describe the safety and the immunogenicity. With 150 enrolled participants in Groups 7+11 combined, the ratio of the lower bound of the one-sample 95% CI for the GMT to the GMT is approximately 0.76 and 0.66, respectively, for an assumed maximum SD of 1.3 for MenB test strains and 2.0 for MenA, MenC, MenW, and MenY test strains, assuming that 70% of the participants will have test results for all the strains and a 15% exclusion rate from the (post–primary vaccination 2) evaluable population. With a similar assumption and 110 enrolled participants in Groups 8+10 combined, the ratio of the lower bound of the one-sample 95% CI for the GMT to the GMT is approximately 0.73 and 0.62, respectively.

Table 9 shows the expected half-width of the 95% CI for the different scenarios of the percentage of participants achieving an hSBA titer ≥ LLOQ for each test strain.

Table 9. Expected Half-Width of One-Sample 95% CIs for Different Scenarios of Percentage of Participants Achieving an hSBA Titer ≥ LLOQ for Each Test Strain

Percentage of Participants	Number of Enrolled Participants per Group	Expected Half-Width of 95% CI (%)
60	110	12.3
70	110	11.6
80	110	9.9
90	110	7.7
60	150	10.5
70	150	9.9
80	150	8.7
90	150	6.7

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation.
Note: 70% of participants are expected to have valid test results for all strains. Exclusion rate from the (post–primary vaccination 2) evaluable population is assumed to be 15%.

The probability of observing at least 1 occurrence of any AE for true event percentages between 0.1% and 5.0%, when MenABCWY is administered to 25, 50, 110, or 150 participants, is displayed in Table 10.

Table 10. Probability of Observing at Least 1 Event by Assumed True Event Rates

Assumed True Event Percentage	Probability (N=25)	Probability (N=50)	Probability (N=110)	Probability (N=150)
0.1%	0.02	0.05	0.10	0.14
0.5%	0.12	0.22	0.42	0.53
1.0%	0.22	0.39	0.67	0.78
2.0%	0.40	0.64	0.89	0.95
5.0%	0.72	0.92	>0.99	>0.99

9.2.2. Blinded Expanded-Enrollment Stage

The sample size for this component of the study is not based on any hypothesis-testing criteria. The study aims to have a sufficient number of participants in this component in order to describe the safety and immunogenicity. At the discretion of the IRC, 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). As the number of participants contributing to each of these regimens will influence what are the appropriate safety analyses, the final details of these analyses will be specified in the SAP. With 400 enrolled participants in each of Group 13 and Group 14 the ratio of the lower bound of the one-sample 95% CI for the GMT to the GMT is approximately 0.85 and 0.78, respectively, for an assumed maximum SD of 1.3 for MenB test strains and 2.0 for MenA, MenC, MenW, and MenY test strains, assuming that 70% of the participants will have test results for all the strains and a 15% exclusion rate from the (post–primary vaccination 2) evaluable population. With similar assumptions and 200 enrolled participants each in Groups 13 and 14, the ratio of the lower bound of the one-sample 95% CI for the GMT to the GMT is approximately 0.79 and 0.70, respectively.

Table 11 shows the expected half-width of the 95% CI for the different scenarios of the percentage of participants achieving an hSBA titer ≥ LLOQ for each test strain.

Table 11. Expected Half-Width of One-Sample 95% CIs for Different Scenarios of Percentage of Participants Achieving an hSBA Titer ≥ LLOQ for Each Test Strain

Percentage of Participants	Number of Enrolled Participants per Group	Expected Half-Width of 95% CI (%)
60	200	9.1
70	200	8.5
80	200	7.5
90	200	5.8
60	400	6.4
70	400	6.0
80	400	5.2
90	400	4.0

Abbreviation: LLOQ = lower limit of quantitation.
Note: 70% of participants are expected to have valid test results for all strains. Exclusion rate from the (post–primary vaccination 2) evaluable population is assumed to be 15%.

The probability of observing at least 1 occurrence of any AE for true event percentages between 0.1% and 5.0%, when MenABCWY is administered to 200 or 400 participants, is displayed in Table 12.

Table 12. Probability of Observing at Least 1 Event by Assumed True Event Rates

Assumed True Event Percentage	Probability (N=200)	Probability (N=400)
0.1%	0.18	0.33
0.5%	0.56	0.87
1.0%	0.87	0.98
2.0%	0.98	>0.99
5.0%	>0.99	>0.99

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants who are assigned a randomization number in the IRT system.
Evaluable	Defined according to post–primary vaccination 2 evaluable and post–booster vaccination evaluable criteria.

