Protocol B1971057

A Phase 3, Randomized, Active-Controlled, Observer-Blinded Study to Assess the Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 When Administered as a 2-Dose Regimen and a First-in-Human Study to Describe the Immunogenicity, Safety, and Tolerability of a Bivalent rLP2086–Containing Pentavalent Vaccine (MenABCWY) in Healthy Subjects ≥10 to <26 Years of Age

Statistical Analysis Plan (SAP)

Version: 5

Date: 28 Feb 2022

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

1. VERSION HISTORY

This statistical analysis plan (SAP) Version 4 for Study B1971057 is based on protocol amendment 2 dated 09 Jul 2019.

Table 1. Summary of Major Changes in SAP Amendments

Version / Date	Associated Protocol Amendment	Rationale	Specific Changes
1 21MAR2017	Final, 16JAN2017	Original SAP	N/A
2 15FEB2018	Amendment 1, 23AUG2017	Protocol Amendment	• Updated the covariates for the subgroup analysis. • Updated to include the pilot safety population in the Stage 1 safety population. • Updated to remove the presentation of p-values in the safety summaries. • Added the requirement to perform mixed-effects model with repeated measures (MMRM)/generalized linear mixed-effects model with repeated measures (GLIMMIX) analyses on immunogenicity data. • Clarified the methods used in the noninferiority (NI) analyses. Added the criteria for NI analyses. • Added section for additional immunogenicity analyses. • Updated the derivation of age at vaccination to follow prior Trumenba® studies.
3 29OCT2018	Amendment 1, 23AUG2017	Regulatory input, Clarification Clinical team input	• Added sensitivity analysis for composite response to address regulatory request. • Clarified the modified intent-to-treat (mITT) population definition. • Added the lower limits of quantitation (LLOQs) for *Neisseria meningitidis* group A, group C, group W, and/or group Y (MenA/C/W/Y) assays and for secondary *Neisseria meningitidis* group B (MenB) strains. • Clarified race categorization in subgroup analyses. • Added planned positive predictive value (PPV) analyses for assessment of association between results for primary MenB and secondary MenB strains. • Added description of the variability assessment of ACWY data endpoints. • Removed previously included exploratory analyses.

Table 1. Summary of Major Changes in SAP Amendments

Version / Date	Associated Protocol Amendment	Rationale	Specific Changes
4 17MAY2021	Amendment 2, 09JUL2019	Protocol Amendment	• Moved the booster dose safety endpoints from secondary to primary safety endpoints. • Moved some immunogenicity endpoints (related to persistence evaluation) from secondary to exploratory endpoints. • Removed the 1:4 endpoint for ACWY strains for the persistence and booster endpoints. • Updated the Stage 2 enrollment, for ACWY-experienced subjects in addition to ACWY-naïve subjects to obtain data on the persistence of the immune response after 2 doses of *Neisseria meningitidis* group A, B, C, W, and Y vaccine (MenABCWY) as well as on the safety and immunogenicity of the booster response in individuals who had previously received an ACWY-containing vaccine. • Removed the persistence and booster endpoints for defined titers; removed the persistence endpoints for geometric mean titers (GMTs).
5 28 Feb 2022	N/A	Table reduction initiative, including reducing redundancy Adding additional analyses Administrative changes	• Removed from Stage 2 analyses the exploratory 4-fold rise and the composite response endpoint for MenB strains. • Replaced some study conduct tables for Stage 2 with listings in Section 6.6. • Added exploratory analyses for MenA/C/W/Y to investigate the relationship between the pre–booster dose and the post–booster dose titers in Section 6.4. • Added in Section 7.1 a new planned reporting event performed when subjects have completed the 1-month postbooster blood draw. • Updated the temperature scale of severity for fever for Stage 2 (Table 14) in Section 3.5.2.2 to allow for consistency in severity designation between temperatures recorded in Fahrenheit and Celsius. • Added the definition of the booster safety population in Section 4.4.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B1971057. A brief description of the study design and the study objectives are given. Subsequent sections include analysis population and the definitions of the immunogenicity and safety endpoints followed by details around statistical analysis and reporting. A list of tables, listings, and figures, mock-up tables, listings, and figures, and programming rules are prepared separately based on the methods described in this document. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

2.1.1. Primary Immunogenicity Objective

- To assess the immune response induced by bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086) as measured by serum bactericidal assay using human complement (hSBA) performed with 4 primary MenB test strains, 2 expressing an rLP2086 subfamily A protein and 2 expressing an rLP2086 subfamily B protein, measured 1 month after the second vaccination, in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.

2.1.2. Primary Safety Objective

- To describe the safety profile of bivalent rLP2086, as measured by local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended AEs (MAEs), and immediate AEs, following Vaccinations 1 and 2 in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.

- To describe the safety profile of *Neisseria meningitidis* group A, B, C, W, and Y vaccine (MenABCWY), as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs, after the booster vaccination.

- To describe the safety profile of bivalent rLP2086, as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs, after the booster vaccination.

2.1.3. Secondary Immunogenicity Objectives

- To describe the immune response induced by bivalent rLP2086 as measured by hSBA performed with 4 primary *Neisseria meningitidis* group B (MenB) test strains, 2 expressing an rLP2086 subfamily A protein and 2 expressing an rLP2086 subfamily B protein, measured 1 month after the second vaccination, in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.

- To describe the immune response induced by bivalent rLP2086 as measured by hSBA performed with secondary MenB test strains measured 1 month after the second vaccination in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.

- To describe the immune response induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria conjugate vaccine (MenACWY-CRM), as measured by hSBA performed with ACWY test strains, in ACWY-naïve and ACWY-experienced subjects separately.

- To describe the immune response induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, as measured by hSBA performed with ACWY test strains, in ACWY-naïve and ACWY-experienced subjects separately.

- To describe the immune response induced by MenABCWY compared to the immune response induced by bivalent rLP2086 as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an rLP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the second vaccination in the ACWY-naïve and ACWY-experienced subjects combined.

- To describe the immune response induced by MenABCWY compared to the immune response induced by MenACWY-CRM and bivalent rLP2086 as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, 2 expressing an rLP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, at blood sampling time points prior to the booster vaccination (Stage 1).

- To describe the immune response induced by MenABCWY compared to the immune response induced by MenACWY-CRM and bivalent rLP2086, as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, at blood sampling time points prior to the booster vaccination (Stage 2).

- To describe the immune response induced by MenABCWY as measured by hSBA performed with ACWY and 4 primary MenB test strains, 1 month after a booster vaccination in Groups 1 and 3.

- To describe the immune response induced by bivalent rLP2086, as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an rLP2086 subfamily A protein and 2 expressing an rLP2086 subfamily B protein, measured 1 month after the booster vaccination in Groups 2 and 4.

2.1.4. Secondary Safety Objectives

- To describe the safety profile of MenABCWY as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs, after Vaccinations 1 and 2 in the ACWY-naïve and ACWY-experienced subjects separately.

2.1.5. Exploratory Objectives

- To describe the immune response induced by MenACWY-CRM as measured by hSBA performed with ACWY test strains, 1 month after a booster vaccination in Groups 2 and 4.

- To describe the immune response induced by bivalent rLP2086 as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an rLP2086 subfamily A protein and 2 expressing an rLP2086 subfamily B protein, measured 1 month after the first vaccination, in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.

- To further describe the immune response induced by MenABCWY compared to the immune response induced by MenACWY-CRM and bivalent rLP2086, as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, at blood sampling time points prior to the booster vaccination (Stage 2).

- To further describe the immune response induced by MenABCWY, as measured by hSBA performed with ACWY and 4 primary MenB test strains, 1 month after a booster vaccination in Groups 1 and 3.

- To further describe the immune response induced by bivalent rLP2086, as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the booster vaccination in Groups 2 and 4.

The endpoints (specified in Section 3.3) related to the exploratory objective to further describe the immune response induced by MenABCWY compared to the immune response induced by MenACWY-CRM and bivalent rLP2086, as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, at blood sampling time points prior to the booster vaccination (Stage 2) are not planned to be reported.

The endpoints (specified in Section 3.3) related to the exploratory objective to further describe the immune response induced by bivalent rLP2086 and MenABCWY for the proportions of subjects with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB and ACWY test strains and the endpoints of the proportion of subjects who achieve the 5 MenB endpoints 1 month after the booster vaccination are not planned to be reported.

2.2. Study Design

2.2.1. Description

This is a Phase 3, randomized, active-controlled, observer-blinded multicenter trial in which approximately 1590 subjects will be randomly assigned to receive either MenABCWY (Trumenba+meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine [MenACWY-TT] reconstituted) and saline or bivalent rLP2086 and MenACWY-CRM. All subjects will be naïve to any meningococcal group B vaccine prior to enrollment.

Randomization will be stratified by prior vaccination history; approximately 795 ACWY-naïve subjects and 795 ACWY-experienced (having received 1 prior dose of vaccine containing 1 or more ACWY groups ≥4 years prior to the date of randomization) subjects will be enrolled.

Randomization will also be stratified by geographic region. Approximately 1320 subjects from United States (US) investigator sites and 270 subjects from ex-US countries will be randomized. Regional stratification will ensure sufficient population representation. The study is powered to meet the primary objective for immunogenicity based upon US subjects alone and additionally for the US and ex-US subjects.

The study will be conducted in 2 stages:

- Stage 1: comprises visits from study entry (Visit 1) through Visit 6. A pilot cohort consisting of 10 subjects 18 to <26 years of age will initially be enrolled and assigned to either Group 1 or 3, depending on prior vaccination history, and will receive MenABCWY at Vaccination 1. Seven days after the last pilot cohort subject has received MenABCWY, 7-day electronic diary (e-diary) and AE data will be summarized for review by the sponsor's independent review committee (IRC). No further enrollment will be permitted until review of these safety data is complete. If the IRC finds the safety data from the pilot cohort acceptable, enrollment will be opened to all ages and randomization groups, and the pilot cohort subjects will proceed in the study as planned. During Stage 1, the sponsor will be blinded to vaccine assignment beyond the completion of pilot cohort enrollment.

  Subjects will receive 2 vaccinations, their first at the randomization visit (Visit 1) and a second vaccination at Month 6 (Visit 3). In support of assay development, a subset of approximately 600 subjects 18 to 25 years of age will have approximately 100 mL, rather than 20 mL, of blood drawn at Visits 1, 2, and 4; a subset of up to approximately 150 subjects 18 to 25 years of age will have up to 100 mL, rather than 20 mL, of blood drawn at Visit 11. Stage 1 will be observer-blinded. See Table 2.

- Stage 2: from Months 18 to 60 (Visits 7 to 12). Subjects from both ACWY-naïve and ACWY-experienced strata will participate in Stage 2 (approximately 132 subjects from each of Groups 1 and 3 and approximately 65 subjects from each of Groups 2 and 4). Stage 2 will be open label. See Table 3.

  In Stage 2, the total number subjects for Groups 1 and 3 combined will be approximately 264 and the total number of subjects for Groups 2 and 4 combined will be approximately 130.

2.2.2. Number of Subjects

Approximately 1590 subjects (1320 from US sites and 270 from ex-US sites) will be randomized to participate in this study. A minimum total of 880 subjects will be enrolled from US sites to receive bivalent rLP2086+MenACWY-CRM to meet the postmarketing approval commitment (PAC) requirements.

Subjects will be stratified into 1 of 2 groups depending on their ACWY vaccination history: ACWY-naïve and ACWY-experienced. A total of 795 subjects will be enrolled into each stratum. All subjects in the study will be naïve to any meningococcal serogroup B vaccine at randomization.

