

CLINICAL PROTOCOL

A PHASE 2, RANDOMIZED, CONTROLLED, OBSERVER-BLINDED STUDY CONDUCTED TO DESCRIBE THE IMMUNOGENICITY, SAFETY, AND TOLERABILITY OF A *NEISSERIA MENINGITIDIS* SEROGROUP B BIVALENT RECOMBINANT LIPOPROTEIN 2086 VACCINE (BIVALENT rLP2086) WHEN ADMINISTERED TO HEALTHY TODDLERS AGED 12 TO <18 MONTHS OR 18 TO <24 MONTHS

Compound: PF-05212366

Compound Name Neisseria meningitidis Serogroup B Bivalent

Recombinant Lipoprotein 2086 Vaccine

(Bivalent rLP2086)

United States Investigational New Drug 13812

(IND) Number

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Document History

Document	Version Date	Summary of Changes and Rationale
Protocol Amendment 2	19 Apr 2016	 Updated the unblinding strategy based on the actual enrollment rate in the study. Clarified when the primary analysis will be performed. Incorporated updates from administrative change letters dated 02 September 2015 and 12 November 2015. Corrected typographical errors and clarified text throughout. Clarified the timing of the stages of the study. Deleted the appendix detailing the enrollment plan. Updated the required freezer temperature for storing serum samples. Updated the Adverse Event Reporting section and Communication of Results by Pfizer section to be consistent with the Pfizer template.
Protocol Amendment 1	03 Feb 2015	 Updated the description of the control vaccine (pediatric HAV vaccine) and removed references to a specific brand of control vaccine (Havrix Junior). Clarified the administration site instructions. Updated the Clinical Experience section for bivalent rLP2086. Updated background section to include current licensure status of Bexsero and Trumenba. Corrected typographical errors related to the DMC ("blinded" to "unblinded," consistent with other sections). Other minor administrative changes.

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

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CTA	clinical trial application
DAI	dosage administration and instructions
DTaP	diphtheria, tetanus, and acellular pertussis
DU	dispensable unit
EC	ethics committee
e-diary	electronic diary
EDMC	external data monitoring committee
EudraCT	European Clinical Trials Directive
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GMT	geometric mean titer
HAV	hepatitis A virus
hSBA	serum bactericidal assay using human complement
IB	investigator's brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IMD	invasive meningococcal disease

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IND	investigational new drug application
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISC	independent statistical center
LFT	liver function test
LLOQ	lower limit of quantitation
LOD	limit of detection
LP2086	lipoprotein 2086
LSLV	last subject last visit
MAE	medically attended event
MAR	missing at random
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measurement
MnB	Neisseria meningitidis serogroup B
NDCMC	newly diagnosed chronic medical condition
NIP	national immunization program
OMV	outer membrane vesicle
PCD	primary completion date
PDA	personal digital assistant
PI	principal investigator
PRP-OMP	polyribosylribitol phosphate oligosaccharide of <i>Haemophilus influenzae</i> type b conjugated to outer membrane protein
RCDC	reverse cumulative distribution curve
rLP2086	recombinant lipoprotein 2086
RRI	research-related injury
SAE	serious adverse event
SAP	statistical analysis plan
SBA	serum bactericidal assay

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SRM	study reference manual
SRSD	single reference safety document
ULN	upper limit of normal
USPI	United States package insert

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PROTOCOL SUMMARY

Neisseria meningitidis is a leading cause of bacterial meningitis in infants, adolescents, and young adults in developed countries. In particular, *Neisseria meningitidis* serogroup B (MnB) is responsible for approximately two-thirds of the cases of observed meningococcal infections in Europe, with a case-fatality rate of 6% to 8% from 1999 to 2006. Australian national surveillance data show the peak incidence of disease in children aged 4 years or less, with a secondary peak in adolescents and young adults; approximately 85% of all cases are attributed to serogroup B disease.

A recombinant, multicomponent MnB vaccine (Bexsero) is licensed in Europe, Canada, Australia, Chile, and the United States. Trumenba® (bivalent recombinant lipoprotein 2086 vaccine [bivalent rLP2086]), developed by Pfizer, is approved in the United States for use in individuals 10 through 25 years of age for active immunization to prevent invasive meningococcal disease (IMD) caused by MnB. Recommendations for MnB vaccination are under consideration in various countries. However, to date, no broadly effective vaccine against MnB disease is available worldwide. General availability of a safe and immunogenic MnB vaccine remains an unmet medical need, and a successful vaccine will provide substantial improvement in prevention of meningococcal infection and a reduction in the burden of disease.