Population	Description
Modified intent-to-treat	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	All randomized participants who were eligible through Visit 4, received the investigational products at Visits 1 and 3 as randomized, had blood drawn for assay testing within the required time frame at Visit 4 (1 month after primary vaccination 2 [window 28-42 days]), had at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result at Visit 4, had received no prohibited vaccines or treatment through Visit 4, and had no important protocol deviations through Visit 4. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine.
Post–booster vaccination evaluable	All randomized participants who were eligible through Visit 6, received the investigational products following the vaccination series at Visits 1, 3, and 5 as randomized, had blood drawn for assay testing within the required time frame at Visit 6 (1 month after the booster vaccination [window 28-42 days]), had at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result at Visit 6, had received no prohibited vaccines or treatment through Visit 6, and had no important protocol deviations through Visit 6. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg,

Defined Population for Analysis	Description
	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.
Post–primary vaccination 2 modified intent-to-treat	All participants who received at least 1 primary series study vaccination and have at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result available at Visit 4.
Post–booster vaccination modified intent-to-treat	All participants who received the booster study vaccination and have at least 1 valid and determinate MenA, MenC, MenW, MenY, or MenB assay result available at Visit 6.

9.4. Statistical Analyses

9.4.1. Immunogenicity Analyses

9.4.1.1. Open-Label Sentinel-Cohort and Open-Label Expanded-Enrollment Stages

Endpoint	Statistical Analysis Methods
Primary	For each of the 4 MenA, MenC, MenW, and MenY test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combinations 7+11 and 8+10 at 1 month after primary vaccination 2 will be calculated. For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combinations 7+11 and 8+10 at 1 month after primary vaccination 2 will be calculated. For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combination 3+4 and Group 5 at 1 month after primary vaccination 2 will be calculated. The analysis at 1 month after primary vaccination 2 for the MenA, MenC, MenW, and MenY and the MenB test strains is based on the post–primary vaccination 2 evaluable population. For each of the 4 MenA, MenC, MenW, and MenY test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combinations 7+11 and 8+10 at 1 month after the booster vaccination will be calculated.

Endpoint	Statistical Analysis Methods
	For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combinations 7+11 and 8+10 at 1 month after the booster vaccination will be calculated. For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combination 3+4 and Group 5 at 1 month after the booster vaccination will be calculated. The analysis at 1 month after the booster vaccination for the MenA, MenC, MenW, and MenY and the MenB test strains is based on the post–booster vaccination evaluable population. Exact 2-sided 95% CIs for the percentages will be provided using the Clopper-Pearson method. Supportive analyses will be performed based on the post–primary vaccination 2 mITT population for post–primary vaccination 2 results, and the post–booster vaccination mITT population for postbooster results. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary	**The following analyses for the MenB test strains are based on the post–primary vaccination 2 evaluable population**: For each of the MenB test strains, the hSBA GMTs for group combination 3+4 and Group 5 at 1 month after primary vaccination 2 will be calculated. **The following analyses for the MenB test strains are based on the post–booster vaccination evaluable population:** For each of the MenB test strains, the hSBA GMTs for group combination 3+4 and Group 5 at 1 month after the booster vaccination will be calculated.

Endpoint	Statistical Analysis Methods
Exploratory	**The following analyses for the MenA, MenC, MenW, and MenY and the MenB test strains are based on the post–primary vaccination 2 evaluable population:** For each of the 4 MenA, MenC, MenW, and MenY test strains, the hSBA GMTs for group combinations 7+11 and 8+10 at 1 month after primary vaccination 2 will be calculated. For each of the MenB test strains, the hSBA GMTs for group combinations 7+11 and 8+10 at 1 month after primary vaccination 2 will be calculated. **The following analyses for the MenA, MenC, MenW, and MenY and the MenB test strains are based on the post–booster vaccination evaluable population:** For each of the 4 MenA, MenC, MenW, and MenY test strains, the percentages of participants achieving hSBA titers of ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for group combinations 7+11 and 8+10 at 1 month after the booster vaccination will be calculated. For each of the 4 MenA, MenC, MenW, and MenY test strains, the hSBA GMTs for group combinations 7+11 and 8+10 at 1 month after the booster vaccination will be calculated. For each of the MenB test strains, the hSBA GMTs for group combinations 7+11 and 8+10 at 1 month after the booster vaccination will be calculated. **The following analyses for the MenA, MenC, MenW, and MenY and the MenB test strains by protocol-assigned paracetamol status are based on the post–primary vaccination 2 evaluable population**: For each of the 4 MenA, MenC, MenW, and MenY test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combinations 7+11 (with SLP), or Groups 8 (with PLP), 11 (with TLP), and 10 (without PLP) at 1 month after primary vaccination 2 will be calculated. For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for group combinations 7+11 (with SLP), 8 (with PLP), 11 (with TLP), and 10 (without PLP) at 1 month after primary vaccination 2 will be calculated.