Subjects will further be randomized into 2 vaccine groups within each stratum. Subjects randomized to Group 1 or 3 will be given MenABCWY and subjects randomized to Group 2 or 4 will be given bivalent rLP2086+MenACWY-CRM. A pilot cohort consisting of 10 subjects 18 to <26 years of age will first be enrolled into the study in Group 1 or 3 depending on ACWY history. These 10 subjects will be enrolled by US sites and vaccination will be open label.

Subjects from both ACWY-naïve and ACWY-experienced strata, approximately 132 from each of Groups 1 and 3 and approximately 65 from each of Groups 2 and 4, will participate in Stage 2.

A subset of 540 subjects will be randomly selected (composed of 450 subjects from US sites and 90 subjects from ex-US sites) from Groups 2 and 4 and will have secondary test strains assayed so that 125 evaluable subjects in US and 25 evaluable subjects from ex-US sites for each subset will be obtained. A total of 3 subsets will be included. Each subset will include 150 subjects from US sites and 30 subjects from ex-US sites to be assayed. In the first 2 subsets, subjects will each be assayed for 3 secondary test strains and the subjects in the last subset will be assayed for 4 secondary test strains. Therefore, not all subjects in the subsets will be tested for all 10 secondary strains. The subset for the secondary strain testing will be randomly selected to allow the 540 subjects from Groups 2 and 4 across the 3 subsets; the independent statistical center (ISC) will randomly allocate the 540 subjects from Groups 2 and 4 across the 3 subsets.

Table 2. Stage 1 Study Design

		Vaccination 1	Post–Vaccination 1 Blood Draw	Vaccination 2	Post–Vaccination 2 Blood Draw	Safety Telephone Call	Telephone Call
	Approximate Month	**0**	**1**	**6**	**7**	**12**	
	Visit Number	**1**	**2**	**3**	**4**	**5**	**6**
ACWY-Naïve Subjects	Group 1[a] (n=265)	MenABCWY + saline		MenABCWY			
	Group 2 (n=530)	Bivalent rLP2086 + MenACWY-CRM		Bivalent rLP2086			
	Blood draw for serum collection	20 mL (or up to 100 mL in subset)	20 mL (or up to 100 mL in subset)	20 mL	20 mL (or up to 100 mL in subset)		
ACWY-Experienced Subjects	Group 3[a] (n=265)	MenABCWY + saline		MenABCWY			
	Group 4 (n=530)	Bivalent rLP2086 + MenACWY-CRM		Bivalent rLP2086			
	Blood draw for serum collection	20 mL (or up to 100 mL in subset)	20 mL (or up to 100 mL in subset)	20 mL	20 mL (or up to 100 mL in subset)		
Subjects 18 to 25 Years of Age (Naïve or Experienced)	Optional blood draw for whole blood collection				50 mL		

a. Pilot cohort subjects will be assigned to either Group 1 or 3, but will receive only MenABCWY and not saline at Vaccination 1.

[redacted]

[redacted]

Table 3. Stage 2 Study Design

		Antibody Persistence	Booster Vaccination	Postbooster Blood Draw	Safety Telephone Call
	Approximate Month	**18-42**	**54**	**55**	**60**
	Visit Number	**7-9**	**10**	**11**	**12**
ACWY-Naïve Subjects	Group 1 (n~132)		MenABCWY		
	Group 2 (n~65)		Bivalent rLP2086 + MenACWY-CRM		
ACWY-Experienced Subjects	Group 3 (n~132)		MenABCWY		
	Group 4 (n~65)		Bivalent rLP2086 + MenACWY-CRM		
	Blood draw for serum collection	20 mL × 3	20 mL	20 mL (or up to 100 mL in subset)	

[redacted]

[redacted]

2.2.3. Schedule of Activities

The Schedule of Activities table provides and overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections 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 on the Schedule of Activities table in order to conduct evaluations or assessments required to protect the well-being of the subjects.

Table 4. Schedule of Activities

Stage 1						
Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Visit Description	**Vaccination 1**	**Post–Vaccination 1 Blood Draw**	**Vaccination 2**	**Post–Vaccination 2 Blood Draw**	**Telephone Contact**	**Telephone Contact**
Approximate Month	**0**	**1**	**6**	**7**	**6 Months After Last Study Vaccination**	
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days After Visit 3**	**After Study Unblinding and Before Transition to Stage 2[a]**
Informed consent	X					
Informed consent for optional blood draw for whole blood collection[b]				X		
Review eligibility criteria	X					
Demography	X					
Confirm continued eligibility[c]		X	X	X		
Medical history and physical examination	X					
Record previous PRP-OMP vaccinations	X					
Record any previous meningococcal vaccinations	X					

Table 4. Schedule of Activities

Stage 1						
Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Visit Description	**Vaccination 1**	**Post–Vaccination 1 Blood Draw**	**Vaccination 2**	**Post–Vaccination 2 Blood Draw**	**Telephone Contact**	**Telephone Contact**
Approximate Month	**0**	**1**	**6**	**7**	**6 Months After Last Study Vaccination**	
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days After Visit 3**	**After Study Unblinding and Before Transition to Stage 2[a]**
Record use of antipyretics and other pain medications received on the day prior to vaccination	X		X			
Urine pregnancy test for female subjects	X		X			
Oral temperature	X		X			
Randomization	X					
Obtain blood sample(s) for serum collection[d]	20 mL (up to 100 mL in subset)	20 mL (up to 100 mL in subset)	20 mL (20 mL in subset)	20 mL (up to 100 mL in subset)		
Additional optional blood draw for whole blood collection[e]				50 mL		
Investigational product administration and observation[f]	X		X			
Record nonstudy vaccinations		X	X	X	X	
Provide subject with an e-diary, caliper, measuring tape/ruler, and thermometer, if necessary	X		X			
Review and collect e-diary		X		X		
Assess reactogenicity and record use of antipyretic medication[g]	Days 1 to 7		Days 1 to 7			
Provide the subject with a contact card	X					
Provide the subject with a memory aid				X		
Complete Study Visit/Telephone Contact AE Checklist[h]		X	X	X	X	

[redacted]

[redacted]

Table 4. Schedule of Activities

Stage 1						
Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Visit Description	**Vaccination 1**	**Post–Vaccination 1 Blood Draw**	**Vaccination 2**	**Post–Vaccination 2 Blood Draw**	**Telephone Contact**	**Telephone Contact**
Approximate Month	**0**	**1**	**6**	**7**	**6 Months After Last Study Vaccination**	
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days After Visit 3**	**After Study Unblinding and Before Transition to Stage 2[a]**
Record concomitant medications used to treat AEs	X	X	X	X	X	
(S)AE collection appropriate for the visit[i]	X	X	X	X	X	
Notification of Stage 2 participation						X

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

a. Visit 6 must be conducted prior to Visit 7.
b. Applicable only at designated sites. This consent relating to the whole blood sample may be obtained at prior visits if appropriate.
c. Ensure that the subject continues to be eligible for the study and continues to comply with contraception requirements, as appropriate.
d. Subject participation in the subset will be voluntary for subjects 18 to 25 years of age, and the volume of blood drawn (either 50 mL or 100 mL) will depend on the consent obtained.
e. Applicable only for subjects at designated sites who have given consent for this additional blood draw.
f. Observe the subject for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions.
g. Between visits, review the e-diary data online at frequent intervals. Contact the subject in order 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.
h. Checklist includes questions regarding newly diagnosed chronic medical conditions, medically attended adverse events, and missed days of school or work, as well as about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
i. Please refer to protocol Section 8.1.4.

Stage 2						
Visit ID	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Visit Description	**Antibody Persistence Blood Draw 1**	**Antibody Persistence Blood Draw 2**	**Antibody Persistence Blood Draw 3**	**Booster Vaccination**	**Postbooster Blood Draw**	**Telephone Contact**
Approximate Month	**18**	**30**	**42**	**54**	**55**	**6 Months After Booster Vaccination**
Visit Window	**336 to 694 Days After Visit 3**	**700 to 756 Days After Visit 3[a]**	**1064 to 1120 Days After Visit 3**	**1428 to 1484 Days After Visit 3**	**28 to 42 Days After Visit 10**	**168 to 196 Days After Visit 10**
Informed consent	X					
Confirm continued eligibility[b]	X	X	X	X	X	
New medical history and physical examination				X		
Urine pregnancy test for female subjects				X		
Oral temperature				X		
Obtain blood sample	20 mL	20 mL	20 mL	20 mL	20 mL (up to 100 mL in subset)	
Record use of antipyretics and other pain medications received on the day prior to vaccination				X		
Investigational product administration and observation[c]				X		
Record nonstudy vaccinations	X	X	X	X	X	
Provide subject with an e-diary, caliper, measuring tape/ruler, and thermometer, if necessary				X		
Review and collect e-diary					X	
Assess reactogenicity and record use of antipyretic medication[d]				Day 1 to 7		
Provide the subject with a memory aid					X	
Complete Study Visit/Telephone Contact AE Checklist[e]					X	X

Stage 2						
Visit ID	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Visit Description	**Antibody Persistence Blood Draw 1**	**Antibody Persistence Blood Draw 2**	**Antibody Persistence Blood Draw 3**	**Booster Vaccination**	**Postbooster Blood Draw**	**Telephone Contact**
Approximate Month	**18**	**30**	**42**	**54**	**55**	**6 Months After Booster Vaccination**
Visit Window	**336 to 694 Days After Visit 3**	**700 to 756 Days After Visit 3[a]**	**1064 to 1120 Days After Visit 3**	**1428 to 1484 Days After Visit 3**	**28 to 42 Days After Visit 10**	**168 to 196 Days After Visit 10**
Record concomitant medications used to treat AEs	X	X	X	X	X	X
(S)AE collection appropriate for the visit[f]	X	X	X	X	X	X

Abbreviation: e-diary = electronic diary.

a. Visit 7 and Visit 8 should be conducted within no less than 30 days of each other. If Visit 7 cannot be conducted within the protocol-defined visit window, Visit 7 can be omitted and Visit 8 performed directly.
b. Ensure that the subject continues to be eligible for the study and continues to comply with contraception requirements, as appropriate.
c. Observe the subject for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions.
d. Between visits, review the e-diary data online at frequent intervals. Contact the subject in order 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.
e. Checklist includes questions regarding newly diagnosed chronic medical conditions, medically attended adverse events, and missed days of school or work, as well as about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
f. Please refer to protocol Section 8.1.4.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoints

Five coprimary endpoints are defined for the primary objectives; they are defined for hSBA performed with each of the 4 primary test strains: PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).

- One of the 5 coprimary endpoints is the composite endpoint defined as the proportion of subjects achieving an hSBA titer ≥ lower limit of quantitation (LLOQ: 1:16 for A22 and 1:8 for A56, B24, and B44) for all 4 primary test strains combined, 1 month after the second vaccination (Visit 4) in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.

- Four of the coprimary endpoints are defined as the proportion of subjects achieving at least a 4-fold increase in hSBA titer from baseline to 1 month after the second vaccination (Visit 4) in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined for each of the 4 primary test strains.

    - For subjects with a baseline hSBA titer below the limit of detection (LOD, or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16 or the LLOQ (whichever titer is higher).

    - For subjects with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ.

    - For subjects with a baseline hSBA of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.

3.1.2. Primary Safety Endpoints

The following endpoints will be described after Vaccinations 1 and 2 in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.

- Percentage of subjects reporting local reactions (pain, redness, and swelling) and by severity within 7 days after each vaccination visit.

