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

Investigational Product Number:	PF-05212366
Investigational Product Name:	*Neisseria meningitidis* Serogroup B Bivalent Recombinant Lipoprotein 2086 Vaccine (Bivalent rLP2086)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	2016-004421-17
Protocol Number:	B1971057
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	09 July 2019	• Added edits included in the administrative letters dated 13 July 2018, 18 February 2019, and 29 March 2019. • Opened enrollment in Stage 2 to ACWY-experienced subjects in addition to ACWY-naïve subjects. This is based on the recommendation from the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) to obtain data on the persistence of the immune response after 2 doses of MenABCWY as well as on the safety and immunogenicity of the booster response in individuals who had previously received an ACWY-containing vaccine. • Moved the booster dose safety endpoints from secondary to primary safety endpoints. These changes were made in consideration of a potential schedule that would include a booster for adolescents Safety of the booster dose was, therefore, reprioritized to a primary safety endpoint. • Moved some immunogenicity endpoints (related to persistence evaluation) from secondary to exploratory endpoints. As booster responses were not previously assessed for MenABCWY, certain secondary immunogenicity endpoints for persistence and booster response were reconsidered and deemed more appropriate as exploratory endpoints. • Removed the 1:4 endpoint for ACWY strains for the persistence and booster endpoints. As the ACWY assay qualification had established that the lower limit of quantitation (LLOQ) could not be qualified at the start of the study, but subsequently qualified prior to unblinding with the LLOQ ≥1:8 for all 4 serogroups, the 1:4 titer was uninterpretable and therefore removed from analysis. • Added LLOQs for the ACWY strains. This was added because the LLOQ was established during assay qualification. • Updated the grading for redness and swelling in the mild and moderate categories in Table 7 to be consistent with the analyses performed in Stage 1.
Amendment 1	23 August 2017	• Addition of edits included in the administrative letter dated 24 February 2017. • Increase in Visit 6 and 7 windows to allow additional time for unblinding of all subjects prior to Visit 6 completion. • Increase in the volume of the subset blood draws at Visits 1, 2, and 4 from 50 to 100 mL to support assay development. The volume of blood drawn will depend on the consent obtained. • Addition of a subset of subjects having a 100-mL blood draw at Visit 11 rather than 20 mL. • Correction in Section 3.1 of the duration of Stage 1 participation for subjects in the ACWY-naive stratum.

Document	Version Date	Summary of Changes and Rationale
		• Clarification of laboratory testing personnel blinding status in Section 5.3. • Clarification added to Sections 9.5.2 and 9.6 as to what the primary analysis population is for MnB and MenA/C/W/Y responses. • Addition of an optional blood draw of 50 mL of whole blood at Visit 4 at designated sites. Several changes were made throughout this protocol amendment to adjust blood volumes collected at Visit 4 and to modify language in order to allow whole blood sample testing for exploratory purposes. Additional exploratory analyses will be performed on study samples to augment vaccine assay development.
Original Protocol	16 January 2017	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale

Neisseria meningitidis is an obligate human pathogen that colonizes the upper respiratory tract and in some individuals can cause serious, life-threatening disease. Under certain instances that are not well understood, *N meningitidis* is capable of invading the human host, leading to bacteremia, which then manifests as life-threatening invasive meningococcal disease (IMD). Five (5) *N meningitidis* serogroups (groups A, B, C, W, and Y) currently cause virtually all IMD globally. In the United States, meningococcal disease is primarily caused by groups B, C, and Y, which are responsible for approximately 64% of disease across all ages.

Temporal variations in IMD incidence occur naturally. In industrialized countries, disease rates range from 0.1 cases per 100,000 individuals during endemic periods to 5 to 15 or more cases per 100,000 individuals during prolonged epidemics. In the United States, prevention of meningococcal disease through vaccination has been focused on routine immunization of adolescents and also individuals identified at increased risk of disease due to either medical or situational factors.

Results from Phase 2 Study B1971012, a randomized, single-blind, multicenter trial conducted in Europe comparing the safety and immunogenicity of bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086) administered using various 2- and 3-dose schedules, demonstrated the safety and immunogenicity of bivalent rLP2086 administered on a 2-dose 0- and 6-month schedule; these results supported the licensure of bivalent rLP2086 (Trumenba®) in the United States under Accelerated Approval (AA) regulations. As part of the AA approval, a Phase 3 postmarketing commitment is required to confirm the data observed in Phase 2. This study will fulfill the Food and Drug Administration (FDA) postapproval requirement (PAR) to verify and describe the clinical benefit of a 2-dose schedule for the use of bivalent rLP2086 administered at Months 0 and 6 in healthy subjects ≥10 years to <26 years of age.

In the United States, it is recommended to routinely immunize 11- to 12-year-olds with a meningococcal group A, C, W, and Y conjugate vaccine (MenACWY) (as a single dose), followed by the addition of a booster vaccination at 16 years of age. The recommendation and use of meningococcal vaccines differ in other regions. Monovalent meningococcal group C vaccines have been used in a number of ex-US countries and continue to be administered in response to increases in disease (eg, Italy). In the United Kingdom, there has been an increase in group W disease, and a campaign has started to vaccinate adolescents with quadrivalent meningococcal conjugate vaccines (ie, MenACWY). France has also seen recent group B outbreaks and has responded with local (as opposed to national) vaccination campaigns to manage the outbreaks.

Recommendations remain complicated for preventive immunization against IMD due to the different age groups targeted for MenACWY and *N meningitidis* group B (MnB) vaccination, the dosing regimens for the different vaccines, and regional differences. Currently, no

combination pentavalent (containing groups A, B, C, W, and Y) meningococcal vaccine is available.

Development and licensure of a pentavalent vaccine for the prevention of IMD due to groups A, B, C, W, and Y would allow for optimization of the current schedules, offer the possibility of using a single vaccine to meet the current recommendations, and offer a comprehensive approach to prevent meningococcal disease against all 5 disease-causing *N meningitidis* groups (A, B, C, W, and Y).

Pfizer intends to develop a pentavalent meningococcal vaccine (*N meningitidis* group A, B, C, W, and Y vaccine [MenABCWY]) by combining bivalent rLP2086 and Nimenrix® (meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine [MenACWY-TT]). This study is primarily designed to fulfill the FDA PAR to verify the clinical benefit of a 2-dose schedule for the use of bivalent rLP2086 administered at Months 0 and 6 in healthy subjects 10 years to <26 years of age. This study will also describe the safety, tolerability, and immunogenicity of MenABCWY, and describe the immune response to groups A, C, W, and Y following administration of MenABCWY, or bivalent rLP2086 and a meningococcal group A, C, W-135, and Y conjugate vaccine (MenACWY-CRM).

Objectives and Endpoints

Primary Immunogenicity Objective:	Primary Immunogenicity Endpoints:
• To assess the immune response induced by bivalent rLP2086 as measured by serum bactericidal assay using human complement (hSBA) performed with 4 primary MnB test strains, 2 expressing a lipoprotein 2086 (LP2086) subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the second vaccination, in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.	Five (5) coprimary endpoints are defined for the primary objective; they are defined for hSBA performed with each of the 4 primary test strains: PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44). • One (1) 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 in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined. • Four (4) 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 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 titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.
Primary Safety Objectives:	**Primary Safety Endpoints:**

• 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, medically attended AEs, and immediate AEs, following Vaccinations 1 and 2 in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.	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 medication 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 medically attended 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]).

	• 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 newly diagnosed chronic medical condition 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. • Subject days missing school or work because of AEs during the Stage 1 vaccination phase (Visit 1 though Visit 4).

• To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, newly diagnosed chronic medical conditions, medically attended AEs, and immediate AEs, after the booster vaccination.
 	
• To describe the safety profile of bivalent rLP2086, as measured by local reactions, systemic events, AEs, SAEs, newly diagnosed chronic medical conditions, medically attended AEs, and immediate AEs, after the booster vaccination.
	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 medically attended 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]).
	  • 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 newly diagnosed chronic medical condition 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. • Subject days missing school or work because of AEs.

Study Design

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 and placebo (saline), or bivalent rLP2086 and MenACWY-CRM. All subjects will be naive to any meningococcal group B vaccine prior to enrollment. Randomization will be stratified by prior vaccination history; approximately 795 ACWY-naive subjects and 795 ACWY-experienced (having received 1 prior dose of a 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 US investigative sites and 270 subjects from ex-US countries will be randomized. Regional stratification will ensure sufficient population representation.

The study will be conducted in 2 stages as shown below. In order to support assay development, a subset of up to approximately 600 subjects 18 to 25 years of age will have up to 100 mL, rather than 20 mL, of blood drawn at Visits 1, 2, and 4. Additionally, at designated sites, an additional optional whole blood sample of approximately 50 mL will be obtained at Visit 4 from up to approximately 30 subjects 18 to 25 years of age. This sample will be used for exploratory purposes.

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 1 will be observer-blinded and Stage 2 will be open-label.

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-Naive 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 to100 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 at Vaccination 1. Pilot cohort subjects will not receive saline at Vaccination 1.

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-Naive 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)	

Investigational Products

For this study, the investigational products are bivalent rLP2086 (Trumenba), MenABCWY (consisting of MenACWY-TT [Nimenrix] and bivalent rLP2086 [Trumenba]), MenACWY-CRM (Menveo), and placebo. Any reference to normal saline or placebo refers to a solution containing 0.85% sodium chloride and water for injection. The placebo solution is also referred to as "saline" throughout the protocol.

Statistical Methods

Both hypothesis testing and estimation will be performed. The hypothesis-testing component will address the need to confirm the immunogenicity of bivalent rLP2086 administered at Months 0 and 6 in all subjects 10 through 25 years of age, using prespecified criteria for the primary MnB immunogenicity endpoints. Safety of bivalent rLP2086 administered at Months 0 and 6 will also be described. Immunogenicity and safety information for the MenABCWY arms will be described.

Hypothesis testing will be performed on the 5 coprimary MnB endpoints in all subjects, which includes a 4-fold rise from baseline in hSBA titers for each of the 4 primary strains and the composite response (hSBA titer ≥ LLOQ for all 4 primary strains combined) 1 month after the second vaccination. If the lower limit of the 2-sided 95% confidence interval exceeds each of the target lower limit of the confidence interval (LCI) values, the study's primary objective will be met.

The study sample size is mainly based on hypothesis-testing criteria to verify the clinical benefit of a 2-dose schedule for the use of bivalent rLP2086 administered at Months 0 and 6 in healthy subjects 10 years to <26 years of age. With 900 evaluable subjects in Group 2 and Group 4, the primary objectives (based on all 5 primary endpoints) will be met with a power of 95.2% as shown in the table below.

Overall Power to Meet the Primary Objectives

	Primary Endpoint Test Strain (Variant)	LCI Criteria	Study B1971012 0- and 6-Month Responses With 95% Confidence Interval (%)[a]	Number of Evaluable Subjects	Power
hSBA titer fold rise ≥4 from baseline	PMB80 (A22)	LL of 95% CI >75%	82.3 (76.3, 87.3)	900	99.97%
	PMB2001 (A56)	LL of 95% CI >85	90.1 (85.1, 93.8)	900	99.60%
	PMB2948 (B24)	LL of 95% CI >55	64.5 (57.4, 71.1)	900	99.99%
	PMB2707 (B44)	LL of 95% CI >60	66.0 (58.9, 72.6)	900	95.7%
Composite response (hSBA titer ≥ LLOQ for all of 4 primary strains combined)		LL of 95% CI >65	72.9 (65.9, 79.1)	900	99.92%

Overall Power to Meet the Primary Objectives

	Primary Endpoint Test Strain (Variant)	LCI Criteria	Study B1971012 0- and 6-Month Responses With 95% Confidence Interval (%)[a]	Number of Evaluable Subjects	Power
Overall power					95.2%

Abbreviations: hSBA = serum bactericidal assay using human complement; LCI = lower limit of the confidence interval; LL = lower limit; LLOQ = lower limit of quantitation.
a. The power calculation was based on Study B1971012 with a vaccine schedule of 0 and 6 months.

Assuming ~85% evaluable subjects, ~1060 subjects should be enrolled to receive bivalent rLP2086 and MenACWY-CRM.

An additional 530 subjects will be enrolled in the MenABCWY-MenABCWY regimen, which will allow a probability of 93.0% to observe at least 1 AE with a true incidence of 0.5%.

A total of 1590 subjects will therefore be enrolled into this study. The randomization will be performed separately for ACWY-naive and ACWY-experienced subjects. Equal numbers of subjects will be recruited into each stratum.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an 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 subject.

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					
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					

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]**
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	
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.

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]**

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 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 were 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 were ongoing on the last day that the e-diary was completed.
e. Checklist includes questions regarding newly diagnosed chronic medical conditions, medically attended adverse events, and missed days of school or work, as well as about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
f. Please refer to protocol Section 8.1.4.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086; Trumenba®) is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* group B. Bivalent rLP2086 is approved for use in individuals 10 through 25 years of age.

Pfizer intends to develop a pentavalent meningococcal vaccine (*N meningitidis* group A, B, C, W, and Y vaccine [MenABCWY]) by combining bivalent rLP2086 and Nimenrix® (meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine [MenACWY-TT]). The target indication for the candidate pentavalent vaccine is active immunization to prevent invasive disease caused by *N meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age.