Endpoint	Statistical Analysis Methods
	Empirical RCDCs will be provided for hSBA titers. Percentages will be presented with 2-sided 95% CIs using the Clopper-Pearson method. Geometric means and their 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, then exponentiating the results. Titers below LLOQ will be set to 0.5 × LLOQ for analysis. Supportive analyses will be done using the applicable mITT population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed. **The following analyses for the MenA, MenC, MenW, and MenY and the MenB test strains are based on the post–primary vaccination 2 evaluable population**: For each of the 4 MenA, MenC, MenW, and MenY test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for the group combination 1+2 at 1 month after primary vaccination 2 will be calculated. For each of the 4 MenA, MenC, MenW, and MenY test strains, the hSBA GMTs for the group combination 1+2 at 1 month after primary vaccination 2 will be calculated. For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for the group combination 1+2 at 1 month after primary vaccination 2 will be calculated. For each of the MenB test strains, the hSBA GMTs for the group combination 1+2 at 1 month after primary vaccination 2 will be calculated. **The following analyses for the MenA, MenC, MenW, and MenY and the MenB test strains are based on the post–booster vaccination evaluable population:** For each of the 4 MenA, MenC, MenW, and MenY test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for the group combination 1+2 at 1 month after the booster vaccination will be calculated.

Endpoint	Statistical Analysis Methods
	For each of the 4 MenA, MenC, MenW, and MenY test strains, the hSBA GMTs for the group combination 1+2 at 1 month after the booster vaccination will be calculated. For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for the group combination 1+2 at 1 month after the booster vaccination will be calculated. For each of the MenB test strains, the hSBA GMTs for the group combination 1+2 at 1 month after the booster vaccination will be calculated.

9.4.1.2. Blinded Expanded-Enrollment Stage

Endpoint	Statistical Analysis Methods
Primary	For each of the 4 MenA, MenC, MenW, and MenY test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for Groups 13 and 14 at 1 month after primary vaccination 2 will be calculated. For each of the 4 MenA, MenC, MenW, and MenY test strains, the hSBA GMTs for Groups 13 and 14 at 1 month after primary vaccination 2 will be calculated. For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for Groups 13 and 14 at 1 month after primary vaccination 2 will be calculated. For each of the MenB test strains, the hSBA GMTs for Groups 13 and 14 at 1 month after primary vaccination 2 will be calculated. The analysis at 1 month after primary vaccination 2 for the MenA, MenC, MenW, and MenY and the MenB test strains is based on the post–primary vaccination 2 evaluable population. For each of the 4 MenA, MenC, MenW, and MenY test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for Groups 13 and 14 at 1 month after the booster vaccination will be calculated.

Endpoint	Statistical Analysis Methods
	For each of the 4 MenA, MenC, MenW, and MenY test strains, the hSBA GMTs for Groups 13 and 14 at 1 month after the booster vaccination will be calculated. For each of the MenB test strains, the percentages of participants achieving an hSBA titer ≥ LLOQ for Groups 13 and 14 at 1 month after the booster vaccination will be calculated. For each of the MenB test strains, the hSBA GMTs for Groups 13 and 14 at 1 month after the booster vaccination will be calculated. Exact 2-sided 95% CIs for the percentages will be provided using the Clopper-Pearson method. Supportive analyses will be performed based on the post–primary vaccination 2 mITT population for post–primary vaccination 2 results and the post–booster vaccination mITT population for postbooster results. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

9.4.2. Safety Analyses

9.4.2.1. Open-Label Sentinel-Cohort and Expanded-Enrollment Stages

All safety analyses will be performed on the safety population. Separate safety populations will be defined for each vaccination visit and follow-up phase (primary vaccination 1, primary vaccination 2, primary vaccination 2 follow-up, booster vaccination, and booster vaccination follow-up phases) and will be detailed in the SAP.