- Percentage of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain) and by severity within 7 days after each vaccination visit.

- Percentage of subjects reporting the use of antipyretic medications within 7 days after each vaccination visit.

- Percentage of subjects with at least 1 SAE during the following time periods:
  - 30 Days after each vaccination
  - 30 Days after any vaccination
  - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4])
  - During the Stage 1 follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5])
  - Throughout Stage 1 (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5])
- Percentage of subjects with at least 1 MAE occurring during the following time periods:
  - 30 Days after each vaccination
  - 30 Days after any vaccination
  - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4])
  - During the Stage 1 follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5])
  - Throughout Stage 1 (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5])
- Percentage of subjects with at least 1 NDCMC occurring during the following time periods:
  - 30 Days after each vaccination
  - 30 Days after any vaccination
  - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4])
  - During the Stage 1 follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5])
  - Throughout Stage 1 (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5])

- Percentage of subjects with at least 1 AE occurring during the following time periods:
    - 30 Days after each vaccination
    - 30 Days after any vaccination
    - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4])
- Percentage of subjects reporting at least 1 immediate AE after each vaccination.
- The number of days subjects missed school or work because of AEs during the Stage 1 vaccination phase (Visit 1 through Visit 4).

The following endpoints will be described after the booster vaccination in Groups 1 through 4:

- Percentage of subjects reporting local reactions (pain, redness, and swelling) and by severity within 7 days after the booster vaccination.
- Percentage of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain) and by severity within 7 days after the booster vaccination.
- Percentage of subjects reporting the use of antipyretic medication within 7 days after the booster vaccination.
- Percentage of subjects with at least 1 SAE during the following time periods:
    - During the booster vaccination phase (from the booster vaccination [Visit 10] through 1 month after the booster vaccination [Visit 11])
    - During the booster follow-up phase (from 1 month after the booster vaccination [Visit 11] through 6 months after the booster vaccination [Visit 12])
    - From the booster vaccination (Visit 10) through 6 months after the booster vaccination (Visit 12)
- Percentage of subjects with at least 1 MAE occurring during the following time periods:
    - During the booster vaccination phase (from the booster vaccination [Visit 10] through 1 month after the booster vaccination [Visit 11])
    - During the booster follow-up phase (from 1 month after the booster vaccination [Visit 11] through 6 months after the booster vaccination [Visit 12])

- From the booster vaccination (Visit 10) through 6 months after the booster vaccination (Visit 12)

- Percentage of subjects with at least 1 NDCMC occurring during the following time periods:
  - During the booster vaccination phase (from the booster vaccination [Visit 10] through 1 month after the booster vaccination [Visit 11])
  - During the booster follow-up phase (from 1 month after the booster vaccination [Visit 11] through 6 months after the booster vaccination [Visit 12])
  - From the booster vaccination (Visit 10) through 6 months after the booster vaccination (Visit 12)

- Percentage of subjects with at least 1 AE occurring during the following time periods:
  - During the booster vaccination phase (from the booster vaccination [Visit 10] through 1 month after the booster vaccination [Visit 11]).

- Percentage of subjects reporting at least 1 immediate AE after the booster vaccination.
- The number of days subjects missed school or work because of AEs after the booster vaccination.

3.2. Secondary Endpoints

3.2.1. Secondary Immunogenicity Endpoints

Immune response induced by 2 doses of bivalent rLP2086 arms (Group 2 and 4 subjects) combined as measured by 4 primary MenB test strains (A22, A56, B24, and B44) and by secondary MenB test strains: PMB3175 (A29), PMB3010 (A06), PMB824 (A12), PMB3040 (A07), PMB1672 (A15), PMB1989 (A19), PMB648 (B16), PMB866 (B09), PMB1256 (B03), and PMB431 (B15).

- Proportions of subjects with hSBA titers ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visit 4.

- hSBA geometric mean titers (GMTs) for each of the 4 primary MenB test strains at Visit 4.

- Proportions of subjects with hSBA titers ≥ LLOQ (1:16 for A06, A19, and A12 and 1:8 for A07, A15, A29, B03, B09, B15, and B16) for each of the secondary MenB test strains 1 month after the second vaccination (Visit 4).

- Proportions of subjects with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the secondary MenB test strains 1 month after the second vaccination (Visit 4).

- hSBA GMTs for each of the secondary test strains 1 month after the second vaccination (Visit 4).

Immune response induced by 1 dose of MenABCWY compared to 1 dose of MenACWY-CRM arms in ACWY-naïve and ACWY-experienced subjects separately.

- Proportion of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visit 2.
- Proportion of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visit 2.
- hSBA GMTs for each of the ACWY test strains at Visit 2.

Immune response induced by 2 doses of MenABCWY compared to 1 dose of MenACWY-CRM arms in ACWY-naïve and ACWY-experienced subjects separately.

- Proportion of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visit 4 in Groups 1 and 3 and at Visit 2 in Groups 2 and 4.
- Proportion of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visit 4 in Groups 1 and 3 and Visit 2 in Groups 2 and 4.
- hSBA GMTs for each of the ACWY test strains at Visit 4 in Groups 1 and 3 and Visit 2 in Groups 2 and 4.

Immune response induced by 2 doses of MenABCWY compared to immune response induced by 2 doses of bivalent rLP2086 arms in ACWY-naïve and ACWY-experienced subjects combined.

- Proportion of subjects who achieve the 5 MenB endpoints 1 month after the second vaccination, which are defined for hSBA performed with each of the 4 primary test strains: PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), as detailed below:
    - One of the 5 endpoints is the composite endpoint defined as the proportion of subjects achieving an hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for all 4 primary test strains combined, 1 month after the second vaccination.
    - Four of the endpoints are defined as the proportion of subjects achieving at least a 4-fold increase in hSBA titer from baseline to 1 month after the second vaccination for each of the 4 primary test strains.

[redacted]

[redacted]

  - For subjects with a baseline hSBA titer below the LOD (ie, an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16 or the LLOQ (whichever titer is higher).
  - For subjects with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ.
  - For subjects with a baseline hSBA of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.

- Proportion of subjects with hSBA titers ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visit 4.
- hSBA GMTs for each of the 4 primary MenB test strains at Visit 4.

Immune response induced by MenABCWY compared to MenACWY-CRM and bivalent rLP2086 during Stage 1.

- Proportions of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visits 1 and 3, in the ACWY-naïve and ACWY-experienced subjects separately.
- Proportions of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visits 1 and 3, in the ACWY-naïve and ACWY-experienced subjects separately.
- hSBA GMTs for each of the ACWY test strains at Visits 1 and 3, in the ACWY-naïve and ACWY-experienced subjects separately.
- Proportions of subjects with hSBA titers ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visits 1 and 3, in the ACWY-naïve and ACWY-experienced subjects combined.
- hSBA GMTs for each of the 4 primary MenB test strains at Visits 1 and 3, in the ACWY-naïve and ACWY-experienced subjects combined.

Immune response induced by MenABCWY compared to MenACWY-CRM and bivalent rLP2086 at blood sampling time points prior to the booster vaccination (Stage 2).

- Proportions of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visits 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced subjects separately.

- Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary MenB test strains at Visits 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced subjects combined.

Immune response induced by MenABCWY 1 month after a booster vaccination in Groups 1 and 3.

- Proportions of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visit 11 in Groups 1 and 3 separately.

- Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary MenB test strains at Visit 11 in Groups 1 and 3 combined.

Immune response induced by bivalent rLP2086 measured 1 month after the booster vaccination in Groups 2 and 4.

- Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary MenB test strains at Visit 11 in Groups 2 and 4 combined.

3.2.2. Secondary Safety Endpoints

The following endpoints will be described after each vaccination in Groups 1 and 3:

- Percentage of subjects reporting local reactions (pain, redness, and swelling) and by severity within 7 days after each vaccination visit.

- Percentage of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain) and by severity within 7 days after each vaccination visit.

- Percentage of subjects with at least 1 SAE during the following time periods:

    - 30 Days after each vaccination

    - 30 Days after any vaccination

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

    - During the Stage 1 follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5])

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

- Percentage of subjects with at least 1 MAE occurring during the following time periods:
    - 30 Days after each vaccination
    - 30 Days after any vaccination
    - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4])
    - During the Stage 1 follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5])
    - Throughout Stage 1 (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5])
- Percentage of subjects with at least 1 NDCMC occurring during the following time periods:
    - 30 Days after each vaccination
    - 30 Days after any vaccination
    - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4])
    - During the Stage 1 follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5])
    - Throughout Stage 1 (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5])
- Percentage of subjects with at least 1 AE during the following time periods:
    - 30 Days after each vaccination
    - 30 Days after any vaccination
    - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]).
- Percentage of subjects reporting at least 1 immediate AE after each vaccination.
- The number of days school or work was missed by the subject because of AEs after vaccination.

3.3. Other Objectives and Endpoints

3.3.1. Exploratory Objectives and Endpoints

Objective	Endpoint
• To describe the immune response induced by MenACWY-CRM as measured by hSBA performed with ACWY test strains, 1 month after a booster vaccination in Groups 2 and 4.	• Proportion of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visit 11, in Groups 2 and 4 separately.
• To describe the immune response induced by bivalent rLP2086 as measured by hSBA performed with 4 primary MenB test strains, measured 1 month after the first vaccination, in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.	• Proportion of subjects who achieve the 5 MenB endpoints at Visit 2. • Proportions of subjects with hSBA titers ≥ LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visit 2. • hSBA GMTs for each of the 4 primary MenB test strains at Visit 2.
• To further describe the immune response induced by MenABCWY compared to the immune response induced by MenACWY-CRM and bivalent rLP2086, as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, at blood sampling time points prior to the booster vaccination (Stage 2).	• Proportions of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visits 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced subjects separately. • hSBA GMTs for each of the ACWY test strains at Visits 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced subjects separately. • Proportions of subjects with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visits 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced subjects combined. • hSBA GMTs for each of the 4 primary MenB test strains at Visits 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced subjects combined.
• To further describe the immune response induced by MenABCWY, as measured by hSBA performed with ACWY and 4 primary MenB test strains, 1 month after a booster vaccination in Groups 1 and 3.	• Proportions of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visit 11, in Groups 1 and 3 separately. • hSBA GMTs for each of the ACWY test strains at Visit 11, in Groups 1 and 3 separately. • Proportion of subjects who achieve the 5 MenB endpoints at Visit 11, in Groups 1 and 3 combined. • Proportions of subjects with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visit 11, in Groups 1 and 3 combined. • hSBA GMTs for each of the 4 primary MenB test strains at Visit 11, in Groups 1 and 3 combined.

Objective	Endpoint
• To further describe the immune response induced by bivalent rLP2086, as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the booster vaccination in Groups 2 and 4.	• Proportion of subjects who achieve the 5 MenB endpoints 1 month after the booster vaccination, in Groups 2 and 4 combined. • Proportions of subjects with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visit 11, in Groups 2 and 4 combined. • hSBA GMTs for each of the 4 primary MenB test strains at Visit 11, in Groups 2 and 4 combined.

The endpoints related to the exploratory objective to further describe the immune response induced by MenABCWY compared to the immune response induced by MenACWY-CRM and bivalent rLP2086, as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein at blood sampling time points prior to the booster vaccination (Stage 2), are not planned to be reported.

Furthermore, for the last 2 exploratory objectives related to the further description of the immune response following the booster vaccination, the endpoints related to the proportion of subjects with titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 and the endpoints related to the proportion of subjects who achieve the 5 MenB endpoints are not planned to be reported.