1.2. Background and Rationale

1.2.1. Background of Disease and Medical Need

N meningitidis is an obligate human pathogen that colonizes the upper respiratory tract and in some individuals can cause serious, life-threatening disease. Transmission with *N meningitidis* is via contact with droplets from the upper respiratory tract, typically resulting in colonization and asymptomatic carriage in otherwise healthy individuals. Under certain instances that are not well understood, *N meningitidis* is capable of invading the human host, leading to bacteremia, which then manifests as life-threatening invasive meningococcal disease (IMD).[1] Twelve (12) serogroups of *N meningitidis* have been identified based on structural differences in their polysaccharide capsule. Five (5) of these groups (A, B, C, W, and Y) currently cause virtually all IMD globally.[2,3]

Temporal variations in IMD incidence occur naturally. In industrialized countries, disease rates range from 0.1 cases per 100,000 individuals during endemic periods to 5 to 15 or more cases per 100,000 individuals during prolonged epidemics.[3,4,5,6] In Europe, meningococcal disease has been declining in general over the past decade. This decline can be attributed, in part, to the introduction of meningococcal group C conjugate vaccine programs; however, IMD caused by *N meningitidis* group B (MnB) has also declined. In 2007, overall meningococcal rates were 3.76 per 100,000 in Ireland and 2.50 per 100,000 in the United Kingdom but had decreased to 1.99 in Ireland and 1.66 in the United Kingdom by 2011.[5,6] While IMD is at a historic low in the United States,[7] the Centers for Disease Control and Prevention (CDC) estimates that in 2014 approximately 450 cases of meningococcal disease occurred, resulting in a disease incidence nationally of 0.14 per 100,000 individuals.[8] In the United States, meningococcal disease is primarily caused by groups B, C, and Y, which are responsible for approximately 64% of disease across all ages.[8] Higher rates of meningococcal disease due to groups B and C are seen in younger individuals, whereas disease due to group Y tends to occur in older individuals.[8]

Results from Phase 2 Study B1971012, a randomized, single-blind, multicenter trial conducted in Europe comparing the safety and immunogenicity of bivalent rLP2086 administered using various 2- and 3-dose schedules, demonstrated the safety and

immunogenicity of bivalent rLP2086 administered on a 2-dose 0- and 6-month schedule; these results supported the licensure of bivalent rLP2086 in the United States under Accelerated Approval (AA) regulations. As part of the AA approval, a Phase 3 postmarketing commitment is required to confirm the data observed in Phase 2. This study will fulfill the Food and Drug Administration (FDA) postapproval requirement (PAR) to verify and describe the clinical benefit of a 2-dose schedule for the use of bivalent rLP2086 administered at Months 0 and 6 in healthy subjects ≥10 years to <26 years of age.

In the United States, prevention of meningococcal disease through vaccination has been focused on routine immunization of adolescents and also individuals identified at increased risk of disease due to either medical or situational factors. In the United States it is recommended to routinely immunize 11- to 12-year-olds with a meningococcal group A, C, W, and Y conjugate vaccine (MenACWY) (as a single dose), followed by the addition of a booster vaccination at 16 years of age.[9,10,11] In addition to these age-based recommendations for meningococcal vaccines, there are recommendations in place to vaccinate at-risk individuals aged ≥2 months to 55 years for meningococcal groups A, C, W, and Y and ≥10 years for meningococcal group B (MenB).[10,12]

The recommendation and use of meningococcal vaccines differ in other regions. Monovalent meningococcal group C vaccines have been used in a number of ex-US countries and continue to be administered in response to increases in disease (eg, Italy).[13] In the United Kingdom, there has been an increase in group W disease, and a campaign has started to vaccinate adolescents with quadrivalent meningococcal vaccines.[14,15] The United Kingdom is one of only a limited number of countries to recommend Bexsero in the infant population.[16] Over the past 10 years there have been outbreaks of meningococcal diseases recorded in Europe in varied settings, including kindergarten classes, nursery schools, and a family cluster.[17,18,19,20] France has also seen recent group B outbreaks and has responded with local (as opposed to national) vaccination campaigns to manage the outbreaks.[21]

Recommendations remain complicated for preventive immunization against IMD due to the different age groups targeted for MenACWY and MnB vaccination, the dosing regimens for the different vaccines, and regional differences. Currently, no combination pentavalent (containing groups A, B, C, W, and Y) meningococcal vaccine is available. Development and licensure of a pentavalent vaccine for the prevention of IMD due to groups A, B, C, W, and Y would allow for optimization of the current schedules in terms of convenience to patient and healthcare providers to prevent meningococcal disease in those considered at increased risk. A pentavalent vaccine would also offer the possibility of using a single vaccine to meet the current recommendations and the ability to simplify the interpretation of the schedule for vaccine providers. For example, in countries where MenACWY is recommended at 11 years of age, followed by a MenACWY booster approximately 5 years later, use of a pentavalent vaccine could address the recommendation for quadrivalent vaccination while also confer protection against MenB disease.

Meningococcal disease epidemiology is dynamic, and fluctuations in the prevalence of different groups are observed. Examples such as the increase in group W observed in the

United Kingdom and South America[14,22] illustrate the need for a comprehensive approach to prevent meningococcal disease both in terms of vaccine characteristics and implementation of any recommendations. Development of a safe and immunogenic pentavalent vaccine would support these aims.

1.2.2. Prior Clinical Experience

1.2.2.1. Bivalent rLP2086 (Trumenba)

Bivalent rLP2086 is composed of 2 recombinant lipidated factor H binding protein (fHBP) variants from MnB, one from fHBP subfamily A and one from subfamily B (A05 and B01, respectively).

Bivalent rLP2086 was approved on 29 October 2014, under 21 Code of Federal Regulations (CFR) 601 Subpart E - Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses, for active immunization of individuals aged 10 through 25 years to prevent invasive disease caused by meningococcal group B.

Approval of bivalent rLP2086 was based on demonstration of safety and a serological correlate that showed in Phase 2 studies the induction of serum bactericidal activity against 4 group B strains that are representative of the prevalent US strains. These were measured using serum bactericidal assays using human complement (hSBAs). As a requirement of licensure, Phase 3 studies were conducted to confirm the safety and immune responses associated with the 3-dose schedule. As of 21 January 2016, it is estimated that 21,607 subjects have participated in the bivalent rLP2086 clinical development program: 11,436 subjects were exposed to bivalent rLP2086. A total of 4145 subjects received bivalent rLP2086 in combination with the following: diphtheria, tetanus, and acellular pertussis, *Haemophilus influenzae* type b, and hepatitis B virus vaccine combined with inactivated poliomyelitis virus vaccine (DTaP-Hib-HBV+IPV)/Prevnar® (32); dTaP-IPV (372); quadrivalent human papillomavirus vaccine (HPV4) (992); quadrivalent meningococcal polysaccharide conjugate (MCV4)/tetanus, diphtheria, and acellular pertussis (Tdap) vaccine (884); or saline (1865). In addition, 417 subjects are currently receiving blinded therapy, and 5609 subjects have received control. The total unit distribution in the United States from launch through 21 January 2016 is approximately 210,380 doses.

Results from 11 Phase 1, 2, and 3 completed clinical trials concluded that robust functional and broadly protective immune responses were observed in individuals receiving bivalent rLP2086 on the 2-dose 0- and 6-month schedule in Phase 2 Study B1971012, and on a 3-dose schedule in the Phase 3 program (0-, 2-, and 6-month schedule), as measured in hSBAs that used MnB strains (4 primary or 10 additional) that were prospectively selected to represent the diversity of the target antigen fHBP. Each primary and each additional strain expressed fHBPs that were heterologous (to vaccine) fHBP variants.

Preliminary results of a persistence-of-immunity and booster study, B1971033, show that persistence of immunity following any of the 2- and 3-dose primary bivalent rLP2086 series schedules utilized in Study B1971012 follows similar patterns over 4 years. Of note, 4-year persistence immunity data were comparable following a 2-dose 0- and 6-month or 3-dose 0-,

2-, and 6-month primary bivalent rLP2086 series. Similarly, the immune response following a booster dose with bivalent rLP2086 4 years after the primary bivalent rLP2086 series resulted in high hSBA titers, irrespective of whether subjects received a 2-dose or 3-dose primary bivalent rLP2086 series. hSBA titers observed following the booster vaccination are higher than those seen 1 month following a 2- or 3-dose primary bivalent rLP2086 series.

Clinical studies also demonstrated that bivalent rLP2086 may be coadministered with MCV4, Tdap, HPV4, and dTap-IPV vaccines, which may facilitate introduction of bivalent rLP2086 into national immunization programs. In addition, a consistent favorable safety and reactogenicity profile supports the use of bivalent rLP2086 to prevent invasive MnB disease in individuals 10 years of age and older in the European Union (EU).

1.2.2.2. Nimenrix (MenACWY-TT)

Nimenrix is composed of capsular polysaccharides from each of the A, C, W, and Y groups of *N meningitidis* conjugated to tetanus toxoid.

Nimenrix was first approved in the EU on 20 April 2012 via the centralized procedure and is currently marketed in 67 countries. Nimenrix is not presently licensed in the United States, though there is an open investigational new drug application (IND) (BB-IND 13278). Licensure outside of the United States was based on safety and demonstration of immunologic noninferiority (based mainly on comparing proportions of subjects with serum bactericidal assay using rabbit complement [rSBA] titers of at least 1:8) to licensed meningococcal vaccines. Immunogenicity was measured using rSBA or hSBAs.

In the EU, Nimenrix is indicated for active immunization of individuals from the age of 12 months and above against IMD caused by *N meningitidis* groups A, C, W-135, and Y.

The cumulative number of subjects who have received Nimenrix within GlaxoSmithKline (GSK)-sponsored interventional studies is estimated to be 13,533 subjects in primary study groups and 992 in booster study groups (note that some subjects from booster study groups also participated in primary study groups). Additionally, 1991 subjects in primary study groups have received treatment that is still blinded to the GSK/Pfizer study team. Finally, 1219 subjects enrolled in the clinical development program for Nimenrix were vaccinated with a MenACWY-TT formulation other than the one that is currently on the market. Information on exposure is sourced from the clinical trial databases as of 19 October 2015.

Since launch in the EU to 30 September 2015, it is estimated that 2,953,217 doses of Nimenrix have been distributed. As vaccination with Nimenrix consists of 1 dose per subject in accordance with the local recommendations and assuming compliance with the vaccination schedule, the postmarketing exposure to Nimenrix is estimated to be 2,953,217 individuals.

The immunogenicity studies conducted in subjects from 12 months of age and above demonstrate that 1 dose of MenACWY-TT induces a response that is similar to or higher than the response induced by licensed meningococcal vaccines used as control, and that the

vaccine is able to induce an immunologic memory against the 4 meningococcal groups in individuals vaccinated as toddlers 12 to 14 months of age, historically an age group that is not responsive to meningococcal polysaccharide vaccines. Follow-up studies demonstrate that persistence of the responses elicited by the vaccine is similar or higher than persistence of those elicited by the licensed meningococcal polysaccharide vaccines Meningitec® and Mencevax® when assessed using the GSK rSBA. A variation is under review to extend the age indication to 6 weeks of age.

1.2.3. MenA, MenC, MenW, and MenY Functional Antibody Assays as a Surrogate of Efficacy

Meningococcal clearance from the bloodstream is primarily by complement-mediated bacteriolysis, and an effective complement system is critical for resistance against infections caused by *N meningitidis*. Individuals with complement deficiencies have an increased risk of developing meningococcal disease.[23,24] The in vivo complement-mediated bacteriolysis of meningococcus is mimicked by the in vitro serum bactericidal assay (SBA), a functional serological assay shown to be the surrogate of protection for meningococcal disease.[25]

For meningococcal group C conjugate vaccines, postlicensure efficacy estimates in the United Kingdom demonstrated that a cutoff of 1:8 in the rSBA was the most consistent with observed efficacy at 4 weeks after vaccination.[26] The established correlate of protection for the SBA-MenC assay using human serum as the exogenous complement source is a titer ≥1:4.[25,27] Even though no correlate of protection has been established for meningococcal groups A, W, and Y,[28] it is common practice to extend the 1:8 cutoff for rSBA using meningococcal groups A, W, and Y (rSBA-MenA, rSBA-MenW, and rSBA-MenY) and the 1:4 cut-off for hSBA-MenA, hSBA-MenW, and hSBA-MenY.[25,29]

hSBA responses have been used routinely as surrogates of efficacy and as the basis for licensure of MnB vaccines.[30,31] Outer membrane vesicle (OMV) vaccines have been deployed in some countries in response to outbreaks caused by specific epidemic MnB strains,[32] and large-scale efficacy studies with OMV vaccines have been conducted in Cuba, Brazil, Chile, Norway, and New Zealand.[33,34,35,36,37,38] In each instance, a relationship between responses measured by hSBA and protection from MnB disease was demonstrated[39] with a 1:4 cutoff for hSBA MnB as the correlate of protection.[25,27,40]

Use of hSBA in clinical trials of MenABCWY is scientifically reasonable as a surrogate of vaccine efficacy and necessary, because a traditional trial with an efficacy endpoint is not feasible because of the low incidence of meningococcal disease, <1/100,000 in the United States and Europe,[7,40,41] meaning that extremely large numbers of subjects (>100,000) would be required to support a statistically significant assessment.