Endpoint	Statistical Analysis Methods
Primary	The proportion of participants reporting local reactions at the investigational product administration site and systemic events within the 7-day period after each vaccination will be descriptively summarized by the following group or combined groups: Group combination 7+11 (with SLP) (MenABCWY + SLP recipients) Group 8 (with PLP) (Bexsero + PLP recipients) Group 11 (with TLP) (MenABCWY recipients) Group 10 (without PLP) (Bexsero recipients)

Endpoint	Statistical Analysis Methods
	Additionally, summaries without regard to **protocol-assigned paracetamol** administration will be provided for the following combined groups: Group combination 7+11 (MenABCWY recipients) Group combination 8+10 (Bexsero recipients) Two-sided 95% CIs based on the Clopper Pearson method will be presented with the proportions. Severities of local reactions and systemic events reported after each vaccination will also be descriptively summarized by the same group or combined groups. Local reactions will be summarized only for the left thigh, which is the MenABCWY, Trumenba, Bexsero, or placebo injection site. The proportion of participants reporting the use of antipyretic medication for Days 1 to 7 will be summarized for the group or combined groups after each vaccination. All AEs and SAEs will be categorized according to the latest version of MedDRA. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. An NDCMC is defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects. AEs, SAEs, MAEs, and NDCMCs will be summarized by group or combined groups as for local reactions and systemic events. Participants will be analyzed according to the vaccine they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules. Detailed analyses for each safety endpoint will be addressed in the SAP.
Secondary	Similar summaries to those proposed for the primary safety endpoint will be done for the secondary safety endpoint as well, but using the following groups instead: 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)

Endpoint	Statistical Analysis Methods
Exploratory	Similar summaries to those proposed for the primary safety endpoint will be done for the exploratory safety endpoint as well, but using the following groups instead: Group 1 (MenABCWY + PLP recipients) Group 2 (MenABCWY recipients)

9.4.2.2. Blinded Expanded-Enrollment Stage

Endpoint	Statistical Analysis Methods
Primary	The proportion of participants reporting local reactions at the investigational product administration site and systemic events within the 7-day period after each vaccination will be descriptively summarized by the following groups: Double-blind only: Group 13 (with TLP) (MenABCWY + TLP recipients) Group 14 (with TLP) (Bexsero + TLP recipients) Double-blind and single-blind: Single-blind groups: Group 13 (with SLP) (MenABCWY + SLP recipients) Group 14 (with PLP) (Bexsero + PLP recipients) Double-blind groups: Group 13 (with TLP) (MenABCWY + TLP recipients) Group 14 (with TLP) (Bexsero + TLP recipients) Two-sided 95% CIs based on the Clopper Pearson method will be presented with the proportions. Severities of local reactions and systemic events reported after each vaccination will also be descriptively summarized by the same group. Local reactions will be summarized only for the left thigh, which is the MenABCWY, Trumenba, Bexsero, or placebo injection site. The proportion of participants reporting the use of antipyretic medication for Days 1 to 7 will be summarized for the group after each vaccination. All AEs and SAEs will be categorized according to the latest version of MedDRA. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. An NDCMC is defined as a disease or

Endpoint	Statistical Analysis Methods
	medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects. AEs, SAEs, MAEs, and NDCMCs will be summarized by group as for local reactions and systemic events. Participants will be analyzed according to the vaccine they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules. Detailed analyses for each safety endpoint will be addressed in the SAP.

9.5. Interim Analyses

9.5.1. Analysis Timing

Statistical analyses will be carried out when the final 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.

Note that Analysis 1 and Analysis 4 represent the final analyses at the specified time point for the specified vaccine group.

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.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

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 may also determine the number of participants to be enrolled to receive MenABCWY with SLP or TLP in the open-label expanded-enrollment stage and decide the enrollment progression and stratification of protocol-assigned paracetamol regimens for the blinded expanded-enrollment stage based on the safety data gathered during the study. The IRC will also review safety data after all sentinel-cohort participants and expanded-enrollment stage participants have completed primary vaccination 2.