3.4. Baseline Variables

Prevaccination blood draw (Visit 1) will be performed according to the Schedule of Activities Table 4. The immunogenicity results from Visit 1 are considered the baseline results for the immunogenicity analyses during Stage 1. The prevaccination blood draw prior to the booster vaccination (Visit 10) will be considered the baseline result for the immunogenicity analyses during Stage 2.

Day 1 is defined as the day of vaccination (Visit 1, Month 0) and also the start of when local reactions and systemic events are to be reported in the e-diary.

3.4.1. Demographic, Medical History, and Baseline Characteristic Variables

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

- Black or African American
- American Indian or Alaska Native
- Asian

- Native Hawaiian or other Pacific Islander
- White
- Other

Ethnicity includes:

- Hispanic or Latino
- Non-Hispanic/non-Latino

For countries where the full date of birth is collected, age at the time of the first vaccination and age at randomization will be derived based on birthday. For example, if the first vaccination date is 1 day before the subject's 13th birthday, the subject is 12 years old.

Medical history will be assessed at Visit 1 and Visit 10 and categorized according to the current version (at the time of reporting) of the Medical Dictionary for Regulatory Activities (MedDRA).

Physical examination will be assessed prior to vaccination at Visit 1 and each body system examined will be recorded in the case report form (CRF) as normal, abnormal, or not done.

3.4.2. Previous Vaccinations

For subjects who have received a polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugate to outer membrane protein (PRP-OMP) vaccine, the name of the vaccine (PedvaxHIB and Comvax/Procomvax) and date of administration will be recorded on the CRF.

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

3.5. Safety Endpoints

3.5.1. Adverse Events

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

The time period for actively eliciting and collecting (S)AEs, MAEs, NDCMCs, and research-related injuries (RRIs) for each subject is outlined in Table 5.

Table 5. Summary of AE Collection

	Visits 1-4	Visit 5	Visit 6	Visits 7-9	Visits 10-11	Visit 12
Approximate Month	0-7	12	12-18	18-42	54-55	60
Nonserious AEs	ICD through and including Visit 4			Within 48 hours of blood draw	From Visit 10 to Visit 11	
SAEs	ICD through and including Visit 4	Since Visit 4	Nonactive SAE collection period		From Visit 10 to Visit 11	Since Visit 11
MAEs	ICD through and including Visit 4	Since Visit 4			From Visit 10 to Visit 11	Since Visit 11
NDCMCs	ICD through and including Visit 4	Since Visit 4			From Visit 10 to Visit 11	Since Visit 11
RRIs				Within 48 hours of blood draw		

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

An MAE, which is defined as a nonserious AE that results in an evaluation at a medical facility, and the number of days subjects missed school or work because of AEs will be captured on the AE checklist (see Schedule of Activities Table 4). Neuroinflammatory and autoimmune conditions will also be captured on the AE checklist. An NDCMC is defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects.

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

An AE is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time after vaccination has occurred and was not present prior to vaccination, or
- the event was present prior to vaccination but increased in severity after vaccination.

Events occurring prior to the first vaccination are not considered treatment emergent as defined here and will be excluded from the AE analyses.

3.5.1.1. Analysis Intervals

There will be up to 9 analysis intervals for most of the safety data collected via the CRF (Table 6).

Table 6. Analysis Intervals for AEs, SAEs, MAEs, and NDCMCs

No.	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)	Safety Data
1	Within 30 days of Vaccination 1	Vax 1 safety	Vax 1 date	Vax 1 date + 30 days	AE, SAE, MAE, NDCMC
2	Within 30 days of Vaccination 2	Vax 2 safety	Vax 2 date	Vax 2 date + 30 days	AE, SAE, MAE, NDCMC
3	Within 30 days of any Stage 1 vaccination	Safety	Vax 1 date or Vax 2 date	Vax 1 date +30 days or Vax 2 date +30 days	AE, SAE, MAE, NDCMC
4	During Stage 1 vaccination phase	Safety	Visit 1 date	Visit 4 date	AE, SAE, MAE, NDCMC
5	During Stage 1 follow-up phase	Follow-up Stage 1	Visit 4 date +1	Visit 5 date	SAE, MAE, NDCMC
6	Throughout Stage 1	Safety	Visit 1 date	Visit 5 date	SAE, MAE, NDCMC
7	During booster vaccination phase	Booster vax safety	Visit 10 date	Visit 11 date (or end of booster vaccination day)	AE, SAE, MAE, NDCMC
8	During booster vaccination follow-up phase	Follow-up booster	Visit 11 date + 1, or end of booster vaccination date + 1 for early withdrawal subjects	Visit 12 date	SAE, MAE, NDCMC
9	Throughout booster phase	Booster safety	Visit 10 date	Visit 12 date	SAE, MAE, NDCMC

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

Three analysis intervals will be applied to immediate AEs (Table 7).

Table 7. Analysis Intervals for Immediate AEs

No.	Analysis Interval	Analysis Population	Interval Start Date/Time (Inclusive)	Interval Stop Date/Time (Inclusive)
1	Vaccination 1	Vax 1 safety	Vax 1 time	Vax 1 time + 30 minutes
2	Vaccination 2	Vax 2 safety	Vax 2 time	Vax 2 time + 30 minutes
3	Booster vaccination	Booster vax safety	Booster vax time	Booster vax time +30 minutes

Abbreviation: vax = vaccination.

3.5.2. Reactogenicity Data

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

Reactogenicity data will be recorded in the e-diary from the day of each vaccination (Day 1), following investigational product administration, to Day 7. Local reactions will be collected only for the left arm, which is the MenABCWY or bivalent rLP2086 injection site. See Table 8.

Table 8. Analysis Interval for Reactogenicity Data

No.	Analysis Interval	Analysis Population	Interval Start Date (Inclusive)	Interval Stop Date (Inclusive)
1	Vaccination 1	Vax 1 safety	Vax 1 date	Vax 1 date + 6 days (or until resolved day)
2	Vaccination 2	Vax 2 safety	Vax 2 date	Vax 2 date + 6 days (or until resolved day)
3	Any Stage 1 Vaccination	Safety	Vax 1 or Vax 2 date	Vax 1 or Vax 2 + 6 days (or until resolved day)
4	Booster Vaccination	Booster safety	Booster vax date	Booster vax + 6 days (or until resolved day)

Abbreviation: vax = vaccination.

3.5.2.1. Local Reactions Endpoints

Local Reaction Presence (Proportion of Subjects Reporting Each Local Reaction)

For each local reaction, the derivation of whether or not the specific reaction occurred on each day and "any day (Days 1 to 7)" will be made. The variable will be calculated for each vaccination as well as overall reactions for any vaccination. The derivation of this variable is given in Table 9 below.

Table 9. Derived Variables for Local Reactions

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

a. For redness and swelling, "mild," "moderate," or "severe" categories are based on the caliper size reported in the e-diary and as defined in Table 10.
b. For redness and swelling, "none" means 0 to 4 caliper units reported in the e-diary.

A caliper (measuring device) is used to measure the redness or swelling of the injection site area. Caliper units (range: 1-21+) are converted to cm, with 1 caliper unit equal to 0.5 cm, then categorized as none, mild, moderate, or severe based on the grading scale in Table 10. Pain at the injection site will be assessed by the subject/parent/legal guardian according to the grading scale in Table 11.

Table 10. Grading of Redness and Swelling at Injection Site

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

Table 11. Grading of Pain at Injection Site

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

Maximum Severity for Local Reaction

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

= ., if values are missing for all Days 1-7;

= 0, if the subject/parent/legal guardian reports all reactions as 'none' or a combination of missing and 'none' for all Days 1-7;

= *highest grade* (maximum severity) within 7 days of vaccination, if the answer is not 'none' for at least 1 day.

Duration of Each Local Reaction

For subjects experiencing any local reactions (or those with derived reactions as defined in Table 9), the maximum duration (last day of reaction – first day of reaction +1) will be derived for the study vaccination. Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event ends if it is unresolved during the subject diary-recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing.

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

Subjects with no reported reaction have no duration.

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

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

[redacted]

[redacted]

3.5.2.2. Systemic Events Endpoints

Subjects will be asked to assess severity of each systemic event according to Table 12 below.

Table 12. Grading of Systemic Events

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

Abbreviation: IV = intravenous.

Severe vomiting will be queried and if confirmed as an error will be excluded from the analysis.

Oral temperature will be recorded in the e-diary, in the evening, daily for 7 days after each vaccination and at any time during the 7 days when fever is suspected. The highest temperature for each day will be recorded as well. The protocol defines fever as an oral temperature ≥38.0°C (≥100.4°F), with severity scales shown in Table 13 and Table 14.

Table 13. Severity Scale for Fever for Stage 1

38.0-38.4°C
38.5-38.9°C
39.0-40.0°C
>40.0°C

Table 14. Severity Scale for Fever for Stage 2

38.0-38.4°C
>38.4-38.9°C
>38.9-40.0°C
>40.0°C

Temperatures <35.0°C and >42.0°C will be excluded from the analysis.

The original temperature scale (Table 13) was used in Stage 1 reporting and the updated temperature scale (Table 14) will be used in Stage 2 analyses.

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

1. Each systemic event on each day (Days 1 to 7) after each vaccination.

2. Each systemic event on any day (Days 1 to 7) after each vaccination and any vaccination.

3. Any systemic event on any day (Days 1 to 7) after each vaccination and after any vaccination.

4. Maximum severity of each systemic event on any day (Days 1 to 7) after each vaccination and any vaccination.

5. Maximum duration of each systemic event after each vaccination.

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

3.5.2.3. Use of Antipyretic Medication

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

The following variables will be derived:

1. Use of antipyretic medication on each day (Days 1 to 7) after each vaccination.

2. Use of antipyretic medication on any day (Days 1 to 7) after each vaccination and any vaccination.

3. Maximum duration of use of antipyretic medication after each vaccination.

3.6. Study Conduct

3.6.1. E-Diary Completion

For any given day, an e-diary will be transmitted and considered as complete if all expected data (the 3 local reactions and the 6 systemic events [including fever]) are available. If all data are missing for all items on the e-diary, for all days following vaccination, the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all days are available (ie, not missing) and data are valid. Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

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

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

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

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

3.6.2. Nonstudy Vaccines and Concomitant Medications

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the informed consent document (ICD) up to Visit 11 will be recorded on the CRF. If the subject 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. Similarly, if the subject has received any prior meningococcal vaccines or vaccines containing 1 or more ACWY group, the trade name (if known) and date of administration will be recorded on the CRF.

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 12 will be recorded in the CRF.

The use of antipyretic and other pain medications received by the subject on the day prior to investigational product administration will be recorded in the CRF.

Permitted during the study:

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed.

- Nonstudy vaccines (other than any meningococcal vaccines or vaccines containing 1 or more ABCWY groups, or vaccines containing all or individual antigens included in tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed [Tdap]) that are part of recommended immunization schedules are allowed any time during the study but should not be administered within 14 days (for nonlive vaccines) or 28 days (for live vaccines) of study vaccine administration.

- Antipyretic medication may be administered.

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

- Topical antibiotics are permitted.

- Topical and inhaled corticosteroids are permitted.

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

4. ANALYSIS SETS

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

The PAC population will include subjects in bivalent rLP2086 Groups 2 and 4 (bivalent rLP2086+MenACWY-CRM) only.

4.1. Full Analysis Set

A Stage 1 intent-to-treat (ITT) population will be defined and will include all subjects who are randomized at Visit 1. A Stage 2 ITT population will be defined as all subjects who signed the ICD at Visit 7.