1.2.4. Study Rationale

The study design is described in Section 3. This is a Phase 3 study to verify and describe the clinical benefit of a 2-dose schedule for the use of bivalent rLP2086 administered at Months 0 and 6 in healthy subjects 10 years to <26 years of age.

This study will also describe the safety, tolerability, and immunogenicity of MenABCWY, and describe the immune response to groups A, C, W, and Y following administration of MenABCWY, or bivalent rLP2086 and a meningococcal group A, C, W-135, and Y conjugate vaccine (MenACWY-CRM).

Pfizer considers the available information from prior studies with MenACWY-TT (PF-06866681) and bivalent rLP2086 (PF-05212366) sufficient to support an expectation of a favorable benefit-risk profile for this study using MenABCWY (PF-06886992).

Additional information for this compound (MenABCWY) may be found in the single reference safety document (SRSD), which for this study is the MenABCWY investigator's brochure (IB). Additional information for bivalent rLP2086 may be found in the SRSD, which for this study is the IB for bivalent rLP2086. The SRSD for the comparator agent MenACWY-CRM is the Menveo US package insert.

Refer to the most recent version of the MenABCWY IB for a summary of findings from nonclinical studies that potentially have clinical significance and from clinical studies that are relevant to this study. Also refer to the most recent version of the MenABCWY IB for a summary of the known and potential risks and benefits, if any, to human subjects.

Refer to the most recent version of the Menveo US package insert for a summary of the known and potential risks and benefits, if any, to human subjects.

2. STUDY OBJECTIVES AND ENDPOINTS

Subjects having received a vaccine containing 1 or more ACWY groups prior to enrollment will be randomized in the ACWY-experienced stratum but, for the purposes of A, C, W, and Y analyses, will be considered A, C, W, Y-naive or -experienced based on what group(s) were present in the prior ACWY-containing vaccine.

The secondary strain immunogenicity objective is based on hSBA results from subjects in Groups 2 and 4 using 10 test strains expressing the following variants: A29, A06, A12, A07, A15, A19, B16, B09, B03, and B15. Three (3) subsets of study subjects will be selected for this analysis. Each subset will be used to assess the response to 3 or 4 of the 10 secondary test strains in addition to the 4 primary test strains.

Primary Immunogenicity Objective:	Primary Immunogenicity Endpoints:

• To assess the immune response induced by bivalent rLP2086 as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the second vaccination, in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.	Five (5) coprimary endpoints are defined for the primary objective; they are defined for hSBA performed with each of the 4 primary test strains: PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).
	• One (1) 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 in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.
	• Four (4) 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 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 titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.

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

• 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, medically attended AEs, and immediate AEs, following Vaccinations 1 and 2 in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.	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 medication 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 medically attended 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]). • 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 newly diagnosed chronic medical condition 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. • Subject days missing school or work because of AEs during the Stage 1 vaccination phase (Visit 1 though Visit 4).

• To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, newly diagnosed chronic medical conditions, medically attended AEs, and immediate AEs, after the booster vaccination.
 	
• To describe the safety profile of bivalent rLP2086, as measured by local reactions, systemic events, AEs, SAEs, newly diagnosed chronic medical conditions, medically attended AEs, and immediate AEs, after the booster vaccination.
	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 medically attended 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]).
	  • 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 newly diagnosed chronic medical condition 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 missed, school or work, by the subject because of AEs after the booster vaccination.

Secondary Immunogenicity Objectives:	Secondary Immunogenicity Endpoints:
• To describe the immune response induced by bivalent rLP2086 as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the second vaccination, in the bivalent rLP2086 arms (Group 2 and 4 subjects) combined.	• 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 MnB test strains at Visit 4.
• To describe the MenB immune response as measured by hSBA performed with secondary MenB test strains measured 1 month after the second vaccination in Groups 2 and 4 combined.	The secondary immunogenicity endpoints for the subsets tested with the additional hSBA test strains are as follows: • Proportions of subjects with hSBA titers ≥ LLOQ (1:16 for A06, A12, and A19 and 1:8 for A07, A15, A29, B03, B09, B15, and B16) for each of the secondary test strains 1 month after the second vaccination. • Proportions of subjects with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the secondary test strains 1 month after the second vaccination. • hSBA GMTs for each of the secondary test strains 1 month after the second vaccination.
• To describe the immune response induced by 1 dose 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-naive and ACWY-experienced subjects separately.	• Proportions of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visit 2. • 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 Visit 2. • hSBA GMTs for each of the ACWY test strains at Visit 2.
• 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-naive and ACWY-experienced subjects separately.	• Proportions 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. • 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 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.

• 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 MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the second vaccination in the ACWY-naive and ACWY-experienced subjects combined.	• Proportions of subjects who achieve the 5 MnB 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 (1) 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 (4) 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.
	  • 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 titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.
	• 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 GMTs for each of the 4 primary MnB test strains at Visit 4.

• 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 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-naive 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-naive and ACWY-experienced subjects separately. • hSBA GMTs for each of the ACWY test strains at Visits 1 and 3, in the ACWY-naive 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-naive and ACWY-experienced subjects combined. • hSBA GMTs for each of the 4 primary MenB test strains at Visits 1 and 3, in the ACWY-naive 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 LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, at blood sampling time	• 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-naive and ACWY-experienced subjects separately. • Proportions of subjects with hSBA titers ≥ LLOQ for each

points prior to the booster vaccination (Stage 2).	of the 4 primary MenB test strains at Visits 7, 8, 9, and 10, in the ACWY-naive and ACWY-experienced subjects combined.
• To describe the immune response induced by MenABCWY, as measured by hSBA performed with ACWY and 4 primary MnB 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 (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.
• To describe the immune response induced by bivalent rLP2086, as measured by hSBA performed with 4 primary MnB 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.	• 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.
Secondary Safety Objectives:	**Secondary Safety Endpoints:**

• To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, newly diagnosed chronic medical conditions, medically attended AEs, and immediate AEs, after Vaccinations 1 and 2 in the ACWY-naive and ACWY-experienced subjects separately.	The following endpoints will be described after Vaccinations 1 and 2 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 reporting the use of antipyretic medication 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 medically attended 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]).

	• 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 newly diagnosed chronic medical condition 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 missed, school or work, by the subject because of AEs after vaccination.
Exploratory Objectives:	**Exploratory Endpoints:**
• 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 MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, 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 MnB 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 MnB 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-naive and ACWY-experienced subjects separately. • hSBA GMTs for each of the ACWY test strains at Visits 7, 8, 9, and 10, in the ACWY-naive 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-naive 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-naive and ACWY-experienced subjects combined.
• To further describe the immune response induced by MenABCWY, as measured by hSBA performed with ACWY and 4 primary MnB 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 MnB 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 MnB test strains at Visit 11, in Groups 1 and 3 combined.
• To further describe the immune response induced by bivalent rLP2086, as measured by hSBA performed with 4 primary MnB 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 MnB 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 MnB test strains at Visit 11, in Groups 2 and 4 combined.

3. STUDY DESIGN

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 and placebo, or bivalent rLP2086 and MenACWY-CRM. All subjects will be naive to any meningococcal group B vaccine prior to enrollment.

Randomization will be stratified by prior vaccination history; approximately 795 ACWY-naive subjects and 795 ACWY-experienced (having received 1 prior dose of a 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 US investigative sites and 270 subjects from ex-US countries will be randomized. Regional stratification will ensure sufficient population representation.

Enrollment targets will also be adjusted to achieve appropriate representation by age (subjects 10 to <18 years old and subjects 18 to <26 years old), age within ACWY strata, and ACWY strata within a geographic region. Additional details will be provided during pretrial assessment and site initiation visits.

The study will be conducted in 2 stages:

- Stage 1: from study entry (Visit 1) through Visit 6. See Table 1. A pilot cohort consisting of 10 subjects 18 to <26 years of age will first be enrolled at selected site(s). These pilot cohort subjects will be assigned to either Group 1 or 3, and therefore will receive MenABCWY at Vaccination 1. The sponsor will be unblinded to vaccine assignment for the pilot cohort. Seven (7) 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 pilot cohort subjects will proceed through the study. During Stage 1, the sponsor will be blinded to vaccine assignment beyond completion of pilot cohort enrollment (Section 5.4).

  In order to support assay development, a subset of up to approximately 600 subjects 18 to 25 years of age will have up to 100 mL, rather than 20 mL, of blood drawn at Visits 1, 2, and 4; and 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. Subject participation in this subset will be voluntary, and the volume of blood drawn will depend on the consent obtained. Stage 1 will be observer-blinded.

  At designated sites, an additional optional whole blood sample of approximately 50 mL will be obtained at Visit 4 from up to approximately 30 subjects 18 to 25 years of age. This sample will be used for exploratory purposes.

- Stage 2: from Months 18 to 60 (Visits 7 to 12). Subjects from both the 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. Stage 1 will be observer-blinded and Stage 2 will be open-label.

Table 1. 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-Naive 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)		

Table 1. Stage 1 Study Design

		Vaccination 1	Post–Vaccination 1 Blood Draw	Vaccination 2	Post–Vaccination 2 Blood Draw	Safety Telephone Call	Telephone Call
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 (up to 100 mL in subset)	20 mL (up to 100 mL in subset)	20 mL	20 mL (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 at Vaccination 1. Pilot cohort subjects will not receive saline at Vaccination 1.

Table 2. 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-Naive Subjects	Group 1(n ~132)		MenABCWY		
	Group 2 (n ~65)		Bivalent rLP2086 + MenACWY-CRM		

Table 2. 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-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)	

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.

3.1. Approximate Duration of Subject Participation

Subjects will participate in Stage 1 for approximately 18 months. This includes a telephone contact 6 months after the last Stage 1 study vaccination.

Subject participation in Stage 2 will last for approximately 4 years.

The total study duration for subjects who complete Stage 2 will be approximately 5 years (60 months).

3.2. Approximate Duration of Study

This study will be completed in approximately 66 months.

3.3. Approximate Number of Subjects

Approximately 1590 subjects will be randomized to participate in this study. Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal.

Approximately 394 subjects may continue into Stage 2. 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. Stage 1 will be observer-blinded and Stage 2 will be open-label.

4. SUBJECT ELIGIBILITY CRITERIA

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

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject (or parent(s)/legal guardian) has been informed of all pertinent aspects of the study.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male and female subject aged ≥10 and <26 years, at the time of randomization.

4. Subjects who have never received a prior dose, or who have received not more than 1 prior dose no sooner than 4 years prior to the date of randomization, of a vaccine containing 1 or more ACWY groups. Written confirmation of ACWY vaccination history should be obtained prior to randomization; however, if written ACWY vaccination history is not available, history obtained verbally from the subject (or parent(s)/legal guardian) is acceptable, if deemed reliable by the investigator.

5. Available for the entire study period and can be reached by telephone.

6. Healthy subject as determined by medical history, physical examination, and judgment of the investigator.

7. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout Stage 1 (through the follow-up telephone contact at Month 12), and from Visit 10 (booster vaccination) to Visit 11. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

8. Negative urine pregnancy test for all female subjects.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Previous vaccination with any meningococcal group B vaccine or any purely polysaccharide (nonconjugate) meningococcal vaccine. Written vaccination history should be obtained prior to randomization; however, if written vaccination history is not available, history obtained verbally from the subject (or parent(s)/legal guardian) is acceptable, if deemed reliable by the investigator.

2. Previous vaccination with >1 dose of a vaccine containing 1 or more ACWY group.

3. Subjects having received 1 prior dose of a vaccine containing 1 or more ACWY group <4 years prior to the date of randomization.

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

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

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

7. A known or suspected defect of the immune system that would prevent an immune response to the vaccine, such as subjects with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, intravenous, or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy. Subjects in the United States with terminal complement deficiency are excluded from participation in this study. Please refer to the study reference manual (SRM) for additional details.

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

9. Significant neurological disorder or history of seizure (excluding simple febrile seizure).

10. Receipt of any blood products, including immunoglobulin, within 6 months before the first study vaccination.

11. Current chronic use of systemic antibiotics.

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

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

14. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

15. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

16. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in Section 4.5.

4.3. Criteria for Temporarily Delaying Vaccine Administration

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

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

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

3. Subject has received a vaccine containing all or individual antigens included in Tdap vaccine within the previous 28 days.

4. Subject is less than 5 days into a course of systemic antibiotic therapy.

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

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

4.4. Criteria for Temporarily Delaying Blood Collection

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

1. Subject has received systemic antibiotic therapy within the last 5 days.

4.5. Lifestyle Requirements

4.5.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly throughout Stage 1 (through the follow-up telephone contact at Month 12), and from Visit 10 (booster vaccination) to Visit 11. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use.

At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.6. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study.

The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. INVESTIGATIONAL PRODUCTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product(s) to be provided are:

- Bivalent rLP2086 (bivalent rLP2086 and meningococcal group B vaccine [Trumenba] may be used interchangeably)
- MenABCWY, consisting of:
    - Bivalent rLP2086
    - MenACWY-TT (Nimenrix)
- MenACWY-CRM (Menveo)
- Placebo (normal saline). Any reference to normal saline or placebo refers to a solution containing 0.85% sodium chloride and water for injection. The placebo solution is also referred to as "saline" throughout the protocol.