Bivalent rLP2086 is targeted to a conserved, surface-exposed lipoprotein, lipoprotein 2086 (LP2086), a meningococcal virulence factor that binds human factor H. *N meningitidis* serogroup B recombinant lipoprotein 2086 (rLP2086) has been expressed in *Escherichia coli* and formulated in a bivalent vaccine composed of 1 subfamily A strain and 1 subfamily B strain of rLP2086.

This study will describe the safety, tolerability, and immunogenicity of bivalent rLP2086 administered at 2 dose levels (60 μ g and 120 μ g) in 2 age strata (12 to <18 and 18 to <24 months old), given in a Month 0, 2, and 6 schedule. The younger age stratum will be substratified into toddlers 12 to <15 and 15 to <18 months of age. Within each age stratum, examination of the 120- μ g dose level will proceed only after the 60- μ g dose level is shown to be safe and tolerable in a sentinel cohort. This study will be conducted in 2 stages:

- Stage 1 includes Visit 1 to Visit 10.
- Stage 2 will assess the duration of the immune response to bivalent rLP2086; hence, only those subjects randomly assigned to bivalent rLP2086 (irrespective of dose level) will be eligible for Stage 2. For eligible subjects, Stage 2 commences at Visit 11 (approximately 24 months) and concludes at Visit 13 (approximately 48 months) after Vaccination 3.

Bivalent rLP2086 has previously been studied in toddlers aged 18 to 36 months using the earlier vaccine formulation at doses up to $200~\mu g$. It has also been studied in children, adolescents, and adults with results in these populations that have demonstrated a satisfactory safety, tolerability, and immunogenicity profile. This study, with the final formulation of bivalent rLP2086, now seeks to confirm the safety and immunogenicity profile of the final

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formulation of the vaccine in toddlers aged 18 to <24 months and to provide data about the use of the vaccine in toddlers aged 12 to <18 months. In addition, the duration of MnB-specific immune response, measured by serum bactericidal assay using human complement (hSBA), will be assessed for up to 4 years.

Analysis of the primary immunogenicity endpoints will include the following:

- Proportions of subjects achieving an hSBA titer ≥ the lower limit of quantitation (LLOQ) 1 month after the third vaccination, for each of the 4 primary MnB test strains in healthy toddlers aged 12 to <18 months at study entry.
- Proportions of subjects achieving an hSBA titer ≥ LLOQ 1 month after the third vaccination, for each of the 4 primary MnB test strains in healthy toddlers aged 18 to <24 months at study entry.

Objectives

Primary Immunogenicity Objectives

- To describe the immune response as measured by hSBA performed with 4 primary MnB strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy toddlers aged 12 to <18 months at study entry.
- To describe the immune response as measured by hSBA performed with 4 primary MnB strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy toddlers aged 18 to <24 months at study entry.

Primary Safety Objective

• To evaluate the safety profile of bivalent rLP2086 compared to a control (pediatric hepatitis A virus [HAV] vaccine), as measured by local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions, medically attended events, and immediate AEs in healthy toddlers 12 to <18 months and 18 to <24 months of age at study entry, and in both age strata combined.

Secondary Immunogenicity Objectives

- To describe the immune response 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 third vaccination with bivalent rLP2086, in healthy toddlers aged 12 to <24 months at study entry (ie, both age strata combined).
- To describe the immune response 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, and 6, 12, 24, 36, and 48 months after the third vaccination in healthy toddlers aged 12 to <18 months and

18 to <24 months at study entry, and in both age strata combined.



Study Design

The study is a Phase 2, randomized, active-controlled, observer-blinded, sponsor-unblinded, multicenter study in which approximately 396 healthy toddlers stratified by age, 12 to <18 months or 18 to <24 months old, will be randomly assigned in a 2:1 ratio to receive either 1 of 2 dose levels (60 µg or 120 µg) of bivalent rLP2086 or a licensed pediatric HAV vaccine.

The study will be conducted in 2 stages:

• Stage 1 includes a vaccine phase and a follow-up phase after Vaccination 3. Stage 1 will assess vaccine immunogenicity, safety, and tolerability across 2 phases: a sentinel-enrollment phase and an expanded-enrollment phase. Within the sentinel-enrollment phase, 2 sentinel cohorts will be enrolled: one composed of subjects aged 12 to <15 months and the other of subjects aged 18 to <24 months. The expanded-enrollment phase will be open to subjects aged 12 to <18 months and 18 to <24 months.