4.2. Modified Intent-to-Treat Population

All randomized subjects who have received at least 1 study vaccination and who have at least 1 valid and determinate primary strain MenB or MenA/C/W/Y assay result available at any time point from Visit 1 to Visit 4 will be included in the modified intent-to-treat (mITT) population for Stage 1.

The mITT population for Stage 2 is defined as all subjects who signed the ICD at Visit 7 and who have at least 1 valid and determinate primary strain MenB or MenA/C/W/Y assay result available in Stage 2.

The mITT population will be analyzed according to the investigational product to which subjects were randomized (see handling of mis-stratified subjects in Section 4.5).

Subjects included in the pilot cohort will be included in the Stage 1 mITT population for immunogenicity analyses.

4.3. Per-Protocol Analysis Set (Evaluable Immunogenicity Population)

The per-protocol analysis set will be referred to as the evaluable immunogenicity population, which is the primary population for the primary immunogenicity objective assessments.

All randomized subjects who are included in the Stage 1 mITT population as well as who meet the following criteria will be included in the Stage 1 evaluable immunogenicity population. The Stage 1 MenB strain secondary immunogenicity endpoints will also be reported on this population.

1. Were randomized to the study group of interest.

2. Were eligible throughout the study, ie, fulfilling all of the inclusion criteria and none of the exclusion criteria at each visit where eligibility criteria were collected and confirmed.

3. Received all investigational products as randomized.

4. Had blood drawn for assay testing within the required time frames at Months 0 (Visit 1: before Vaccination 1) and 7 (Visit 4: 1 month after Vaccination 2: window 28-42 days).

5. Had valid and determinate assay results for the proposed analysis.

6. Had received no prohibited vaccines or treatment.

7. Had no other major protocol violations as determined by the sponsor's global medical monitor.

The booster evaluable immunogenicity population includes subjects who were eligible for the study (ie, meet all Stage 1 eligibility criteria as well as continually meeting Stage 2 eligibility criteria), received a booster dose as intended (the same vaccine as they received in Stage 1), had blood drawn for assay testing within the required time frame at Month 55 (Visit 11), and had a valid and determinate MenB or MenA/C/W/Y assay result after the booster dose, as well as no major protocol violations as determined by the sponsor's global medical monitor.

The evaluable immunogenicity population is the analysis population for assessing the primary immunogenicity objective. Specifically, this includes the evaluable immunogenicity US subset that would be used to assess the primary objective of the study. The evaluable immunogenicity population is also the analysis population for assessing the secondary immunogenicity MenB endpoint in Stage 1.

The Stage 1 mITT population is the analysis population for assessing the ACWY endpoint in Stage 1.

The booster evaluable immunogenicity population is the analysis population for assessing the ACWY and serogroup B endpoints following the booster dose.

The Stage 2 mITT population is the analysis population for assessing the secondary immunogenicity endpoint of antibody persistence.

The Stage 1 mITT population will also be used to perform additional analysis for serogroup B endpoint assessment in Stage 1.

[redacted]

[redacted]

4.4. Safety Analysis Set

The safety population will be used for all safety analyses and will be defined for each stage of the study.

1. The safety population for Stage 1 will include subjects who have received at least 1 dose of investigational product during Stage 1 and for whom safety data are available.

2. The safety population for Stage 2 will include subjects who received the booster vaccination and for whom safety data are available.

For the safety analysis, subjects will be analyzed according to the investigational product received.

Separate safety populations will be defined for each vaccination visit: Vaccination 1, Vaccination 2, follow-up phase for Stage 1, persistence phase, booster vaccination visit, and follow-up phase for Stage 2.

1. Vaccination 1 safety population: this population will include subjects who receive the first dose of investigational product (MenABCWY+saline or bivalent rLP2086+ MenACWY-CRM) at Visit 1, and for whom safety information from Visit 1 to prior to Visit 3 is available.

2. Vaccination 2 safety population: this population will include subjects who receive the second dose of investigational product (MenABCWY or bivalent rLP2086) at Visit 3, and for whom safety information from Visit 3 up to and including Visit 4 is available.

3. Follow-up safety population for Stage 1: this population will include subjects who receive at least 1 dose of investigational product and for whom safety information is available from after Visit 4 up to and including Visit 5.

4. Persistence safety population: this population will include all subjects who signed the ICD at Visit 7. This population is analogous to the Stage 2 ITT population.

5. Booster vaccination safety population: this population will include all subjects who receive the booster dose of investigational product (MenABCWY or bivalent rLP2086) at Visit 10, and for whom safety information from Visit 10 up to and including Visit 11 is available.

6. Follow-up safety population for Stage 2: this population will include all subjects who receive the booster dose of investigational product and for whom safety information is available from after Visit 11 up to and including Visit 12.

7. Booster safety population: this population will include all subjects who receive the booster dose of investigational product at Visit 10, and for whom safety information from Visit 10 up to and including Visit 12 is available.

The safety analysis set is the primary population for the safety endpoints.

Subjects who are withdrawn early after booster vaccination during Stage 2 will be included in the follow-up safety population for Stage 2, in case they have any type of AEs in the booster vaccination follow-up interval.

4.5. Treatment Misallocation

- Randomized into the wrong ACWY stratum: these subjects will be included in the mITT population for immunogenicity analyses if data are available and will be reported under the ACWY strata according to their true ACWY history (ACWY experience recorded on the CRF for prior ACWY history). Subjects who received prior polysaccharide meningococcal vaccine or subjects whose prior ACWY history is unknown will also be included in the mITT population as ACWY experienced. Subjects will also be included in the Stage 1 evaluable immunogenicity population as the analyses using this population are independent of ACWY history (Groups 2 and 4 combined). These subjects will also be included in the safety population for the safety analysis and will be reported under the ACWY strata according to true ACWY history.

  A subject's true ACWY history will be ascertained programmatically from the prior meningococcal vaccine data set in the clinical database. Subjects having received prior monovalent C meningococcal vaccines will be determined by the sponsor's global medical monitor. Please refer to Section 6.2.1 and Section 6.2.1.2 as to how data from subjects having received prior monovalent C meningococcal vaccines will be reported for immunogenicity endpoints relating to MenA/C/W/Y strains.

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

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

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

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Hypothesis testing will be performed on the US evaluable subjects alone to meet the PAC objective. Similar hypothesis testing will be performed on US and ex-US subjects (combined) included in the evaluable immunogenicity Stage 1 population.

Testing will be performed on the 5 coprimary MenB endpoints, which include a 4-fold rise from baseline in hSBA titers for each of the 4 primary strains (A22, A56, B24, and B44) and the composite response (hSBA titer ≥ LLOQ for all 4 primary strains combined) 1 month after the second vaccination in Stage 1.

The lower limits of the 2-sided 95% confidence intervals (CIs) must exceed each of the target lower limit for the confidence interval (LCI) values presented in Table 15 for the null hypothesis to be rejected.

The null hypothesis will be that the true proportion of subjects is less than or equal to the target LCI criterion for 1 or more coprimary endpoints. The alternative hypothesis is that the true proportion of subjects for all of the coprimary immunogenicity endpoints exceeds the target LCI.

Table 15. Target Lower Limit of the 2-Sided 95% Confidence Interval Criteria

	Primary Endpoint Test Strain (Variant)	Target LCI Criterion (%)
hSBA titer fold rise ≥4 from baseline	PMB80 (A22)	75
	PMB2001 (A56)	85
	PMB2948 (B24)	55
	PMB2707 (B44)	60
Composite response (hSBA titer ≥ LLOQ for all 4 strains combined)		65

Abbreviations: hSBA = serum bactericidal assay using human complement; LCI = lower limit of the confidence interval; LLOQ = lower limit of quantitation.

5.2. General Methods

Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation (SD), minimum, and maximum. Descriptive statistics for categorical variables are: n, percentage, and total (N).

All CIs for proportions will be 2-sided 95% intervals obtained using the exact Clopper-Pearson method as described by Agresti.[1]

5.2.1. Analyses for Binary Data

5.2.1.1. Exact Confidence Intervals

The exact CI for a proportion will be computed using the F distribution. If *r* equals the number of responses and *n* equals the number of subjects, then it follows that $p = r / n$ is the estimate of the proportion of responses. An exact 95% CI (or Clopper-Pearson confidence limit) can be computed by solving the following 2 equations. For the lower limit p_L, use

$$p_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$ and for the upper limit p_U, use

$$p_U = \frac{(r+1)F_U}{(n-r) + (r+1)F_U}$$

where F_L is the quantile from the F distribution for α=0.025, with numerator degrees of freedom equal to 2r and denominator degrees of freedom equal to 2(n-r+1). F_U is the quantile from the F distribution for α=0.975, with numerator degrees of freedom equal to 2(r+1) and denominator degrees of freedom equal to 2(n-r). When r equals 0, F_L should be set equal to 1.0 so that p_L equals 0. When r equals n, F_U should be set equal to 1.0 so p_U equals 1. The CI using the F distribution is described in Collett (1991).[2]

5.2.1.2. Immunogenicity Data

Each primary MenB strain has a validated LLOQ value defined, and each secondary MenB strain and each ACWY serogroup has a qualified LLOQ (Table 16).

Table 16. Validated hSBA LOD and LLOQs for Primary MenB Strains and Qualified LLOQs and LODs for Secondary MenB Strains and ACWY Assays

Strain/Serogroup Type	Strain Variant/Serogroup	LOD	LLOQ
Primary MenB	A22	1:4	1:16
	A56	1:4	1:8
	B24	1:4	1:8
	B44	1:4	1:8
Secondary MenB	A29	1:4	1:8
	A06	1:4	1:16
	A12	1:4	1:16
	A07	1:4	1:8
	A15	1:4	1:8
	A19	1:4	1:16
	B16	1:4	1:8
	B09	1:4	1:8
	B03	1:4	1:8
	B15	1:4	1:8

Table 16. Validated hSBA LOD and LLOQs for Primary MenB Strains and Qualified LLOQs and LODs for Secondary MenB Strains and ACWY Assays

Strain/Serogroup Type	Strain Variant/Serogroup	LOD	LLOQ
ACWY	MenA	1:4	1:8
	MenC	1:4	1:8
	MenW	1:4	1:8
	MenY	1:4	1:8

Abbreviations: ACWY = *Neisseria meningitidis* group A, C, W, Y; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = *Neisseria meningitidis* serogroup B.

All hSBA titers assessed for either MenB or MenA/C/W/Y will be analyzed as follows. At each visit where assay titers are analysed (Visits 1, 2, 3, 4, 7, 8, 9, 10, and 11), subjects with hSBA titers ≥ LLOQ will be derived as follows:

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

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

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

Similarly for all hSBA titers assessed, binary variables of assay results at each visit where assay titers are analyzed and who achieve a specific threshold (≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128) will also be derived.

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

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

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

A composite response will be computed for Stage 1, 1 month after the second vaccination (Visit 4). The composite response is defined as subjects who have assay results that are ≥ LLOQ for all 4 of the primary MenB strains at the same visit.

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

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

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

[redacted]

[redacted]

In Section 6.4, a supportive analysis is included describing different handling of missing values for the composite response.

For MenB-related endpoints, the 4-fold response in assay titers from baseline (Visit 1 prevaccination) to 1 month after the second vaccination (Visit 4) will be defined as follows:

- For subjects with a baseline hSBA titer < LOD or an hSBA titer of <1:4, a 4-fold response is defined as an hSBA titer of ≥1:16 or the LLOQ (whichever titer is higher).
- For subjects with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ.
- For subjects with a baseline hSBA of > LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.