The investigational products will be provided by the sponsor to each study site. Study vaccines will be packed into kits and labeled as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. Investigational product kits will be labeled with a unique dispensable unit (DU) or container number.

Subjects will receive investigational products at each of the vaccination visits (Visits 1, 3, and 10) according to Table 1 and Table 2.

5.1. Allocation to Investigational Product

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) system that is accessible 24 hours a day, 365 days a year. Having

logged in, the site personnel (study coordinator or specified designee) will be required to enter or select certain information including but not limited to the user's identification (ID) and password, protocol number, the subject number, if the subject should be considered ACWY naive or experienced, and the date of birth of the subject. The site personnel will then be provided with a subject randomization number and DU or container number. The randomization number and the date on which the randomization number was assigned will be recorded on the case report form (CRF). Once subject numbers, DU numbers, and randomization numbers have been assigned, they cannot be reassigned. The IRT system will provide a confirmation report containing the subject randomization number and DU or container number assigned. The confirmation report must be stored in the site's files.

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

5.2. Blinding of Site Personnel

In this observer-blinded study, the study staff dispensing, preparing, and administering the vaccine will be unblinded. All other study and site personnel, including the investigator, investigator staff, subjects, and subjects' parent(s)/legal guardian, will be blinded to investigational product assignments during Stage 1. In particular, the individuals who evaluate subject safety will be blinded during Stage 1. Because the study vaccines are different in physical appearance, the study vaccine syringes will be administered in a manner that prevents the study subjects from identifying the vaccine type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study subjects. Contact between the unblinded dispenser and study subjects and unblinded administrator and study subjects should be kept to a minimum. The remaining site personnel must not know investigational product assignments.

5.3. Blinding of the Sponsor

Those study team members who are involved in ensuring that protocol requirements for investigational product preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). An unblinded clinician who is not a direct member of the study team will review unblinded protocol deviations. All other study team members and all laboratory testing personnel performing serology assays will remain blinded to vaccine assigned/received throughout Stage 1 of the study to Visit 5. All laboratory testing personnel performing serology assays will also remain blinded to visit number throughout Stage 1 of the study.

5.4. Blinding of the Pilot Cohort

Depending on prior ACWY vaccination history, pilot cohort subjects will be assigned to either Group 1 or 3, and therefore will receive MenABCWY at Vaccination 1. For these

subjects only, the subjects, study personnel at the investigational site, and study personnel at the sponsor will be unblinded to vaccine assignment during Stage 1.

5.5. Breaking the Blind

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

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

5.5.1. Planned Unblinding

Pfizer will release unblinding information to the investigators after all subjects have completed Visit 5 and will inform the investigators prior to Visit 7 which subjects may be invited to progress to Stage 2. Additional information is included in the SRM.

The booster vaccination will be open-label.

5.6. Subject Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

5.7. Investigational Product Supplies

5.7.1. Dosage Form(s) and Packaging

Bivalent rLP2086 is a 0.5-mL dose supplied as a prefilled syringe and formulated to contain 60 µg each of a purified subfamily A and a purified subfamily B rLP2086 protein, 0.15 M sodium chloride, 2.8 molar ratio polysorbate 80, and 0.25 mg of Al^{3+} as aluminum phosphate ($AlPO_4$) in 10 mM histidine-buffered saline at pH 6.0.

MenACWY-TT is supplied as a single-dose vial containing lyophilized powder to be reconstituted for injection. The vaccine is formulated on the basis of purified capsular polysaccharide content and the amount of protein carrier is dependent on the polysaccharide-to-protein ratio. The vaccine is nonadjuvanted and preservative-free. The quantitative composition of the lyophilized vaccine is shown in the Nimenrix IB.

MenACWY-TT will be reconstituted with bivalent rLP2086 as detailed in the investigational product (IP) manual, and 0.5 mL of the resultant MenABCWY will be administered via intramuscular injection. The final MenABCWY composition includes rLP2086 subfamily A and B proteins formulated at 120 µg/mL/subfamily, purified capsular polysaccharides of

N meningitidis types A, C, W, and Y at concentration of 10 µg/mL/type conjugated to tetanus toxoid at ratios of ~1:3, ~1:3, ~1:1.5, and ~1:1.3, respectively, in 10 mM histidine and 1.2 mM Tris buffer containing 150 mM sodium chloride, 0.5 mg/mL aluminum as $AlPO_4$, 0.035 mg/mL polysorbate 80, and 56 mg/mL sucrose.

Menveo is supplied in 2 vials that must be combined prior to administration: the MenA lyophilized conjugate vaccine component is reconstituted with the meningococcal group C, Y, and W-135 (MenCYW-135) liquid conjugate vaccine component immediately before administration as a 0.5-mL intramuscular injection.

The placebo is sterile normal saline solution for injection and will be administered as a 0.5-mL intramuscular injection.

5.7.2. Preparation and Dispensing

See the IP manual or appropriate package inserts for instructions on how to prepare the investigational products for administration. Investigational product should be prepared and dispensed by an unblinded, appropriately qualified, and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. The investigational product will be administered to subjects who are blinded.

5.8. Administration

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

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

Because the study vaccines are different in physical appearance, the study vaccine syringes will be administered in a manner that prevents the study subjects from identifying the vaccine type based on its appearance.

Investigational product administration details will be recorded on the CRF.

Table 3 below describes the administration details for each vaccine. Each vaccine will be administered as a 0.5-mL dose in the upper deltoid muscle of the left or right arm.

Table 3. Investigational Product Administration Schedule

Investigational Product	Group(s)	Visit(s)	Upper Deltoid Muscle Injection Location
MenABCWY	1 and 3	1, 3, 10	Left arm
Placebo (normal saline) [a]	1 and 3	1	Right arm
Bivalent rLP2086	2 and 4	1, 3, 10	Left arm
MenACWY-CRM	2 and 4	1, 10	Right arm

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

MenABCWY is administered intramuscularly by injecting 0.5 mL into the upper deltoid muscle of the left arm at Visits 1, 3, and 10 (Groups 1 and 3).

Placebo is administered intramuscularly by injecting 0.5 mL into the upper deltoid muscle of the right arm at Visit 1 (Groups 1 and 3); pilot cohort subjects will not receive placebo at Vaccination 1.

Bivalent rLP2086 is administered intramuscularly by injecting 0.5 mL into the upper deltoid muscle of the left arm at Visits 1, 3, and 10 (Groups 2 and 4).

MenACWY-CRM is administered intramuscularly by injecting 0.5 mL into the upper deltoid muscle of the right arm at Visits 1 and 10 (Groups 2 and 4).

In the event of a product quality complaint, please refer to Section 8.5.

5.9. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparator and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the IP manual and package insert(s) for storage conditions of the products (eg, MenABCWY) once reconstituted.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for

continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

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

5.10. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.10.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Unused investigational product may be destroyed according to procedures and local environmental regulations after all investigational product accountability documentation has been completed, unless there are regulatory requirements for this to be returned. Empty investigational product containers may be destroyed after the sponsor has performed accountability. Only outer containers are used to perform accountability while syringes and vials are discarded at the point of use. Investigational product return must be documented on the accountability log.

5.11. Concomitant Treatment(s)

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD up to Visit 11 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 name, start and stop dates, and route of administration of antipyretic and other pain medications received by the subject on the day prior to investigational product administration will be recorded in the CRF.

5.11.1. Prohibited During the Study

- Receipt of any blood products, including immunoglobulin.
- Nonstudy meningococcal vaccines or vaccines containing 1 or more ABCWY group are prohibited throughout the course of the study.
- Nonlive or live nonstudy vaccines are not permitted within 14 and 28 days, respectively, of any study vaccination.
- Vaccine containing all or individual antigens included in Tdap vaccine are not permitted within 28 days of any study vaccination.
- Intramuscular/sublingual allergen immunotherapy is not permitted within 14 days of any study vaccination.
- Systemic (oral, intravenous, or intramuscular) corticosteroid therapy within 28 days of any study vaccination.

5.11.2. Permitted During the Study

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed. However, while prioritizing standard clinical care, efforts should be made not to administer nonstudy vaccines within 14 days (for nonlive vaccines) or 28 days (for live vaccine) as specified below.
- Nonstudy vaccines (other than any meningococcal vaccines or vaccines containing 1 or more ABCWY group, or vaccines containing all or individual antigens included in Tdap vaccine) that are part of recommended immunization schedules are allowed anytime during the study but should not be administered within 14 days (for nonlive vaccines) and 28 days (for live vaccines) of study vaccine administration. Please refer to Section 5.11.1 restrictions on administration on meningococcal vaccines or vaccines containing 1 or more ABCWY group, and on administration of all or individual antigens included in Tdap vaccines.

- Antipyretic medication may be administered.
- A local anesthetic may be used at the site of the blood draw.
- Topical antibiotics are permitted.
- Topical and inhaled corticosteroids are permitted.

5.11.3. Prior Treatment

If the subject is known to have ever received a polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein (PRP-OMP) vaccine, the name of the vaccine and date of administration will be recorded on the CRF. Please refer to the SRM for a list of PRP-OMP–containing vaccines that are or have been commercially available.

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. Please refer to the SRM for a list of ACWY-containing vaccines that are or have been commercially available. Written confirmation of ACWY vaccination history should be obtained prior to randomization; however, if written ACWY vaccination history is not available, history obtained verbally from the subject (or parent(s)/legal guardian) is acceptable, if deemed reliable by the investigator.

If the subject has received antipyretic and other pain medications on the day prior to investigational product administration at Visit 1, the name, start and stop dates, and route of administration of the medication will be recorded on the CRF.

5.11.4. Prohibited Prior Treatments

The following are prohibited:

- Receipt of any blood products, including immunoglobulin, within 6 months before the first study vaccination.

6. STUDY PROCEDURES

6.1. Informed Consent Process

The investigator or authorized designee is responsible for obtaining written informed consent for each subject enrolled prior to any study procedures. Each signature on the ICD must be personally dated by the signatory. A copy of the signed and dated ICD will be given to the subject. The subject's source documents must reflect that informed consent was obtained before participation in the study.

For subjects who have not reached the legal age of majority and are not legally able to provide informed consent, the investigator or authorized designee is responsible for obtaining written informed consent from the parent(s)/legal guardian. In addition, a study-specific

assent form will be provided to the subject (age dependent on local requirements). It is to be understood as the child's will to participate in a study after having received age-appropriate information and is sometimes also referred to as "knowing agreement." It is understood that wherever informed consent is used in this document, this also applies to assent for minor subjects.

If a subject reaches the age at which he or she is legally able to provide consent during the study, consent must be obtained. Since the subject is no longer a minor, the parent/legal guardian consent is no longer valid. References in this protocol and other study documents to parent/legal guardian responsibility should be understood to be the direct responsibility of study subjects rather than parent/legal guardian after the subject has reached the legal age of majority.

6.2. Stage 1

6.2.1. Visit 1 (Day 1): Vaccination 1

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

- Obtain written informed consent, and assent if appropriate, before performing study-specific procedures. The date of informed consent will be recorded on the CRF.
- Record the subject's demographic information (including date of birth, sex, race, and ethnicity).
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.
- Record previous PRP-OMP vaccinations as described in the Prior Treatment section (Section 5.11.3).
- Record any prior meningococcal vaccines or vaccines containing 1 or more ACWY groups as described in the Prior Treatment section (Section 5.11.3).
- Record any antipyretics and other pain medications received by the subject on the day prior to investigational product administration as described in Section 5.11.3.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, throat; heart; lungs; abdomen; extremities; neurological; musculoskeletal; and lymph nodes; including worsening of medical history conditions. Results must be recorded on source documents and the CRF. Findings from a physical examination conducted as part of standard routine care and before informed consent may be used for purposes of the study only if the examination was performed no more than 2 days before vaccination. A brief examination must be performed on the day of vaccination to document that no change in health has occurred in the interim.

- On the day of vaccination, perform a urine pregnancy test on female subjects. A negative pregnancy test result is required before the subject may receive the investigational product.

- On the day of and before vaccination, measure and record the subject's oral temperature.

- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.

- If a subject is eligible for the study, randomize the subject to 1 of the 4 groups using an interactive voice response system (IVRS), interactive Web-based response system (IWRS), or an equivalent system.

- On the day of and before vaccination, collect a blood sample (approximately 20 mL) from the subject. Alternatively, for subjects who have consented to participate in the subset, depending on the consent obtained:

  - Collect approximately 50 mL of blood, or

  - Collect approximately 100 mL of blood.

  Collect the blood sample only if the subject is eligible for vaccination on the same day.

- For all subjects apart from the pilot cohort: The unblinded administrator administers a single 0.5-mL intramuscular injection of either MenABCWY (Groups 1 and 3) or bivalent rLP2086 (Groups 2 and 4) into the upper deltoid muscle of the left arm; and either MenACWY-CRM (Groups 2 and 4) or saline (Groups 1 and 3) into the upper deltoid muscle of the right arm. The time of investigational product administration will be recorded on the CRF.

  - For pilot cohort subjects: the unblinded administrator administers a single 0.5-mL intramuscular injection of MenABCWY into the upper deltoid muscle of the left arm. The time of investigational product administration will be recorded on the CRF. Pilot cohort subjects will not receive placebo at Vaccination 1.