Within the study age cohort of 12 to <18 months, an additional subset of subjects aged 12 to <15 months is identified for the sentinel phase of the study. The designation of a subset of subjects aged 12 to <15 months aims to ensure that the sentinel cohort includes adequate enrollment of this youngest age cohort to support assessment of postvaccination reactions and AEs prior to the start of enrollment of the expanded-enrollment phase.

• Stage 2 will assess the duration of the immune response to bivalent rLP2086; hence, only those subjects randomly assigned to bivalent rLP2086 (irrespective of dose level) will be eligible for Stage 2. Subjects who received HAV vaccine or saline during Stage 1 will not be eligible for Stage 2. The subject's parent(s)/legal guardian will be notified of the subject's eligibility to participate in Stage 2 at the Visit 10 telephone contact. For eligible

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subjects, Stage 2 commences at Visit 11 (approximately 24 months after Vaccination 3) and terminates at Visit 13 (approximately 48 months after Vaccination 3).

Investigational Products

The following are defined as investigational products and will be supplied by the sponsor:

- Bivalent rLP2086 (containing 30 μg or 60 μg each of a purified subfamily A and subfamily B rLP2086 protein, adsorbed to aluminum in a sterile buffered isotonic suspension) in a 0.5-mL dose.
- A licensed pediatric HAV vaccine in a 0.5-mL dose for injection.
- The placebo consists of sterile saline for injection (containing 0.85% sodium chloride) in a 0.5-mL dose.

Statistical Method

This is not a hypothesis-testing study; an estimation approach will be used to assess the descriptive immunogenicity objectives in this study. All of the binary endpoints (including primary endpoints) will be summarized with 2-sided 95% confidence intervals (CIs) using the exact method. Geometric mean titers (GMTs) on hSBA results will also be summarized with 95% CIs. All of the immunogenicity data will be summarized by each age stratum (12 to <18 months and 18 to <24 months), as well as for the combined group.

All safety data will be descriptively summarized for each age stratum (12 to <18 months and 18 to <24 months), as well as for the combined age group.

SCHEDULE OF ACTIVITIES

The Schedule of Activities provides an <u>overview</u> of the protocol visits and procedures. Refer to the <u>Study Procedures</u> and <u>Assessments</u> 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, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Schedule of A	ctivities for	r Stage 1								
Visit Identifier	1	2	3	4 ^a	5	6	7	8	9	10
Time Period	Month 0	Week 1	Month 1	Month 2	Month 3	Month 6	Month 7	Month 12	Month 18	End of Stage 1
Visit Description	Vaccination 1	Post– Vaccination 1 Follow-up Visit	Telephone Contact	Vaccination 2	Post– Vaccination 2 Blood Draw	Vaccination 3	Post– Vaccination 3 Blood Draw	6-Month Follow- up Visit ^b	Antibody Persistence Blood Draw ^b	Telephone Contact
			Va	accination Pha	ise			Follow-up Phase		
Visit Window	Day 1 (Baseline)	7 to 10 Days After Visit 1	25 to 35 Days After Visit 1	42 to 70 Days After Visit 1	28 to 42 Days After Visit 4	105 to 126 Days After Visit 4	28 to 42 Days After Visit 6	168 to 196 Days After Visit 6	337 to 365 Days After Visit 6	-
Informed consent ^c	X									
Review eligibility criteria	X									
Confirm continued eligibility		X	Х	X	X	X	X	X	X	
Demography ^d	X									
Medical history ^e	X									
Physical examination ^f	X									
Vaccination History	X									