The 4-fold response variable for the 4 MenB primary strains will be computed as:

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

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

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

5.2.1.3. Safety Data

All safety endpoints (including reactogenicity data recorded from the e-diary and AE data recorded from the CRF) will be summarized with percentages and 95% exact CIs (Clopper-Pearson method) for each group. The difference in the percentages (Group 1 – Group 3) and 2-sided 95% CIs for the difference will be provided to compare the secondary endpoints of reactogenicity, AEs, SAEs, MAEs, NDCMCs, and immediate AEs. The CIs of the difference will be computed using the Miettinen-Nurminen method.[3]

The CIs presented for the safety data will not be used to test hypotheses but will be used to determine which events may need further clinical investigation. No adjustment for multiplicity is needed.

5.2.2. Analyses for Continuous Data

5.2.2.1. Geometric Mean Titers

GMTs will be computed for each hSBA titer for MenB and MenA/C/W/Y strains. If the hSBA result is below LLOQ, it will be set to ½ the LLOQ for the GMT calculation. The assay results at each blood sampling time point will be (natural-log) logarithmically transformed for analysis. GMTs are obtained by log transformations of indicated values, averaging the log values, then exponentiating the result. The associated 2-sided 95% CIs will

be constructed by back transformation of the confidence limits computed for the mean of the logarithmically transformed assay results using Student's t distribution.

5.2.2.2. School and Work Days Missed

Days on which a subject missed school and/or work because of an AE will be captured on the AE checklist. The data captured at each visit will be summed and a total number of days obtained.

5.3. Methods to Manage Missing Data

5.3.1. Immunogenicity Data

As assay data are expected to be missing completely at random, the primary analysis for the primary objectives will be based upon the observed, determinate observations. No imputation will be performed. The proportion of subjects with missing immunogenicity data may be summarized at each blood sampling visit for each primary MenB strain. The denominator will be the ITT population (all randomized). The category of missing reasons (quantity not sufficient [QNS], indeterminate, not done, dropout) may also be summarized. Similar summaries may also be performed to evaluate the proportion of missing hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers.

If 10% or more of the subjects in any strata have missing hSBA data for the 4 primary MenB strains, a sensitivity analysis using mixed-effects model with repeated measures (MMRM) for Groups 2 and 4 will be applied for the primary MenB strains (GMT). The MMRM uses maximum likelihood estimation under the assumption that the missingness is at random (MAR). To account for the intrasubject correlation among the repeated measures, an unstructured covariance matrix will be used. In case the model does not converge, further covariance structures will be explored (ie, first-order autoregressive, compound symmetry).

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

Race categories other than White, Black, or Asian will be combined into a separate category termed "Other."

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

These analyses will use the mITT population, using ½ LLOQ to impute the hSBA values below LLOQ for the primary strains only.

Similar to GMT, GLIMMIX will be utilized. The response variables are binary variables (composite response and 4-fold response) and a Logit link will be used. The model will be similar to the above. As 4 out of 5 endpoints (4-fold responses) will not have a response at Visit 1, the GLIMMIX model will use baseline hSBA titer as covariate and blood sampling time points at Visits 2, 3, and 4 as repeated dependent variables. The composite response

analyses will be similar to the GMT analyses, with composite responses at all 4 visits modeled as dependent variables. This analysis will only be applied to the mITT population. The model-estimated response rates and the 95% CI will be summarized for each of the 5 coprimary endpoints at each applicable time point.

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

5.3.2. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in the safety rulebook summary.

5.3.2.1. Reactogenicity Data

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

The reactogenicity data are collected in the e-diary, which does not allow subjects to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the subject on that day are nonmissing. The e-diary transmission and completion status will be summarized per Section 6.6.3. The e-diary completion summary will provide the missing data information on the reactogenicity data.

Based on data from available studies, the missing data on reactogenicity are minimal, which is consistent with Li et al (2011).[4] No sensitivity analysis is planned for reactogenicity data.

6. ANALYSES AND SUMMARIES

For immunogenicity analysis, Groups 2 and 4 (bivalent rLP2086+MenACWY-CRM) and Groups 1 and 3 (MenABCWY) will be combined for MenB analysis, while MenA/C/W/Y analysis will be reported and analyzed per individual group separately.

6.1. Primary Endpoints

The primary immunogenicity and primary safety endpoints will be summarized for Stage 1 of the study. Report summaries will combine subjects in Groups 2 and 4. Subject data listings may also be produced.

6.1.1. Primary Immunogenicity Endpoints

The 5 coprimary endpoints will be descriptively summarized by reporting the number of subjects with valid and determinate primary MenB assay titers at baseline and 1 month post–Vaccination 2. The number of subjects who have a ≥4-fold rise from baseline will be displayed by the 4 MenB primary strains along with the associated percentage and 2-sided 95% CIs. The composite response will also be similarly displayed (see Table 17).

The 2-sided 95% CIs for the proportions of subjects meeting each of the 5 primary endpoints will be calculated using the Clopper-Pearson method described in Section 5.2.1.1. The analysis will be performed on Groups 2 and 4 combined.

The primary analysis and hypothesis testing will be conducted on the Stage 1 evaluable immunogenicity population. If the LCI of subjects in the Stage 1 evaluable population exceeds the corresponding target LCI for each strain and the composite (Table 15), the null hypothesis will be rejected.

The evaluation for the 5 coprimary endpoints will be performed for the US evaluable subjects separately as well as on all evaluable subjects.

A similar analysis will be performed on the Stage 1 mITT population.

Table 17. Analysis for Primary Immunogenicity Endpoints

Stage of Study	Objective	Randomized Groups	Analysis Time Point	Analysis Population(s)	Variant/Strain	Analysis Endpoint
Stage 1	MenB immune response after 2 doses of bivalent rLP2086	2+4	Visits 1 and 4 (baseline, post–Vaccination 2 blood draw)	Stage 1 evaluable immunogenicity – US subjects only, Stage 1 evaluable immunogenicity, Stage 1 mITT, Stage 1 mITT – US subjects only	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	Composite response (proportion of subjects achieving an hSBA titer ≥ LLOQ for all 4 strains)
						Subjects achieving at least a 4-fold increase in hSBA titer from baseline for each of the 4 strains

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = *Neisseria meningitidis* serogroup B; mITT = modified intent-to-treat.

6.1.2. Primary Safety Endpoints

Safety endpoint data will be summarized according to vaccine received. The safety population at each corresponding AE analysis interval (Table 6, Table 7, and Table 8) will be used for the analysis of each AE endpoint. The primary safety endpoints will be displayed for the Stage 1 safety populations and Groups 2 and 4 combined. The primary safety endpoints for booster vaccination will be displayed for the booster safety population for Groups 1 through 4.

6.1.2.1. Local Reactions and Systemic Events

The derived variables for the presence of each local reaction, each systemic event, any local reaction, and any systemic event occurring within 7 days following each vaccination will be summarized.

The presence and maximum severity of each reaction/event and any reaction/event within 7 days (over all Days 1 to 7) after each vaccination and any vaccination will be summarized through proportions of subjects, percentages, and associated 95% Clopper-Pearson CIs.

For each local reaction and systemic event, the maximum duration of each reaction/event will be descriptively summarized for each vaccination. Only subjects experiencing the reaction/event will be included in the analysis.

Use of antipyretic medication will also be displayed by the number of subjects and percentage who used antipyretic medication on each day and any day after each vaccination and any vaccination. Maximum duration of use will also be summarized by vaccination.

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

The number and percentage of subjects experiencing at least 1 SAE/MAE/NDCMC and the number of events will be descriptively summarized according to the analysis intervals in Table 6 with 95% exact CIs (Clopper-Pearson method) for the percentages (see Section 5.2.1.1).

Summaries will be displayed by system organ class (SOC) and preferred term (PT, coded with MedDRA) and reported in accordance with the Pfizer reporting standards. All displays will be sorted in alphabetical order within SOC and PT. Subjects reporting events with the same SOC or PT will only be counted once; however, all events reported will be included in the number of events.

6.1.2.3. Adverse Events

Adverse events will be summarized similarly to SAEs/MAEs/NDCMCs (Section 6.1.2.2) per the analysis interval described in Table 6. Nonserious AEs are not required to be reported during the follow-up phase. However, if nonserious AEs during the follow-up phase were recorded in the database (excluding MAEs and nonserious NDCMCs), these data will be listed in the overall AE listing.

Note that for the analysis interval of vaccination phase, the AEs will be summarized by SOC and PT with number and percentage of subjects reporting each event and number of events. Subjects reporting events with the same SOC or PT will only be counted once, but all events reported will be included in the number of events. Percentages and 95% CIs will also be provided.

6.1.2.4. Immediate Adverse Events

The number and percentage of subjects reporting AEs occurring within the 30-minute observation period immediately after vaccination will be summarized according to the analysis intervals defined in Table 7. These summaries will include 95% Clopper-Pearson's CIs.

6.1.2.5. School and Work Days Missed

The total number of days a subject missed school and/or work will be descriptively summarized for subjects in Stage 1 and in Groups 2 and 4 combined. Similar descriptive summaries will be presented for the subjects missing school and/or work after booster vaccination in Groups 1 through 4.

6.2. Secondary Endpoints

6.2.1. Secondary Immunogenicity Endpoints

Stage 1 secondary immunogenicity endpoint data will be summarized according to randomized vaccine for subjects included in the Stage 1 mITT population. The Stage 1 MenB strain endpoints will also be summarized on the Stage 1 evaluable immunogenicity population. Vaccine misallocations concerning vaccine history and ACWY strata as described in Section 4.5 will apply.

Persistence will be summarized for subjects included in the Stage 2 mITT populations. Booster vaccination will be summarized for subjects included in the booster evaluable immunogenicity population.

For immunogenicity endpoints relating to MenACWY strains, subjects in the experienced ACWY stratum who received monovalent C vaccine will only contribute to the serogroup C analyses, while subjects who received quadrivalent vaccine will contribute to the full serogroup analyses.

6.2.1.1. Bivalent rLP2086 Immune Response Secondary Objectives

Immune response data will be combined for vaccine Groups 2 and 4 for the Stage 1 analyses for secondary endpoints. Immune response data will be reported for subjects in Groups 2 and 4 combined for the booster analyses for secondary endpoints.

The Stage 1 analysis for secondary endpoints will be descriptively summarized on the 4 MenB primary strains as well as the 10 MenB secondary strains. Analyses of hSBA titers obtained at the analysis time points detailed in Table 18 will be summarized accordingly.

The number and percentage of subjects meeting the following analysis endpoint criteria outlined in Table 18 will be summarized. Primary and secondary strain LLOQs are defined in Table 16. The 2-sided 95% CIs for the proportions of subjects meeting each of the analysis endpoints will be calculated using the Clopper-Pearson method described in Section 5.2.1.1.

The GMTs at each analysis time point and for each strain as outlined below will also be summarized. See Section 5.2.2.1 for calculation of GMTs.

A listing of assay data will be provided by vaccine group, analysis time point, and MenB strain.