- Observe the subject for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period, these AEs are defined as immediate AEs (Section 8).

- Record AEs as described in the AE Reporting Requirements section (Section 8) and the Schedule of Activities. Time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).

- Issue a subject e-diary and provide instruction on its completion. Ask the parent(s)/legal guardian or subject to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination.

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

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

- Ask the parent(s)/legal guardian or the subject to use the caliper to measure the maximum diameter of redness and swelling at the left arm injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 7.4.

- Ask the parent(s)/legal guardian or the subject to contact the investigator immediately if the subject experiences a severe redness or swelling (>20 caliper units) at the left arm injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 6.4).

    - If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 7.4.1), the parent(s)/legal guardian or the subject should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

    - Ask the parent(s)/legal guardian or subject to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units.

- Provide the subject with a contact card (Section 4.6).

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

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

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

- Complete the source documents.

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

Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the subject to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that were ongoing on the last day that the e-diary was

completed. The stop dates should be documented in the source documents and the information entered into the CRF at the next study visit of the subject.

6.2.2. Visit 2 (28 to 42 Days After Visit 1), Post–Vaccination 1 Blood Draw

- Ensure that the subject continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 4.5.
- Ensure that the subject continues to meet none of the withdrawal criteria as described in Section 6.5 and none of the temporary delay of blood draw criteria as described in Section 4.4.
- Collect the subject's e-diary.
- Review the subject's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE Reporting Requirements section (Section 8) and the Schedule of Activities.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).
- Collect a blood sample (approximately 20 mL). Alternatively, for subjects who have consented to participate in the subset, depending on the consent obtained:
    - Collect approximately 50 mL of blood, or
    - Collect approximately 100 mL of blood.

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

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

- Complete the source documents.

- Complete the CRFs.

6.2.3. Visit 3 (173 to 194 Days After Visit 1): Vaccination 2

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

- Ensure that the subject continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 4.5.

- Ensure that the subject continues to meet none of the withdrawal criteria as described in Section 6.5 and none of the temporary delay of vaccination or blood draw criteria as described in Section 4.3 and Section 4.4.

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

    - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.

    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.

- Record AEs as described in the AE Reporting Requirements section (Section 8) and the Schedule of Activities. Time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

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

- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).

- Record any antipyretics and other pain medications received by the subject on the day prior to investigational product administration as described in Section 5.11.

- On the day of and before vaccination, collect a blood sample (approximately 20 mL) from the subject. Collect the blood sample only if the subject is eligible for vaccination on the same day.

- On the day of vaccination, perform a urine pregnancy test on female subjects. A negative pregnancy test result is required before the subject may receive the investigational product.

- On the day of and before vaccination, measure and record the subject's oral temperature.

- The unblinded administrator administers a single 0.5-mL intramuscular injection of either MenABCWY (Groups 1 and 3) or bivalent rLP2086 (Groups 2 and 4) into the upper deltoid muscle of the left arm. The time of investigational product administration will be recorded on the CRF.

- Observe the subject for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8).

- Issue a subject e-diary and provide instruction on its completion. Ask the parent(s)/legal guardian or subject to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination.

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

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

- Ask the parent(s)/legal guardian or the subject to use the caliper to measure the maximum diameter of redness and swelling at the left arm injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 7.4.

- Ask the parent(s)/legal guardian or the subject to contact the investigator immediately if the subject experiences a severe redness or swelling (>20 caliper units) at the left arm injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 6.4).

    - If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 7.4.1), the parent/legal guardian or the subject should also use the

measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

- Ask the parent(s)/legal guardian or subject to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units.

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

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

- Ask the parent(s)/legal guardian or the subject to bring the e-diary to the next visit.

- Complete the source documents.

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

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

6.2.4. Visit 4 (28 to 42 Days After Visit 3), Post–Vaccination 2 Blood Draw

- Ensure that the subject continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 4.5.

- Ensure that the subject continues to meet none of the withdrawal criteria as described in Section 6.5 and none of the temporary delay of blood draw criteria as described in Section 4.4.

- Collect the subject's e-diary.

- Review the subject's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.

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

  - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.

  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.

- Record AEs as described in the AE Reporting Requirements section (Section 8) and the Schedule of Activities.

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

- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).

- Provide the parent(s)/legal guardian or the subject with a memory aid. Instruct the subject to use the memory aid between Visits 4 and 5 to remind him or her to review any significant illnesses, hospitalizations, newly diagnosed medical conditions, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the SRM and Section 7.3 for additional details.

- Collect a blood sample (approximately 20 mL). Alternatively, for subjects who have consented to participate in the subset, depending on the consent obtained:

  - Collect approximately 50 mL of blood, or

  - Collect approximately 100 mL of blood.

- At designated sites participating in collection of blood samples for exploratory purposes, the following additional procedures may be completed:

  - Obtain written informed consent from subjects agreeing to the additional blood sample. This consent may be obtained at prior visits if appropriate.

  - Collect a whole blood sample of approximately 50 mL for exploratory testing. The maximum amount of blood to be obtained at this visit is 150 mL.

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

- Schedule a telephone contact and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.

- Complete the CRFs.

6.2.5. Visit 5 (168 to 196 Days After Last Vaccination), Telephone Contact

- This telephone contact should occur approximately 6 months after the last Stage 1 study vaccination; this contact should be attempted for all subjects who have received at least 1 Stage 1 study vaccination, unless they have withdrawn consent.
- Contact the parent(s)/legal guardian or the subject by telephone.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire about SAEs, newly diagnosed chronic medical conditions, or AEs that resulted in evaluation at a medical facility since the last visit. Please refer to the SRM for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. A checklist will be provided as a guide. Please refer to the SRM for additional details.
- Report any SAEs to the sponsor as defined in Section 8.
- Record AEs as described in the AE Reporting Requirements section (Section 8) and the Schedule of Activities.
- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Complete the source documents.
- Complete the CRFs.
- Inform subjects from the ACWY-naive stratum to expect a telephone contact to confirm if they are able to participate in Stage 2.

6.2.6. Visit 6 (After Study Unblinding and Prior to Transition to Stage 2) Telephone Contact

Visit 6 will be conducted once the sponsor has informed the investigator if the subject may progress to Stage 2 (Section 5.5.1). Visit 6 must be conducted prior to Visit 7.

- Notify the parent(s)/legal guardian or the subject by telephone if the subject may progress to Stage 2.

- For subjects progressing to Stage 2, schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.

6.3. Stage 2

Subjects from both the 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. Stage 1 will be observer-blinded and Stage 2 will be open-label. Investigators will be informed if a subject can be screened for Stage 2 based on a randomly generated list of eligible subjects and a randomly generated backup list to allow for replacement of subjects who decline participation in Stage 2 or are deemed ineligible after screening at Visit 7.

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.

6.3.1. Visit 7 (336 to 694 Days After Visit 3), Antibody Persistence Blood Draw 1

- Obtain written informed consent, and assent if applicable, before performing further study-specific procedures. The date of informed consent will be recorded on the CRF.

- Ensure that the subject continues to be eligible for the study, meets none of the withdrawal criteria as described in Section 6.5, and meets none of the temporary delay of blood draw criteria as described in Section 4.4.

- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).

- Collect a blood sample (approximately 20 mL).

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).

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

- Complete the source documents.

- Complete the CRFs.

6.3.2. Visit 8 (700 to 756 Days After Visit 3), Antibody Persistence Blood Draw 2

- Ensure that the subject continues to be eligible for the study, meets none of the withdrawal criteria as described in Section 6.5, and meets none of the temporary delay of blood draw criteria as described in Section 4.4.
- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).
- Collect a blood sample (approximately 20 mL).
- Record any AEs and research-related injuries (RRIs) occurring within 48 hours after the Visit 7 blood draw as described in Section 8.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).
- Schedule an appointment for the next visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

6.3.3. Visit 9 (1064 to 1120 Days After Visit 3), Antibody Persistence Blood Draw 3

- Ensure that the subject continues to be eligible for the study, meets none of the withdrawal criteria as described in Section 6.5, and meets none of the temporary delay of blood draw criteria as described in Section 4.4.
- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).
- Collect a blood sample (approximately 20 mL).
- Record any AEs and RRIs occurring within 48 hours after the Visit 8 blood draw as described in Section 8.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).
- Schedule an appointment for the next visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

6.3.4. Visit 10 (1428 to 1484 Days After Visit 3): Booster Vaccination

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

- Ensure that the subject continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 4.5.
- Ensure that the subject continues to meet none of the withdrawal criteria as described in Section 6.5 and none of the temporary delay of vaccination or blood draw criteria as described in Section 4.3 and Section 4.4.
- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).
- Record any antipyretics and other pain medications received by the subject on the day prior to investigational product administration as described in Section 5.11.
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history that have been diagnosed since Visit 1.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, throat; heart; lungs; abdomen; extremities; neurological; musculoskeletal; and lymph nodes; including worsening of medical history conditions. Results must be recorded on source documents and the CRF. Findings from a physical examination conducted as part of standard routine care and before informed consent may be used for purposes of the study only if the examination was performed no more than 2 days before vaccination. A brief examination must be performed on the day of vaccination to document that no change in health has occurred in the interim.
- On the day of vaccination, perform a urine pregnancy test on female subjects. A negative pregnancy test result is required before the subject may receive the investigational product.
- On the day of and before vaccination, measure and record the subject's oral temperature.
- On the day of and before vaccination, collect a blood sample (approximately 20 mL) from the subject. Collect the blood sample only if the subject is eligible for vaccination on the same day.
- Administer a single 0.5-mL intramuscular injection of either MenABCWY (Groups 1 and 3) or bivalent rLP2086 (Groups 2 and 4) into the upper deltoid muscle of the left arm; and MenACWY-CRM (Groups 2 and 4) into the upper deltoid muscle of the right arm. The time of investigational product administration will be recorded on the CRF.

- Observe the subject for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8).

- Record AEs as described in the AE Reporting Requirements section (Section 8) and the Schedule of Activities. Time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).

- Issue a subject e-diary and provide instruction on its completion. Ask the parent(s)/legal guardian or subject to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination.

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

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

- Ask the parent(s)/legal guardian or the subject to use the caliper to measure the maximum diameter of redness and swelling at the left arm injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 7.4.

- Ask the parent(s)/legal guardian or the subject to contact the investigator immediately if the subject experiences a severe redness or swelling (>20 caliper units) at the left arm injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 6.4).

    - If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 7.4.1), the parent/legal guardian or the subject should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

    - Ask the parent(s)/legal guardian or subject to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units.

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

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

- Remind parent(s)/legal guardian or subject to bring the e-diary to the next study visit. Complete the source documents.

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

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

6.3.5. Visit 11 (28 to 42 Days After Visit 10), Postbooster Blood Draw

- Ensure that the subject continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 4.5.

- Ensure that the subject continues to meet none of the withdrawal criteria as described in Section 6.5 and none of the temporary delay of blood draw criteria as described in Section 4.4.

- Collect the subject's e-diary.

- Review the subject's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.

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

    - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.

    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.

- Record AEs as described in the AE Reporting Requirements section (Section 8) and the Schedule of Activities.

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

- Record nonstudy vaccinations as described in the Concomitant Treatment(s) section (Section 5.11).

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).

- Provide the parent(s)/legal guardian or the subject with a memory aid. Instruct the subject to use the memory aid between Visits 11 and 12 to remind him or her to review any significant illnesses, hospitalizations, newly diagnosed medical conditions, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the SRM and Section 7.3 for additional details.

- Collect a blood sample (approximately 20 mL). Alternatively, for subjects who have consented to participate in the subset, collect approximately 100 mL of blood.

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

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

- Complete the source documents.

- Complete the CRFs.

6.3.6. Visit 12 (168 to 196 Days After Booster Vaccination), Final Telephone Contact

- The final telephone contact should occur approximately 6 months after the booster vaccination; this contact should be attempted for all subjects who have received the booster vaccination, unless they have withdrawn consent.

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

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

    - Inquire about SAEs, newly diagnosed chronic medical conditions, or AEs that resulted in evaluation at a medical facility since the last visit. Please refer to the SRM for additional details.

    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.

- Report any SAEs to the sponsor as defined in Section 8.

- Record AEs as described in the AE Reporting Requirements section (Section 8) and the Schedule of Activities.

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.11).

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

- Complete the source documents.

- Complete the CRFs.

6.4. Unscheduled Visits

If the subject experiences a severe redness or swelling at the left arm injection site (>20 caliper units), a temperature ≥39.0°C (102.1°F), or a severe headache in the 7 days after vaccination, a study site visit should be arranged as soon as possible to assess the extent of the event. The parent(s)/legal guardian or subject contact will be documented in the CRF.

If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 7.4.1), ensure the parent(s)/legal guardian or subject has also measured the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided. Ask the parent(s)/legal guardian or subject to report the maximum diameter of the redness and/or swelling at the injection site daily until the reaction becomes ≤21 caliper units. Record these measurements in the CRF.