Safety data will be reviewed by the EDMC throughout the study. During the blinded phase, an independent statistical center will provide unblinded safety reports to the EDMC for review.

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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

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

Description of the use of computerized system is documented in the data management plan.

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

- Discontinuation of further study intervention development.

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, “lack of efficacy” or “failure of expected pharmacological action” does not constitute an AE or SAE.

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

10.3.2. Definition of an NDCMC

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

10.3.3. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. **Results in death**
b. **Is life-threatening** The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

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

d. **Results in persistent disability/incapacity**

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

e. **Is a congenital anomaly/birth defect**

f. **Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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

AE and SAE Recording/Reporting

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

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

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

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

AE and SAE Recording/Reporting

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

Assessment of Causality

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

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

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

10.4. Appendix 4: Contraceptive Guidance

Not applicable.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

10.6. Appendix 6: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

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

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

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

10.6.1. Definition of AE and ADE

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

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

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

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

10.6.3. Definition of Device Deficiency

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

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

AE, SAE, and Device Deficiency Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

Follow-up of AE/SAE/Device Deficiency

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

10.6.5. Reporting of SAEs

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

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

10.6.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.7. Appendix 7: Alternative Measures During Public Emergencies

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

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

10.7.1. Telehealth Visits

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

- Assess the severe reactogenicity symptoms that meet the requirement for an unplanned visit. The parent(s)/legal guardian contact outcome will be documented in the CRF. Refer to Section 8.12.
- Review the participant's e-diary data since the last contact and follow up on any ongoing reactogenicity or use of antipyretic medication on the last day that the e-diary was completed. Obtain the stop dates and document in the CRFs. Refer to Section 8.2.1.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications used to treat an AE since the last contact. Refer to Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.

In addition to the above, procedures outlined for a typical safety telephone contact (see Section 8.11.2) may be performed during a telehealth visit.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.7.2. Home Health Visits

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

- Ensure that the participant continues to be eligible for the study and does not meet any withdrawal criteria (Section 7.2).
- Collect a blood sample (approximately 5 mL) from the participant. Local/topical anesthetic may be used to numb the skin prior to the blood draw.
- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Collect the provisioned e-diary device, if previously provided to the participant's parent(s)/legal guardian.
- Collect the provided bottle of paracetamol from parent(s)/legal guardian of participants assigned to receive paracetamol as per protocol for primary vaccinations.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, and medication use. Please refer to the ISF for additional details.
    - Record AEs as described in Section 8.3 and the SoA.
    - Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in Section 6.5.
- Record nonstudy vaccinations as described in Section 6.5.
- Provide the parent(s)/legal guardian with a memory aid. Instruct the parent(s)/legal guardian to use the memory aid between Visit 4 and Visit 5 or Visit 6 and Visit 7 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF for additional details.
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

10.7.3. Adverse Events and Serious Adverse Events

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

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

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
app	application
AST	aspartate aminotransferase
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine
CDS	core data sheet
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DTPa-HBV-IPV-Hib	diphtheria, tetanus, and pertussis acellular; hepatitis B virus; inactivated poliomyelitis; and *Haemophilus influenzae* type b vaccine
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
fHBP	factor H binding protein
FIH	first in human
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMT	geometric mean titer
HIPAA	Health Insurance Portability and Accountability Act
hSBA	serum bactericidal assay using human complement
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification

Abbreviation	Term
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISF	investigator site file
ISO	International Organization for Standardization
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LOD	limit of detection
LP2086	lipoprotein 2086
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
MenACWY-CRM	meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria conjugate vaccine
MenACWY-TT	meningococcal polysaccharide groups A, C, W, and Y tetanus toxoid conjugate vaccine
MenB	*Neisseria meningitidis* group B
MenC	*Neisseria meningitidis* group C
MenW	*Neisseria meningitidis* group W
MenY	*Neisseria meningitidis* group Y
mITT	modified intent-to-treat
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
NSAID	nonsteroidal anti-inflammatory drug
PFS	prefilled syringe
PLP	prophylactic liquid paracetamol regimen
POC	proof of concept
PRP-OMP	polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein
PT	prothrombin time
RCDC	reverse cumulative distribution curve
rDNA	recombinant deoxyribonucleic acid
SADE	serious adverse device effect

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SLP	scheduled liquid paracetamol regimen
SmPC	summary of product characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
TLP	therapeutic liquid paracetamol regimen
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect

11. REFERENCES

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