[redacted]

[redacted]

Table 18. Analysis for Bivalent rLP2086 Immune Response Secondary Objectives

Stage of Study	Objective	Randomized Groups	Analysis Time Point	Analysis Population(s)	Strains	Analysis Endpoint
Stage 1	MenB response after 2 doses of bivalent rLP2086	2+4	Visits 1 and 4 (baseline and post–Vaccination 2 blood draw)	Stage 1 evaluable immunogenicity, Stage 1 mITT	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	Subjects with hSBA titer ≥ LLOQ for each strain
						Subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each strain
						hSBA GMTs for each strain
			Visits 1 and 4 (baseline and post–Vaccination 2 blood draw)		PMB3175(A29) PMB3010(A06) PMB824(A12) PMB3040(A07) PMB1672(A15) PMB1989(A19) PMB648(B16) PMB866(B09) PMB1256(B03) PMB431(B15)	Subjects with hSBA titer ≥ LLOQ for each strain
						Subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each strain
						hSBA GMTs for each strain
Booster	MenB response after bivalent rLP2086 booster dose	2+4	Visits 4, 10, and 11 (post–Vaccination 2, pre–booster vaccination, postbooster blood draw)	Booster evaluable immunogenicity	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	Subjects with hSBA titer ≥ LLOQ for each strain

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = *Neisseria meningitidis* serogroup B.

6.2.1.2. MenABCWY Immune Response Secondary Objectives

MenABCWY immune response data for hSBA-MenA, hSBA-MenB, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers will be descriptively summarized. Descriptive comparisons between vaccine groups will also be displayed for the Stage 1 data. For MenB strain response, as all subjects are naïve to MenB vaccine at entry, comparisons will be between the combined strata vaccine groups (Groups 2+4 versus Groups 1+3). For ACWY strain response, comparisons will be between vaccine groups within ACWY strata (Groups 1 versus 2 and Groups 3 versus 4).

Experienced ACWY strata subjects who only received prior vaccination with monovalent C vaccine will be excluded from immune response assessments for strains MenA/W/Y and will only be included in MenC assessments.

The empirical reverse cumulative distribution curves (RCDCs) will be presented graphically using a step function for each of the 4 primary MenB strains and the hSBA-MenA/C/W/Y strains at Visits 1, 2, and 4. Additional RCDC curves may be presented for persistence and booster analysis time points for the 4 primary MenB strains and the hSBA-MenA/C/W/Y strains.

Immune response in the 4 primary MenB strains and in the hSBA-MenA/C/W/Y strains on blood draw data obtained prior to receiving the booster vaccination will be summarized.

Descriptive analyses on each of the hSBA titers at various analysis endpoints and for the analysis timelines as defined in Table 19 will be similarly summarized as described in Section 6.2.1.1.

Table 19. Analysis for MenABCWY Immune Response Secondary Objectives

Stage of Study	Objective	Randomized Groups	Analysis Time Point	Analysis Population(s)	Strain/Serogroup	Analysis Endpoint
Stage 1	ACWY response after 1 dose of MenABCWY vs 1 dose of MenACWY-CRM	1 vs 2 and 3 vs 4	Visit 2 (post–Vaccination 1 blood draw)	Stage 1 mITT	MenA MenC MenW MenY	Subjects with hSBA titer ≥1:8 (or LLOQ, whichever is higher)[a] for each strain
						Subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each strain
						hSBA GMTs for each strain
	ACWY response after 2 doses of MenABCWY vs 1 dose of MenACWY-CRM	1 vs 2 and 3 vs 4	Visit 4 (MenABCWY, post–Vaccination 2 blood draw) Visit 2 (MenACWY-CRM, post–Vaccination 1 blood draw)	Stage 1 mITT	MenA MenC MenW MenY	Subjects with hSBA titer ≥1:8 (or LLOQ, whichever is higher) for each serogroup
						Subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each serogroup
						hSBA GMTs for each serogroup
	MenB response after 2 doses of MenABCWY vs 2 doses of bivalent rLP2086	1+3 vs 2+4	Visits 1 and 4 (baseline and post–Vaccination 2 blood draw)	Stage 1 evaluable immunogenicity, Stage 1 mITT	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	Composite response (proportion of subjects achieving an hSBA titer ≥ LLOQ for all 4 strains)
						Subjects achieving at least a 4-fold increase in hSBA titer from baseline for each of the 4 strains
						Subjects with hSBA titer ≥ LLOQ for each strain
						Subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each strain
						hSBA GMTs for each strain

Table 19. Analysis for MenABCWY Immune Response Secondary Objectives

Stage of Study	Objective	Randomized Groups	Analysis Time Point	Analysis Population(s)	Strain/Serogroup	Analysis Endpoint
	ABCWY response after MenABCWY vs MenACWY-CRM/bivalent rLP2086 at all blood sampling time points prior to booster dose (during Stage 1)	1+3 vs 2+4	Visits 1, 2, 3, and 4 (baseline, post–Vaccination 1 blood draw, Vaccination 2, post–Vaccination 2 blood draw)	Stage 1 evaluable immunogenicity, Stage 1 mITT	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	Subjects with hSBA titer ≥ LLOQ for each strain
						Subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each strain
						hSBA GMTs for each strain
		1 vs 2 and 3 vs 4	Visits 1, 2, 3, and 4 (baseline, post–Vaccination 1 blood draw, Vaccination 2, post–Vaccination 2 blood draw)	Stage 1 mITT	MenA MenC MenW MenY	Subjects with hSBA titer ≥1:8 (or LLOQ, whichever is higher) for each serogroup
						Subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each serogroup
						hSBA GMTs for each serogroup
Persistence	ABCWY response after MenABCWY vs MenACWY-CRM/bivalent rLP2086 at all blood sampling time points prior to booster dose (during Stage 2)	1+3 vs 2+4	Visits 1, 4, 7, 8, 9, and 10 (baseline, post–Vaccination 2 blood draw, antibody persistence blood draws 1-3, before booster vaccination)	Stage 2 mITT	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	Subjects with hSBA titer ≥ LLOQ for each strain
		1 vs 2 and 3 vs 4	Visits 1, 4, 7, 8, 9, and 10 (baseline, post–Vaccination 2 blood draw, antibody persistence blood draws 1-3, before booster vaccination)	Stage 2 mITT	MenA MenC MenW MenY	Subjects with hSBA titer ≥1:8 (or LLOQ, whichever is higher) for each serogroup

Table 19. Analysis for MenABCWY Immune Response Secondary Objectives

Stage of Study	Objective	Randomized Groups	Analysis Time Point	Analysis Population(s)	Strain/Serogroup	Analysis Endpoint
Booster	ABCWY response after MenABCWY booster dose	1+3 and 2+4	Visits 4, 10, and 11 (post–Vaccination 2 blood draw, before booster vaccination, postbooster blood draw)	Booster evaluable immunogenicity	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	Subjects with hSBA titer ≥ LLOQ for each strain
		1 vs 3	Visits 4, 10, and 11 (post–Vaccination 2 blood draw, before booster vaccination, postbooster blood draw)	Booster evaluable immunogenicity	MenA MenC MenW MenY	Subjects with hSBA titer ≥1:8 (or LLOQ, whichever is higher) for each serogroup

Abbreviations: ACWY = ACWY = *Neisseria meningitidis* group A, C, W, Y; GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA = *Neisseria meningitidis* serogroup A; MenB = *Neisseria meningitidis* serogroup B; MenC = *Neisseria meningitidis* serogroup C; MenW = *Neisseria meningitidis* serogroup W; MenY = *Neisseria meningitidis* serogroup Y.

a. The hSBA titer ≥1:8 (or LLOQ, whichever is higher) is identical to hSBA titer ≥1:8 since LLOQs for the ACWY serogroups have all been confirmed to be 1:8.

[redacted]

[redacted]

6.2.2. Secondary Safety Endpoints

Safety endpoint data will be summarized according to vaccine received and reported in the ACWY strata based on prior vaccine history (see Section 4.5). The safety population at each corresponding analysis interval (Table 6, Table 7, and Table 8) will be used for the analysis of each endpoint. The secondary safety endpoints will be displayed for the Stage 1 safety populations in Groups 1 and 3.

Further statistical analyses will be performed on reactogenicity and AE data specified in the following sections to evaluate the safety profile of MenABCWY.

Listings may be provided by vaccine group and by vaccination.

6.2.2.1. Local Reactions and Systemic Events

Descriptive summary reports will be generated according to each vaccination (Vaccination 1, Vaccination 2, booster) and after any vaccination in Stage 1 and will be similarly displayed as the summary output described in Section 6.1.2.1.

The difference in proportions of subjects (Group 1 – Group 3) who report any reaction or event and severe reactions or events reported after any vaccination in Stage 1 may be presented. The corresponding 2-sided 95% CI of the difference in percentages will be computed using the Miettinen-Nurminen method.

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

Descriptive summary reports will be generated according to all of the analysis intervals defined in Table 6 and will be similarly displayed as the summary output described in Section 6.1.2.2.

Additionally, the differences in subjects in each vaccine group (Group 1 – Group 3) reporting at least 1 SAE, MAE, or NDCMC after any vaccination in Stage 1 may be summarized. The corresponding 2-sided 95% CI of the difference in percentages will be computed using the Miettinen-Nurminen method.

6.2.2.3. Adverse Events

Descriptive summary reports will be generated for AEs reported during the Stage 1 and booster vaccination phases (analysis intervals 1, 2, 3, 4, and 7 in Table 6) and will be similarly displayed as the summary output described in Section 6.1.2.3.

The differences in subjects in each vaccine group (Group 1 – Group 3) reporting at least 1 AE during the Stage 1 vaccination phase may be summarized. The corresponding 95% CIs will also be computed using the Miettinen-Nurminen method.

6.2.2.4. Immediate Adverse Events

The number and percentage of subjects reporting AEs occurring within the 30-minute observation period immediately after vaccination will be summarized according to the analysis intervals defined in Table 7. These summaries will include 95% Clopper-Pearson CIs.

Additionally, statistical analyses similar to Section 6.2.2.3 will be conducted on subjects experiencing an immediate AE after any vaccination in Stage 1.

6.2.2.5. School and Work Days Missed

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

6.2.2.6. Sensitivity Safety Analysis

No sensitivity analyses are planned for safety data.

6.3. Exploratory Endpoints

6.3.1. Bivalent rLP2086 Immune Response Exploratory Objectives

Subjects in the Stage 1 evaluable immunogenicity population will be used for analysis. hSBA titers obtained 1 month after Dose 1 (Visit 2) will be descriptively summarized. The 5 coprimary endpoints will be reported similarly to the primary immunogenicity endpoint (Section 6.1.1).

Additionally, the proportion of subjects with hSBA titer ≥ LLOQ for each MenB strain as well as hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 will be summarized similarly as described in Section 6.2.1.1. Descriptive statistics on the GMTs as defined in Section 5.2.2.1 will also be provided.

The hSBA GMTs for each MenB strain at Visit 11 will be summarized in Groups 2 and 4 combined for 1 month after the booster vaccination. See Table 20.

Table 20. Analysis for Bivalent rLP2086 Immune Response Exploratory Objectives

Stage of Study	Objective	Randomized Groups	Analysis Time point	Analysis Population(s)	Strain	Analysis Endpoint
Stage 1	MenB response after 1 dose of bivalent rLP2086	2+4	Visits 1 and 2 (baseline and post–Vaccination 1 blood draw)	Stage 1 evaluable immunogenicity	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	Composite response (proportion of subjects achieving an hSBA titer ≥ LLOQ for all 4 strains)
						Subjects achieving at least a 4-fold increase in hSBA titer from baseline for each of the 4 strains
						Subjects with hSBA titer ≥ LLOQ for each strain
						Subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 for each strain
						hSBA GMTs for each strain
Booster	MenB response after booster dose	2+4	Visits 4, 10, and 11 (post–Vaccination 2, pre–booster vaccination, postbooster blood draw)	Booster evaluable immunogenicity	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	hSBA GMTs for each strain

Abbreviations: GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB = *Neisseria meningitidis* serogroup B.