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

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

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

6.5. Subject Withdrawal

The investigator and/or sponsor may withdraw a subject from the study if deemed appropriate at any time. Eligibility criteria as listed under inclusion criteria (refer to Section 4.1) and exclusion criteria (refer to Section 4.2) should be taken into consideration when determining if a subject must be withdrawn from the study. The investigator is not

required to repeat the physical examination completed at Visit 1 or 10, unless clinically indicated.

Reasons why a subject may discontinue or be withdrawn from the study may include, but are not limited to, AEs (including any neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis), parent(s)/legal guardian or subject request, investigator request, death, discontinuation of the study by the sponsor, protocol violation, and being lost to follow-up. Subjects who have received investigational product will not be replaced.

An effort must be made to determine why a subject fails to return for the necessary visits or is withdrawn from the study. Information detailing the circumstances leading to the withdrawal of a subject from the study, as well as the date of withdrawal, will be recorded on the study outcome CRF.

The decision to withdraw a subject from the study should be discussed with the sponsor. Every attempt must be made to collect all prompted reactogenicity data, AEs, or SAEs following each vaccination. Any AEs or SAEs that are continuing at the time of withdrawal from the study must be followed until the events have subsided, until values have returned to baseline, or, in case of permanent impairment, until the condition stabilizes. When a subject discontinues or is withdrawn from the study, the investigator will notify the sponsor.

For subjects who withdraw during Stage 1, when possible, the investigator will perform the procedures indicated for the next visit, provide the subject with a memory aid, and complete Visit 5 (telephone contact) if the subject has received at least 1 study vaccination.

For subjects who withdraw during Stage 2 between Visit 6 and the booster vaccination, follow up on AEs as indicated above.

For subjects who withdraw during Stage 2 after having received the booster vaccination, when possible, the investigator will perform the procedures indicated for the next visit, provide the subject with a memory aid, and complete Visit 12 (final telephone contact).

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also Withdrawal From the Study Due to Adverse Events [Section 8.1.3]) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

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

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

7.1. Pregnancy Testing

For the purposes of pregnancy testing in this study, all female subjects are considered to be of childbearing potential.

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of each vaccine dose. A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product but may remain in the study.

7.2. Biological Samples

Serum and whole blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed.

If allowed by the informed consent document, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the subject's genetic material will be performed.

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

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

7.2.1. Immunogenicity

To facilitate immunogenicity analyses, subjects will have approximately 20 mL of blood collected as shown in Table 1 and Table 2. In order to support assay development, a subset of up to approximately 600 subjects 18 to 25 years of age will, depending on the consent obtained, have up to 100 mL, rather than 20 mL, of blood drawn at Visits 1, 2, and 4; and 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.

Sample collection, storage, and shipping information can be found in the SRM.

Serum samples should be processed and stored as indicated in the SRM. All serum samples should be stored in an upright position in a laboratory-grade manual-defrost freezer that does not undergo freeze-thaw cycles and where ice must be removed manually. A frost-free freezer must not be used, as the continuous freeze-thaw cycles of such freezers may affect the integrity of the samples. The freezer must maintain a temperature of -15°C or colder.

It is the responsibility of the investigator(s) (or designee) to record daily freezer temperature readings (working days only), to maintain a daily temperature log for the freezer, and to alert the sponsor of any deviations. Deviations from storage requirements, including any actions taken, must be documented and reported to the sponsor. Guidance on temperature monitoring and procedures for the review of temperature deviations will be provided in the SRM.

7.2.2. Serum Bactericidal Assays

For assessment of the immune response, functional antibodies will be analyzed in hSBAs with meningococcal group A, B, C, W, and Y strains. The hSBA measures antibodies in human sera that result in complement-dependent killing of the target meningococcal strain.

Sera obtained from subjects at all time points as shown in Table 1 and Table 2 will be used in these assays. All MenA, MenC, MenW, and MenY assays and MenB assays using the 10 secondary MnB test strains will be qualified before any testing is performed. All MenB assays using the 4 primary MnB test strains will be validated before any testing is performed.

SBAs will be conducted at one or both of the following laboratories:

- Pfizer Vaccine Research-High Throughput Clinical Testing, 401 N Middletown Road, Pearl River, NY 10965, USA

- Pharmaceutical Product Development, Inc, Bioanalytical Laboratories, 2244 Dabney Road, Richmond, VA 23230, USA

7.2.2.1. MenB Serum Bactericidal Assays

For assessment of the immune response to bivalent rLP2086 and the B component of MenABCWY, 4 primary MnB test strains, PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), will be used in the hSBAs for determination of the immunogenicity endpoints in this study.

Validated hSBA LODs and LLOQs for the 4 primary strains are shown below.

Table 4. Validated hSBA LODs and LLOQs for the 4 Primary MenB Strains

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

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

Ten (10) secondary test strains will be used to perform hSBA testing so that at least 150 (125 from US investigative sites and 25 from other investigative sites) evaluable post-Vaccination 2 hSBA results are available for each secondary test strain. The hSBA assays for the 10 secondary test strains will be performed on up to 750 subjects (up to 600 subjects from US investigative sites and up to 150 subjects from other investigative sites, as described in Step 2 below) from Groups 2 and 4, combined.

Step 1: The 10 secondary test strains will be allocated across the 3 subsets. The first 2 subsets will each include 3 secondary test strains and the last subset will include 4 secondary test strains.

Step 2: Once all subjects have completed enrollment (Visit 1), the independent statistical center (ISC; a statistical team not involved in the conduct of the study) will randomly allocate up to 600 US subjects (up to 200 per subset) and up to 150 subjects (up to 50 per subset) from other investigative sites from Groups 2 and 4 across the 3 subsets.

Among the Group 2 and 4 subjects, a maximum of 8 test strains (up to 4 additional test strains and 4 primary test strains) may be tested.

Stage 1 sera obtained prior to the first vaccination with bivalent rLP2086 and 1 month after the second vaccination with bivalent rLP2086 (Visit 4) will be used for hSBA testing on the 10 secondary test strains.

hSBAs have been qualified for the 10 secondary test strains.

Qualified hSBA LODs and LLOQs for the 10 secondary strains are shown below.

Table 5. Qualified hSBA LODs and LLOQs for the 10 Secondary MenB Strains

Strain Variant	LOD	LLOQ
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

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

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

For assessment of the immune response to MenACWY-CRM and the ACWY components of MenABCWY, test strains specific for each of the ACWY groups (A [PMB277], C [PMB3204], W [PMB 6270], and Y [PMB3385]) will be used in the hSBAs for determination of the immunogenicity endpoints in this study. The qualified LLOQs and LODs for the ACWY test strains are as follows:

Table 6. Qualified hSBA LODs and LLOQs for the ACWY Strains

Strain Variant	LOD	LLOQ
Men A	1:4	1:8
Men C	1:4	1:8
Men W	1:4	1:8
Men Y	1:4	1:8

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

7.2.3. Exploratory Assays

At designated sites, an additional optional whole blood sample of approximately 50 mL will be obtained at Visit 4 from subjects who have consented to this. This sample will be used for exploratory purposes.

7.3. Safety

Any subject who receives at least 1 dose of investigational product will be included in the evaluation for safety. The following safety parameters will be assessed as described in the Study Procedures section (Section 6) and Schedule of Activities:

- Physical examination.
- Reactogenicity: solicited local reactions and systemic events, including fever.
- Use of antipyretic medication.
- Unsolicited AEs and SAEs.

A medical history will be obtained and a physical examination will be performed on all subjects at Visit 1 to establish a baseline, and at Visit 10 prior to the booster vaccination. When taking the medical history and performing the physical examination, particular care must be taken to note any neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Significant medical history and observations from the physical examination will be documented on the CRF. In addition, a urine pregnancy test will be performed on all female subjects.

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

- Local reactions at the site of investigational product administration (redness, swelling, and pain).
- Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain).

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

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

Medically attended AEs and newly diagnosed chronic medical conditions will also be assessed throughout the study and documented on the appropriate AE CRF. A medically

attended AE is defined as a nonserious AE that results in an evaluation at a medical facility. A newly diagnosed chronic medical condition is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

AEs (serious and nonserious), newly diagnosed chronic medical conditions, and visits to other medical facilities will be assessed at study visits as specified in the Schedule of Activities and reported as defined in Section 8. AE-related hospitalizations, visits to other medical facilities, medication use, and days of school or work missed will be collected and recorded in the AE CRF. Hospitalizations and visits to medical facilities not associated with an AE, such as elective hospitalizations, healthcare visits for preventive care, or routine physical examinations, will not be collected. Non–AE-related concomitant medications and days of school or work missed not associated with an AE will not be collected. A Study Visit/Telephone Contact AE Checklist will be used as a guide, will be completed at each scheduled study visit/telephone contact, and will be included in the source documentation. Please refer to the SRM for details.

Subjects will be given a memory aid at Visit 4 and Visit 11. The memory aid will be used to remind subjects to review any significant illnesses, hospitalizations, newly diagnosed medical conditions, or visits to a medical facility with study site personnel. Subjects may use the memory aid as needed during the telephone contact at Visit 5 and Visit 12 to prompt recall of events. These may be used to assist in reporting and discussion of events with study staff, but these memory aids will not be considered source documents and will not be collected at study visits. Only information collected by study staff as part of a study visit or telephone contact (Visit 5 or 12) will be included in the source documents and entered into the CRF.

In addition, AEs and SAEs will be collected as defined in Section 8.

7.4. Electronic Diary

An e-diary will be issued based on a personal digital assistant or equivalent technology, and used to monitor and record the subject's local reactions, systemic events, and use of antipyretic medication for 7 days after each vaccination. Grading scales for local reactions and systemic events are based on US FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[42] The e-diary allows recording of these assessments only within a fixed time-window, thus providing the accurate representation of the subject's experience at that time.

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

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

Investigators will be required to review the e-diary data online at frequent intervals to evaluate subject compliance and as part of the ongoing safety review.

7.4.1. Local Reactions

Local reactions (redness, swelling, and pain) at the site of investigational product administration will be recorded daily for 7 days (Days 1 to 7) after each vaccination. Only local reactions at the site of investigational product administration on the left arm will be recorded.

7.4.1.1. Redness and Swelling

Redness and swelling will be measured and recorded in caliper units (range: 1 to 21+), and then categorized as none, mild, moderate, or severe based on the scale given in Table 7 below. Each caliper unit represents 0.5 cm. A caliper will be issued with instructions for measuring any redness or swelling at the injection site. The caliper will be used to measure and to report the largest diameter of a local reaction. In the event that a caliper measurement is between 2 values, the higher value should be reported. The measurements will then be recorded in the e-diary.

In the event the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units), the parent(s)/legal guardian or subject will also measure the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided and report this immediately to the investigator. The parent(s)/legal guardian or subject will report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units. These measurements will be recorded in the CRF.

Table 7. Grading of Redness and Swelling

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

7.4.1.2. Pain

If the subject experiences injection site pain, the pain will be graded using the scale in Table 8. The assessment will then be recorded in the e-diary.

Table 8. Grading of Pain

Mild	Does not interfere with activity
Moderate	Interferes with activity
Severe	Prevents daily activity

7.4.2. Systemic Events

7.4.2.1. Temperature

A digital thermometer will be given to the parent(s)/legal guardian or the subject with instructions on how to measure the subject's oral temperature at home. Oral temperature will be collected at in the evening daily for 7 days (Day 1 to Day 7) after each vaccination, and at any time during the 7 days when fever is suspected. The highest temperature for each day will be recorded in the e-diary. Fever is defined as temperature of ≥38.0°C (100.4°F).

Temperature will be measured and recorded to 1 decimal place and then categorized according to the severity scale in Table 9:

Table 9. Severity Scale for Fever

Temperature 38.0°C to 38.4°C (100.4°F to 101.1°F)
Temperature 38.5°C to 38.9°C (101.2°F to 102.0°F)
Temperature 39.0°C to 40.0°C (102.1°F to 104.0°F)
Temperature >40.0°C (>104.0°F)

7.4.2.2. Other Systemic Events

The e-diary will be used to record the presence of other systemic events, including vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain daily for 7 days (day 1 to day 7) after each vaccination, using the scales in Table 10.

Table 10. Grading of Other 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

Table 10. Grading of Other Systemic Events

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity

Abbreviation: IV = intravenous.

7.4.3. Use of Antipyretic Medication

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

7.5. Pilot Cohort Safety Assessments

After Vaccination 1, 7-day e-diary and AE data will be collected for each pilot cohort subject. These safety data from the pilot cohort will be reviewed by the sponsor's IRC to determine if the safety, reactogenicity, and tolerability profile of MenABCWY is satisfactory and supports further enrollment into the study.

The external data monitoring committee (EDMC) will not participate in the decision whether or not to open enrollment further after review of the pilot cohort safety data, but will participate in review of safety data from this study as detailed in the EDMC charter (Section 9.7).

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	None	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of vaccine group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

If the investigator is aware of an SAE with an onset on the day of investigational product administration or during the calendar day following investigational product administration, the investigator must contact the Pfizer study physician directly immediately after sending the SAE report form to Pfizer as described above. The investigator must also contact the Pfizer study physician directly as soon as possible after becoming aware of an AE that required medical attention that began on the day of investigational product administration or during the calendar day following investigational product administration. These procedures do not replace any of the standard AE reporting requirements. Additional information regarding such events and the reporting requirements are included in the SRM.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see Serious Adverse Events [Section 8.2.3] below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical

terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian. In addition, each study subject/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (See Also the Subject Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section (Section 8.1) above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject/parent(s)/legal guardian provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 4, and from Visit 10 to Visit 11.