6.3.2. Analysis for MenABCWY Immune Response Exploratory Objectives

Subjects in the booster evaluable immunogenicity population will be used for analysis. See Table 21.

Table 21. Analysis for MenABCWY Immune Response Exploratory Objectives

Stage of Study	Objective	Randomized Group	Analysis Time Point	Analysis Population(s)	Strain/Serogroup	Analysis Endpoint
Booster	ACWY immune response after booster dose	2 vs 4	Visits 4, 10, and 11 (post–Vaccination 2, pre–booster vaccination, postbooster blood draw)	Booster evaluable immunogenicity	MenA MenC MenW MenY	Subjects with hSBA titer ≥1:8 (or LLOQ, whichever is higher)[a] for each serogroup
	ABCWY immune response after booster dose	1+3	Visits 4, 10, and 11 (post–Vaccination 2, pre–booster vaccination, postbooster blood draw)	Booster evaluable immunogenicity	PMB80(A22) PMB2001(A56) PMB2948(B24) PMB2707(B44)	hSBA GMTs for each strain
		1 vs 3	Visits 4, 10, and 11 (post–Vaccination 2, pre–booster vaccination, postbooster blood draw)	Booster evaluable immunogenicity	MenA MenC MenW MenY	hSBA GMTs for each strain

Abbreviations: ABCWY = ACWY = *Neisseria meningitidis* group A, B, C, W, Y; GMT = geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA = *Neisseria meningitidis* serogroup A; MenC = *Neisseria meningitidis* serogroup C; MenW = *Neisseria meningitidis* serogroup W; MenY = *Neisseria meningitidis* serogroup Y.

a. The hSBA titer ≥1:8 (or LLOQ, whichever is higher) is identical to hSBA titer ≥1:8 since LLOQs for the ACWY serogroups have all been confirmed to be 1:8.

[redacted]

[redacted]

6.4. Additional Immunogenicity Analysis

Subjects who received prior polysaccharide meningococcal vaccine or subjects whose prior ACWY history is unknown are included in the mITT population as described in Section 4.5. Additional sensitivity analyses of the secondary immunogenicity endpoints relating to MenA/C/W/Y strains described in Table 19 may be performed by removing these subjects from the mITT population. Similar additional analyses may be done by removing from the analyses those subjects who received nonstudy meningococcal vaccines at any point between Visits 1 and 4.

An additional supportive analysis using the evaluable population (US and overall) is planned for the composite response (described in Section 5.2.1.2). For this supportive analysis, subjects with an assay titer < LLOQ for any of the 4 primary MenB strains will be defined as a nonresponder (composite response = 0) rather than have the status of missing.

Positive predictive value (PPV) analyses of secondary strain response for a given primary strain response within the primary strain subfamily will be performed at 1 month after the second vaccination using the evaluable immunogenicity population. For a specific time point, the PPV between a primary and secondary strain will be defined as follows: for the subjects who had titers ≥ LLOQ for the primary strain, the percentage of subjects who have titers ≥ LLOQ for the secondary strain. The calculation will require available data for both the primary and secondary strains.

Additional analyses may be performed to investigate the relationship of hSBA titers between the pre–booster dose time point and the post–booster dose time point for MenA, MenC, MenW, and MenY test strains separately for MenACWY-naïve and -experienced MenABCWY and Menveo groups. Scatterplots (with Pearson correlation coefficients) of pre–booster dose hSBA titers versus fold-rises from the pre–booster dose time point to the post–booster dose time point using the booster evaluable immunogenicity population will be provided. Similar analyses may be performed for Dose 1 and Dose 2 using the Stage 1 mITT population.

6.5. Subset Analyses

Subgroup analyses may be performed on the primary and secondary immunogenicity (excluding analyses on the secondary MenB strains) and safety endpoints described in Section 6.1 and Section 6.2. No subgroup analyses are planned for rare events (endpoints with less than 1% of subjects in any group). Subgroups include age strata (10 to <18 years of age; 18 to <26 years of age), sex, race, ethnicity, and geographic location (US; ex-US). Race categories other than White, Black, or Asian will be combined into the "other" category for the analysis.

Additional exploratory or subset analyses to investigate the association of the primary and secondary MenB strains with demographic characteristics may be further explored.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Subject Disposition, Vaccine Administration, and Blood Sampling

All subjects in the ITT population will be included in the disposition summaries. Summaries will be displayed by randomized vaccine group separately, Groups 1 and 3 combined, and Groups 2 and 4 combined. Screen failures and reasons for screen failure may be included in a separate tabulation.

Separate disposition summaries will be produced for each stage of the study. The following will be included in the Stage 1 summary:

- N and % of subjects included in each study population (ITT, mITT, evaluable immunogenicity)
- N and % of subjects receiving each vaccination
- N and % of subjects completing the Stage 1 vaccination phase and follow-up phase
- N and % of subjects who withdrew during the vaccination phase (Visits 1 to 4) and reason for withdrawal
- N and % of subjects who withdrew during the follow-up phase (after Visit 4 to Visit 5) and reason for withdrawal

The following will be included in the Stage 2 summary:

- N and % of subjects included in each study population (ITT, mITT, evaluable immunogenicity)
- N and % of subjects receiving booster vaccination
- N and % of subjects completing the Stage 2 vaccination phase and follow-up phase
- N and % of subjects who withdrew during the booster phase (Visits 10 to 11) and reason for withdrawal
- N and % of subjects who withdrew during the booster follow-up phase (after Visit 11 to Visit 12) and reason for withdrawal

For each blood draw, the number and percentage of subjects randomized, vaccinated at each visit (Visits 1, 3, and 10 for Stage 2 subjects), and providing blood samples within the protocol-specified time frame as well as before and after the specified time frame will be tabulated for each stage of the study by randomized vaccine group, Groups 1 and 3 combined, and Groups 2 and 4 combined.

Subject data listings for subjects who are included and excluded from each of the analysis populations and reason for exclusion may be provided by randomized vaccination group. A listing of protocol deviations will also be provided.

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

6.6.2. Demographic, Medical History, and Baseline Characteristics

The ITT population will be used to generate these tables. All summaries in Stage 1 will be presented for each randomized vaccine group separately, Groups 1 and 3 combined, and Groups 2 and 4 combined. Summaries/listings in Stage 2 will be presented by vaccine group.

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

Medical history and baseline physical examinations will be descriptively summarized.

Subject data listings may be provided by randomized vaccination group.

6.6.3. E-Diary Completion

E-diary compliance as defined in Section 3.6.1 will be summarized for each dose (Vaccination 1, Vaccination 2, and booster) by vaccine group, Groups 1 and 3 combined, Groups 2 and 4 combined, and total compliance using descriptive statistics. The safety population will be used to generate the summary reports. The denominator for the e-diary compliance rates will be the total number of subjects who received the specific vaccination.

6.6.4. Nonstudy Vaccine and Concomitant Medications

Nonstudy vaccines and concomitant medications captured throughout the study (Stage 1) will be descriptively summarized separately for subjects in the safety population. Separate summaries will be provided for each stage of the study. The listings of nonstudy vaccines and concomitant medications will be provided for Stage 2.

Antipyretic and other pain medication reported the day prior to vaccine administration will be summarized separately from the concomitant medications and for each vaccination separately. Prior meningococcal vaccine history will be summarized descriptively. Prior PRP-OMP vaccine history will be summarized descriptively.

Subject data listings may be provided by vaccination group.

6.7. Safety Summaries and Analyses

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

6.7.1. Reactogenicity Data

Local reactions and systemic events will be summarized according to Section 6.1.2.1 and Section 6.2.2.1.

An overall listing of reactogenicity data and a separate listing of all severe local reactions and systemic events as well as any reported Grade 4 fever will be provided.

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

6.7.2. Adverse Events

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

The number and percentage of subjects reporting at least 1 AE and the total number of events will be reported and will be summarized by SOC and PT. Associated 95% exact CIs will also be displayed. Summary of AEs occurring in at least 1% of subjects in any group may also be presented.

Listings of AEs/SAEs/MAEs/NDCMCs and immediate AEs may be provided for the Stage 1 safety population and the Stage 2 safety population separately and sorted by analysis interval within each stage.

6.7.2.1. Related Events

Adverse events and SAEs deemed by the investigator to be related to study vaccine will be summarized separately for each stage of the study. The denominator for the percentages will be the safety population for the study stage.

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

6.7.2.2. Severe Events

Adverse events deemed severe by the investigator may be summarized separately for each stage of the study. The denominator for the percentages will be the safety population for the study stage.

The number and percentage of subjects reporting at least 1 severe AE and the total number of severe events will be reported and will be summarized by SOC and PT. Associated 95% exact CIs will also be displayed.

6.7.2.3. Adverse Events and Research-Related Injuries

Such events occurring during the 48-hour period after each blood draw at Visits 7, 8, and 9 will be included in a subject data listing. The denominator for the percentages will be the persistence safety population.

6.7.2.4. Neuroinflammatory and Autoimmune Conditions

A list of PTs to include all of the neuroinflammatory and autoimmune conditions will be provided by the medical monitor prior to database lock. These events can be SAEs or AEs. A listing of conditions matching this PT list may be provided.

6.7.2.5. AEs Leading to Study Withdrawal

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

6.7.2.6. Deaths

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

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis is planned for this study.

One additional reporting event will be performed when subjects have completed the postbooster blood draw (Visit 11), which occurs 1 month after the booster dose.

The final analysis for Stage 2 will be done after all the available data through the end of the study have been collected.

7.2. Interim Analyses and Summaries

No formal interim analysis is planned for this study.

7.3. Pilot Cohort Safety Assessment

The sponsor will be unblinded to the 10 subjects included in the pilot cohort. Enrollment will be on hold until the safety assessment is complete. The sponsor's IRC will review each subject's 7-day e-diary and AE data after Vaccination 1 to determine if the safety,

[redacted]

[redacted]

reactogenicity, and tolerability profile of MenABCWY is satisfactory and supports further enrollment into the study.

7.4. Unblinding

7.4.1. Ongoing Safety Assessments

An external data monitoring committee (EDMC) will review accumulated unblinded safety data throughout the study. The unblinded randomization codes will be released to an ISC prior to the DMC meeting. The ISC is not part of the sponsor's organization and is a statistical team not involved in the conduct of the study. The ISC will produce the unblinded safety reports and provide them to the EDMC members through a secure portal independent of the sponsor. The EDMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. A separate charter will be developed for the EDMC that will include details on timing, responsibility, and reporting.

7.4.2. Assessment of Variability of MenA/C/W/Y Endpoints

Immediately before study unblinding after Visit 5, a sponsor unblinded statistician will access ACWY serology data to compute SDs. The blinded study team will remain blinded until the study unblinding as described in Section 7.4.3.

7.4.3. Unblinding of Stage 1 Data

Once all subjects complete Stage 1, Visit 5, the Stage 1 data (up to and including Visit 5) will be cleaned. The subjects will be unblinded and Stage 1 immunogenicity and safety analyses will be conducted at this time on the locked, unblinded Stage 1 data.

Stage 2 analyses (persistence and booster analyses) will occur once the Stage 2 subjects complete the study and the database is cleaned and ready for analysis.

8. REFERENCES

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

2. Collett D. Statistical inference for binary data. Chapter 2. In: Modelling binary data. London, England: Chapman & Hall; 1991:17-42.

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

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