At Month 12 (Visit 5: telephone contact), the parent(s)/legal guardian or subject will be contacted by telephone to inquire about SAEs, newly diagnosed chronic medical conditions, or AEs that resulted in evaluation at a medical facility since Visit 4. These events must be recorded in the CRF and the event must be followed.

At Month 60 (Visit 12: final telephone contact), the parent(s)/legal guardian or subject will be contacted by telephone to inquire about SAEs, newly diagnosed chronic medical conditions, or AEs that resulted in evaluation at a medical facility since Visit 11. These events must be recorded in the CRF and the event must be followed.

At Visits 7, 8, and 9, the site will inquire about any AEs, as well as RRIs (Section 8.2.4), for events occurring during the 48-hour period after each blood draw. These events must be recorded in the CRF and the event must be followed.

AE collection is summarized in Table 11.

Table 11. Summary of Adverse Event Collection

	Visits 1-4	Visit 5	Visit 6	Visits 7-9	Visits 10-11	Visit 12
Approximate Month	0-7	12		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.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

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

8.1.4.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see Medical Device Complaint Reporting Requirements [Section 8.5]). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;

- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Research-Related Injury

Should a subject, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately.

A medically important research related injury is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a research-related injury.

An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.2.5. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;

- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI.

Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

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

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

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

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

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

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

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

8.4.4. Medication Errors and Lack of Efficacy

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors and lack of efficacy	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Other examples include but are not limited to:

- The administration of expired investigational product.
- The administration of an incorrect investigational product.
- The administration of an incorrect dosage.
- Administration of an investigational product that has undergone temperature excursion from the specified storage range, unless it is determined prior to administration by the sponsor that the investigational product under question is acceptable for use.

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

In the event of a medication dosing error, the sponsor should be notified immediately.

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

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

8.4.4.2. Lack of Efficacy

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

8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

Please note, no unblinded investigational product information should be entered on the medical device complaint CRF when reporting medical device complaints. Please refer to the IP manual for further details regarding reporting medical device complaints.

9. DATA ANALYSIS/STATISTICAL METHODS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and will be further detailed in a statistical analysis plan (SAP). The SAP may modify what is outlined in the protocol where appropriate (however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment) and will be finalized before data unblinding in Stage 1.

9.1. Sample Size Determination

Both hypothesis testing and estimation will be performed. The hypothesis-testing component will address the need to confirm the immunogenicity of bivalent rLP2086 administered at Months 0 and 6 in all subjects 10 through 25 years of age, using prespecified criteria for the primary MnB immunogenicity endpoints. Safety of bivalent rLP2086 administered at Months 0 and 6 will also be described. Immunogenicity and safety information for the MenABCWY arms will be described.

Hypothesis testing will be performed on the 5 coprimary MnB endpoints in all subjects, which will include a 4-fold rise from baseline in hSBA titers for each of the 4 primary strains and the composite response (hSBA titer ≥ LLOQ for all 4 primary strains combined) 1 month after the second vaccination. If the lower limit of the 2-sided 95% confidence interval (CI) exceeds each of the target lower limit of the confidence interval (LCI) values, the study's primary objective will be met.

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 primary endpoints. The alternate hypothesis is that the true proportion of subjects for each of the primary immunogenicity endpoints exceeds the target LCI.

Hypothesis testing will be performed by calculating 2-sided 95% CIs on each of the 5 MnB endpoints limited to Groups 2 and 4 in which ACWY-naive and ACWY-experienced cohorts will be combined. The Clopper-Pearson method will be used to calculate the CIs for the proportions. If the LCI exceeds the corresponding target LCI for each strain and the composite, then the null hypothesis will be rejected.

The study sample size is mainly based on hypothesis-testing criteria to verify the clinical benefit of a 2-dose schedule for the use of bivalent rLP2086 administered at Months 0 and 6 in healthy subjects 10 years to <26 years of age in both Group 2 and Group 4. Given the observed response proportions from Study B1971012 for each endpoint, with 900 evaluable subjects, the primary objective based on all 5 primary endpoints will be met with a power of 95.2% (Table 12). Furthermore, with 748 evaluable subjects from US sites, the LCI criteria for the primary objective will also be met with a power of 89.9%. For the global study, assuming that ~85% of enrolled subjects qualify for the evaluable immunogenicity population, ~1060 subjects should be enrolled to receive bivalent rLP2086 and MenACWY-CRM. This assumes that every subject has sufficient sera for the 4 hSBAs.

Table 12. Overall Power to Meet the Primary Objectives

	Primary Endpoint Test Strain (Variant)	LCI Criteria	Study B1971012 0- and 6-Month Responses With 95% Confidence Interval (%)[a]	Number of Evaluable Subjects	Power
hSBA titer fold rise ≥4 from baseline	PMB80 (A22)	LL of 95% CI >75%	82.3 (76.3, 87.3)	900	99.97%
	PMB2001 (A56)	LL of 95% CI >85	90.1 (85.1, 93.8)	900	99.60%
	PMB2948 (B24)	LL of 95% CI >55	64.5 (57.4, 71.1)	900	99.99%
	PMB2707 (B44)	LL of 95% CI >60	66.0 (58.9, 72.6)	900	95.7%
Composite response (hSBA titer ≥ LLOQ for all 4 primary strains combined)		LL of 95% CI >65	72.9 (65.9, 79.1)	900	99.92%
Overall power					95.2%

Abbreviations: hSBA = serum bactericidal assay using human complement; LCI = lower limit of the confidence interval; LL = lower limit; LLOQ = lower limit of quantitation.
a. The power calculation was based on Study B1971012 with a vaccine schedule of 0 and 6 months.

An additional 530 subjects will be enrolled in the MenABCWY-MenABCWY regimen. Assuming 85% evaluable subjects, there will be 450 evaluable subjects in this regimen. These subjects will be further split between ACWY-naive and ACWY-experienced strata.

Given 530 subjects receiving at least 1 dose of MenABCWY, the probability of observing at least 1 AE will be 93.0% with a true incidence of 0.5% (see Table 13).

Table 13. Probabilities of Detecting AEs at Specified Incidences

Sample Size	True Incidence of AE	Probability of at Least 1 AE
530	0.01%	5.2%
530	0.10%	41.2%
530	0.25%	73.5%
530	0.50%	93.0%
530	1.00%	99.5%

A total of 1590 subjects will therefore be enrolled into this study. The randomization will be performed separately for ACWY-naive and ACWY-experienced subjects. Equal numbers of subjects will be recruited into each stratum.

9.2. Immunogenicity Analyses

Subjects having received a vaccine containing 1 or more ACWY groups prior to enrollment will be randomized in the ACWY-experienced stratum but, for the purposes of group A, C, W, and Y analyses, will be considered A, C, W, Y-naive or -experienced based on what group(s) were present in the prior ACWY-containing vaccine.

For the calculation of GMTs, hSBA results below LLOQ will be set as ½ of LLOQ (see Table 4 and Table 5). Two (2)-sided 95% CIs will be provided for all proportions and GMTs.

Exact 2-sided 95% CIs will be compiled using the Clopper-Pearson method for any proportions of subjects with hSBA titers ≥ cutoff or LCI criteria.

Geometric means will be obtained by log transformation of titers, averaging the transformed values, then exponentiating the results. Ninety-five percent CIs will also be obtained for the geometric means. The CIs will be calculated in the log scale with reference to the appropriate t-distribution. Then the lower and upper limits will be exponentiated.

9.2.1. Analysis of the Primary Immunogenicity Objective

The assessment of the MnB immune response induced by bivalent rLP2086 will be performed by compiling the proportions of subjects (point estimate) in the bivalent rLP2086 + MenACWY-CRM vaccine groups (Group 2 – ACWY-naive and Group 4 – ACWY-experienced) for each MnB coprimary endpoint, along with the exact 2-sided 95% CI for each endpoint. The primary endpoints are defined as a 4-fold rise from baseline in hSBA titer as follows:

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

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.

If each of the LCIs meets or exceeds the associated target LCI (Table 12), then the null hypothesis will be rejected, and the study objective in terms of the immunogenicity will be met.

The evaluation for all 5 primary endpoints will also be performed for US subjects only.

9.2.2. Analyses of the Secondary Objectives

The MnB immune response induced by 2 doses of bivalent rLP2086 will be described by compiling results for Groups 2 and 4.

The MnB immune response induced by 2 doses of MenABCWY (combined Groups 1 and 3) compared to the immune response induced by 2 doses of bivalent rLP2086 (combined Groups 2 and 4) will be described.

The ACWY immune response induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM will be analyzed for the ACWY-naive and ACWY-experienced subjects separately.

The ACWY immune response induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM will be analyzed for the ACWY-naive and ACWY-experienced subjects separately.

Prior to the booster vaccination, the immune response induced by MenABCWY compared to the immune response induced by MenACWY-CRM and bivalent rLP2086 will be described for ACWY test strains in ACWY-naive and ACWY-experienced subjects separately, and for MnB strains for the ACWY-naive and ACWY-experienced subjects combined, at each of the blood sample time points.

The following tables highlight the analyses for the evaluation of the secondary objectives for immunogenicity (all the analyses are descriptive).

Table 14. Highlights of the Analyses for the Secondary Immunogenicity Objectives – Stage 1

Vaccine Group	Analysis Time Point	Strain	Analysis
Bivalent rLP2086 + MenACWY-CRM (Groups 2 and 4 combined)	1 Month after the second dose of bivalent rLP2086 (Visit 4)	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Proportion of subjects with hSBA titer ≥ LLOQ for each strain Proportion of subjects with hSBA titer ≥1;4, ≥1;8, ≥1;16, ≥1;32, ≥1;64, ≥1;128 for each strain hSBA GMTs for each strain
	Baseline and 1 month after the second dose of bivalent rLP2086 (Visit 1 and Visit 4)	Each secondary MenB test strain (see Table 5)	Proportion of subjects with hSBA titer ≥ LLOQ Proportion of subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 hSBA GMTs
MenABCWY (ACWY-naive and ACWY-experienced groups separately) MenACWY-CRM (ACWY-naive and ACWY-experienced groups separately)	1 Month after the first dose of MenABCWY (Visit 2) for Groups 1 and 3 1 Month after the first dose of MenACWY-CRM (Visit 2) for Groups 2 and 4	hSBA-MenA, hSBA-MenC, hSBA-MenW, hSBA-MenY	Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:8 (or LLOQ, whichever is higher) Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 hSBA-MenA/C/W/Y GMTs
MenABCWY (ACWY-naive and ACWY-experienced groups separately) MenACWY-CRM (ACWY-naive and ACWY-experienced groups separately)	1 Month after the second dose of MenABCWY (Visit 4) 1 Month after the first dose of MenACWY-CRM (Visit 2)	hSBA-MenA, hSBA-MenC, hSBA-MenW, hSBA-MenY	Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:8 (or LLOQ, whichever is higher) Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 hSBA-MenA/C/W/Y GMTs

Table 14. Highlights of the Analyses for the Secondary Immunogenicity Objectives – Stage 1

Vaccine Group	Analysis Time Point	Strain	Analysis
MenABCWY (ACWY-naive and ACWY-experienced groups combined)	1 Month after the second dose of MenABCWY (Visit 4)	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Composite response (proportion of subjects achieving an hSBA titer ≥ LLOQ for all 4 strains) Proportion of subjects achieving at least a 4-fold increase in hSBA titer from baseline for each of the 4 strains Proportion of subjects with hSBA titer ≥ LLOQ for each strain Proportion of subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 for each strain hSBA GMTs for each strain
MenABCWY (ACWY-naive and ACWY-experienced groups separately) Bivalent rLP2086 + MenACWY-CRM (ACWY-naive and ACWY-experienced groups separately)	Before and after MenABCWY or MenACWY-CRM + bivalent rLP2086 at Visits 1 and 3	hSBA-MenA, hSBA-MenC, hSBA-MenW, hSBA-MenY	Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:8 (or LLOQ, whichever is higher) Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 hSBA-MenA/C/W/Y GMTs
MenABCWY (ACWY-naive and ACWY-experienced groups combined) Bivalent rLP2086 + MenACWY-CRM (ACWY-naive and ACWY-experienced groups combined)	Before and after MenABCWY vaccination at Visits 1 and 3	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Proportion of subjects with hSBA titer ≥ LLOQ for each strain Proportion of subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 for each strain hSBA GMTs for each strain

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

Table 15. Highlights of the Analyses for the Secondary Immunogenicity Objectives – Persistence

Vaccine Group	Analysis Time Point	Strain	Analysis
MenABCWY (ACWY-naive and ACWY-experienced groups separately) Bivalent rLP2086 + MenACWY-CRM (ACWY-naive and ACWY-experienced groups separately)	At Visits 7, 8, and 9, and before booster vaccination at Visit 10	hSBA-MenA, hSBA-MenC, hSBA-MenW, hSBA-MenY	Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:8 (or LLOQ, whichever is higher)
MenABCWY (ACWY-naive and ACWY-experienced groups combined) Bivalent rLP2086 + MenACWY-CRM (ACWY-naive and ACWY-experienced groups combined)	At Visits 7, 8, and 9, and before booster vaccination at Visit 10	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Proportion of subjects with hSBA titer ≥ LLOQ for each strain

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

Table 16. Highlights of the Analyses for the Secondary Immunogenicity Objectives – Booster

Vaccine Group	Analysis Time Point	Strain	Analysis
MenABCWY (Groups 1 and 3 combined in Stage 2)	1 Month after the booster dose of MenABCWY (Visit 11)	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Proportion of subjects with hSBA titer ≥ LLOQ for each MnB strain
MenABCWY (Groups 1 and 3 separately in Stage 2)	1 Month after the booster dose of MenABCWY (Visit 11)	hSBA-MenA, hSBA-MenC, hSBA-MenW, hSBA-MenY	Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:8 (or LLOQ, whichever is higher)
Bivalent rLP2086 + MenACWY-CRM (Groups 2 and 4 combined in Stage 2)	1 Month after the booster dose of bivalent rLP2086 + MenACWY-CRM (Visit 11)	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Proportion of subjects with hSBA titer ≥ LLOQ for each strain

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

9.2.3. Analyses of Exploratory Objectives

The table below outlines the exploratory analysis for immunogenicity.

Table 17. Analyses for the Exploratory Immunogenicity Objectives – Stages 1 and 2

Vaccine Group	Analysis Time Point	Strain	Analysis
Bivalent rLP2086 + MenACWY-CRM (ACWY-naive and ACWY-experienced groups combined: Groups 2 and 4 in Stage 1)	1 Month after the first dose of bivalent rLP2086 + MenACWY-CRM (Visit 2)	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Composite response (proportion of subjects achieving an hSBA titer ≥ LLOQ for all 4 strains) Proportion of subjects achieving at least a 4-fold increase in hSBA titer from baseline for each of the 4 MnB strains Proportion of subjects with hSBA titer ≥ LLOQ for each MnB strain Proportion of subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 for each MnB strain hSBA GMTs for each MnB strain
Bivalent rLP2086 + MenACWY-CRM (Groups 2 and 4 separately in Stage 2)	1 Month after the booster dose of bivalent rLP2086 + MenACWY-CRM (Visit 11)	hSBA-MenA, hSBA-MenC, hSBA-MenW, hSBA-MenY	Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:8 (or LLOQ, whichever is higher)
MenABCWY (Groups 1 and 3 separately) Bivalent rLP2086 + MenACWY-CRM (Groups 2 and 4 separately)	At Visits 7, 8, and 9, and before booster vaccination at Visit 10	hSBA-MenA, hSBA-MenC, hSBA-MenW, hSBA-MenY	Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 hSBA-MenA/C/W/Y GMTs
MenABCWY (Groups 1 and 3 combined) Bivalent rLP2086 + MenACWY-CRM (Groups 2 and 4 combined)	At Visits 7, 8, and 9, and before booster vaccination at Visit 10	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Proportion of subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 for each strain hSBA GMTs for each strain

Table 17. Analyses for the Exploratory Immunogenicity Objectives – Stages 1 and 2

Vaccine Group	Analysis Time Point	Strain	Analysis
MenABCWY (Groups 1 and 3 combined in Stage 2)	1 Month after the booster dose of MenABCWY (Visit 11)	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Composite response (proportion of subjects achieving an hSBA titer ≥ LLOQ for all 4 MnB strains) Proportion of subjects achieving at least a 4-fold increase in hSBA titer from baseline for each of the 4 MnB strains Proportion of subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 for each MnB strain hSBA GMTs for each MnB strain
MenABCWY (Groups 1 and 3 separately in Stage 2)	1 Month after the booster dose of MenABCWY (Visit 11)	hSBA-MenA, hSBA-MenC, hSBA-MenW, hSBA-MenY	Proportion of subjects with hSBA-MenA/C/W/Y titer ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 hSBA-MenA/C/W/Y GMTs
Bivalent rLP2086 + MenACWY-CRM (Groups 2 and 4 combined in Stage 2)	1 Month after the booster dose of bivalent rLP2086 + MenACWY-CRM (Visit 11)	PMB80 (A22), PMB2001 (A56), PMB2948 (B24), PMB2707 (B44)	Composite response (proportion of subjects achieving an hSBA titer ≥ LLOQ for all 4 strains) Proportion of subjects achieving at least a 4-fold increase in hSBA titer from baseline for each of the 4 strains Proportion of subjects with hSBA titer ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, ≥1:128 for each strain hSBA GMTs for each strain

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

The exploratory analysis to investigate the association of the primary strains and additional MenB testing strains, as well as a sensitivity analysis that may be performed for immunogenicity in Stage 1, will be detailed in the SAP.

9.3. Demographic and Baseline Characteristics

The following demographic characteristics will be descriptively summarized: sex, race, ethnicity, and age at first vaccination. Medical history and baseline physical examination data will also be descriptively summarized. Demographic characteristics will be summarized by cohort and by combined cohorts. Demographic characteristics will also be compiled for subjects participating in Stage 2.

9.4. Safety Analyses

9.4.1. Analysis for Safety and Reactogenicity

The proportion of subjects reporting local reactions at the investigational product administration sites and systemic events within the 7-day period after each vaccination will be descriptively summarized by group. Two (2)-sided 95% CIs based on the Clopper-Pearson method will be presented with the proportions. Severities of local reactions and systemic events reported after each vaccination will also be descriptively summarized by vaccine group. Local reactions will be summarized only for the left arm, which is the MenABCWY or bivalent rLP2086 injection site.

The proportion of subjects reporting the use of antipyretic medication for Days 1 to 7 will be compiled for each vaccine group after each vaccination.

All AEs and SAEs will be categorized according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). A medically attended AE is defined as a nonserious AE that results in an evaluation at a medical facility. A newly diagnosed chronic medical condition is defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects. AEs, SAEs, medically attended AEs, and newly diagnosed chronic medical conditions will be summarized by vaccine group.

All of the analyses will be performed for each ACWY stratum as well as for the combined strata. Safety analyses may also be summarized by other demographic variables.

Detailed analyses for each safety endpoint will be addressed in the SAP.

9.5. Analysis Populations

9.5.1. Full Analysis Set

The full analysis set will be referred to as the intent-to-treat (ITT) population.

9.5.2. Per-Protocol Analysis Set

The per-protocol analysis set will be referred to as the evaluable immunogenicity population, which is the primary population for the primary objective assessments and for the analyses of the secondary endpoints related to MnB strains in Stage 1.

All randomized subjects who are included in the Stage 1 modified intent-to-treat (mITT) population as well as who meet the following criteria will be included in the Stage 1 evaluable immunogenicity population:

1. Were randomized to the study group of interest.

2. Were eligible, ie, fulfilling all of the inclusion criteria and none of the exclusion criteria.

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 the second vaccination: window 28-42 days).

5. Had as least 1 valid and determinate MenB assay result after the second vaccination.

6. Had no important protocol deviations. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine.

An evaluable immunogenicity population for booster response will be used for booster immunogenicity analysis, which includes subjects who were eligible for the study (ie, met all Stage 1 and booster stage eligibility criteria), received a booster dose as intended (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. This population will be referred to as the booster evaluable immunogenicity population.

9.6. Modified Intent-to-Treat (mITT) Population

All randomized subjects who have at least 1 valid and determinate MenB or MenA/C/W/Y assay result available at any time point from Visit 1 to Visit 4 will be included in the mITT population for Stage 1. This will be the primary immunogenicity population for the analyses of the secondary endpoints related to ACWY endpoints in Stage 1.

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

The mITT populations will be used for the evaluation of the primary, secondary, and exploratory immunogenicity endpoints, and subjects will be analyzed according to the investigational product to which they were randomized. Endpoints to assess antibody persistence will include subjects in the Stage 2 mITT population.

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

A booster mITT immunogenicity population will also be defined for supportive analyses for booster endpoints. This population will consist of subjects who received a booster vaccination and who have any booster immunogenicity data.

9.7. Safety Analysis Set

The safety population will be used for all safety analyses. The safety population for Stage 1 will include all subjects who have received at least 1 dose of investigational product during Stage 1 and for whom safety data are available. The safety population for Stage 2 will include all 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. Additionally, a persistence safety population will include all subjects who signed the informed consent to participate in Stage 2.

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

1. Vaccination 1 safety population: This population will include all subjects who received 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 before Visit 3 is available.

2. Vaccination 2 safety population: This population will include all subjects who received 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 all subjects who received at least 1 dose of investigational product and for whom safety information is available from after Visit 4 up to and including Visit 5. Subjects who received the wrong investigational product and are followed for 6 months for safety will not be included in this population.

4. Booster vaccination safety population: This population will include all subjects who received 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.

5. Follow-up safety population for Stage 2: This population will include all subjects who received the booster dose of investigational product and for whom safety information is available from after Visit 11 up to and including Visit 12. Subjects who received the wrong investigational product and are followed for 6 months for safety will not be included in this population.

9.8. Analysis Timing

No formal interim analyses are planned for this study.

The study database will be unblinded after the last subject has completed the Visit 5 telephone contact.

Analyses will be completed after Stage 1 and after Stage 2. The Stage 1 analyses will include immunogenicity analyses up to and including the post–Vaccination 2 blood draw (approximately 1 month after Vaccination 2) and safety assessments up to and including the Visit 5 telephone contact (approximately 6 months after Vaccination 2).

The Stage 2 analyses (persistence and booster analyses) will include all data collected after Visit 5 through the end of the study.

After unblinding following the completion of Stage 1 (through Visit 5) and testing the hypothesis associated with the primary immunogenicity objective, interim summaries of immunogenicity and safety data may be generated. The alpha level (confidence level of 95% CIs) will not be adjusted for these descriptive summaries.

9.9. Data Monitoring Committee

This study will use an EDMC. The ISC will provide unblinded safety reports to the EDMC for review. Safety data will be reviewed by the EDMC throughout the study and no type I error will be adjusted for the multiple looks at the data.

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

Please see the EDMC charter for further details.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records.

The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed

informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a

numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

A study-specific assent form will be provided to pediatric subjects as required by local regulations. It is to be understood as the adolescent's will to participate in a trial after having received age-appropriate information and is sometimes also referred to as "knowing agreement." If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of bivalent rLP2086, MenACWY-TT, and/or MenABCWY at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

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

Abbreviation	Term
AA	Accelerated Approval
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
$AlPO_4$	aluminum phosphate
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine (Trumenba)
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRM	cross-reactive material
CSA	clinical study agreement
CT	clinical trial
CTA	clinical trial application
DILI	drug-induced liver injury
DTaP, dTaP	diphtheria, tetanus, and acellular pertussis vaccine
DU	dispensable unit
EC	ethics committee
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
fHBP	factor H binding protein
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMT	geometric mean titer
GSK	GlaxoSmithKline
HBV	hepatitis B virus
Hib	*Haemophilus influenzae* type b
HPV4	quadrivalent human papillomavirus vaccine
hSBA	serum bactericidal assay using human complement
hSBA-MenA	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A

Abbreviation	Term
hSBA-MenA/C/W/Y	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A, group C, group W, and/or group Y
hSBA-MenC	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group C
hSBA-MenW	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group W
hSBA-MenY	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group Y
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IMD	invasive meningococcal disease
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IPV	inactivated poliomyelitis virus
IRB	institutional review board
IRC	independent review committee
IRT	interactive response technology
ISC	independent statistical center
ITT	intent-to-treat
IUD	intrauterine device
IVRS	interactive voice response system
IWRS	interactive Web-based response system
LCI	lower limit of the confidence interval
LFT	liver function test
LLOQ	lower limit of quantitation
LOD	limit of detection
LP2086	lipoprotein 2086
LSLV	last subject last visit
MCV4	quadrivalent meningococcal polysaccharide conjugate
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* group A
MenABCWY	*Neisseria meningitidis* group A, B, C, W, and Y vaccine
MenACWY	meningococcal groups A, C, W, and Y conjugate vaccine
MenA/C/W/Y	*Neisseria meningitidis* group A, group C, group W, and/or group Y
MenACWY-CRM	meningococcal group A, C, W-135, and Y conjugate vaccine (Menveo)
MenACWY-TT	meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (Nimenrix)
MenB	*Neisseria meningitidis* group B
MenC	*Neisseria meningitidis* group C

Abbreviation	Term
MenCYW-135	meningococcal group C, Y, and W-135
MenW	*Neisseria meningitidis* group W
MenY	*Neisseria meningitidis* group Y
mITT	modified intent-to-treat
MnB	*Neisseria meningitidis* group B
N/A	not applicable
OMV	outer membrane vesicle
PAR	postapproval requirement
PCD	primary completion date
PI	principal investigator
PRP-OMP	polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein
PT	prothrombin time
rLP2086	recombinant lipoprotein 2086
RRI	research-related injury
rSBA	serum bactericidal assay using rabbit complement
rSBA-MenA	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A
rSBA-MenC	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group C
rSBA-MenW	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group W
rSBA-MenY	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group Y
SAE	serious adverse event
SAP	statistical analysis plan
SBA	serum bactericidal assay
SRM	study reference manual
SRSD	single reference safety document
TBili	total bilirubin
Tdap	tetanus, low-dose diphtheria, and low-dose acellular pertussis
ULN	upper limit of normal
US	United States

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