Visit Identifier	1	2	3	4 ^a	5	6	7	8	9	10
Time Period	Month 0	Week 1	Month 1	Month 2	Month 3	Month 6	Month 7	Month 12	Month 18	End of Stage 1
Visit Description	Vaccination 1	Post– Vaccination 1 Follow-up Visit	Telephone Contact	Vaccination 2	Post– Vaccination 2 Blood Draw	Vaccination 3	Post– Vaccination 3 Blood Draw	6-Month Follow- up Visit ^b	Antibody Persistence Blood Draw ^b	Telephone Contact
			V	accination Pha	ise			Follow-up Phase		
Visit Window	Day 1 (Baseline)	7 to 10 Days After Visit 1	25 to 35 Days After Visit 1	42 to 70 Days After Visit 1	28 to 42 Days After Visit 4	105 to 126 Days After Visit 4	28 to 42 Days After Visit 6	168 to 196 Days After Visit 6	337 to 365 Days After Visit 6	-
Brief physical examination ^g				X		X				
Heart rate, respiratory rate	X			X		X				
Axillary temperature	X			X		X				
Obtain 5-mL blood sample	X ^h				X		X	X	X	
Randomization	X									
Vaccination & 30-minute observation ⁱ	X			X		X				
Record nonstudy vaccinations		X	X	X	X	X	X	X	X	X
Provide e-diary, thermometer, measuring tape, and caliper	X			X		X				
Review and collect e-diary		X			X		X			
Assess reactogenicity ^j	Days 1 to 7			Days 1 to 7		Days 1 to 7				

Schedule of A	ctivities for	r Stage I								
Visit Identifier	1	2	3	4 ^a	5	6	7	8	9	10
Time Period	Month 0	Week 1	Month 1	Month 2	Month 3	Month 6	Month 7	Month 12	Month 18	End of Stage 1
Visit Description	Vaccination 1	Post– Vaccination 1 Follow-up Visit	Telephone Contact	Vaccination 2	Post– Vaccination 2 Blood Draw	Vaccination 3	Post– Vaccination 3 Blood Draw	6-Month Follow- up Visit ^b	Antibody Persistence Blood Draw ^b	Telephone Contact
			V	accination Pha	se			Follow-up Phase		
Visit Window	Day 1 (Baseline)	7 to 10 Days After Visit 1	25 to 35 Days After Visit 1	42 to 70 Days After Visit 1	28 to 42 Days After Visit 4	105 to 126 Days After Visit 4	28 to 42 Days After Visit 6	168 to 196 Days After Visit 6	337 to 365 Days After Visit 6	-
Record the use & type of antipyretic medication	Days 1 to 7			Days 1 to 7		Days 1 to 7				
(S)AE collection as appropriate	X ^k	X	X	X^k	X	X^k	X	X		
Record AEs / research-related injury ¹								X	X	
Record concomitant medications used to treat AEs	X	X	X	X	X	X	X	X		
Complete study visit AE checklist ^m		X	X	X	X	X	X	X		
Issue memory aid							X	X ⁿ	X ⁿ	

Schedule of A	ctivities for	r Stage 1								
Visit Identifier	1	2	3	4 ^a	5	6	7	8	9	10
Time Period	Month 0	Week 1	Month 1	Month 2	Month 3	Month 6	Month 7	Month 12	Month 18	End of Stage 1
Visit	Vaccination	Post-	Telephone	Vaccination	Post-	Vaccination	Post-	6-Month Follow-	Antibody	Telephone
Description	1	Vaccination 1	Contact	2	Vaccination 2	3	Vaccination 3	up Visit ^b	Persistence	Contact
		Follow-up			Blood Draw		Blood Draw		Blood	
		Visit							Draw ^b	
			Va	accination Pha	ise			Follow-up		
								Phase		
Visit Window	Day 1	7 to 10	25 to 35 Days	42 to 70	28 to 42	105 to 126	28 to 42	168 to 196	337 to 365	-
	(Baseline)	Days After	After Visit 1	Days After	Days After	Days After	Days After	Days After Visit	Days After	
	,	Visit 1		Visit 1	Visit 4	Visit 4	Visit 6	6	Visit 6	
Notification of										X
randomization group ^o										

- a. See Section 6.1.11 for subjects who do not complete Stage 1 on internal review committee (IRC)/external data monitoring committee (EDMC) recommendations.
- b. Relative to Vaccination 3.
- c. Must be obtained prior to any protocol-required procedures.
- d. Date of birth, sex, race, and ethnicity.
- e. Chronic conditions and/or medical history of significance, including relevant surgical procedures, allergies (drug/nondrug).
- f. General appearance, skin, head, eyes, nose, ears, throat, heart, lungs, abdomen, extremities, neurologic, musculoskeletal, lymph nodes, height (or length for nonwalking subjects) and weight.
- g. General appearance, ears, throat, heart, and lungs.
- h. Blood must be collected before vaccination and only after eligibility has been confirmed.
- i. Injection performed by unblinded administrator; acute reactions assessed by blinded observer. Location of vaccination should be noted in the source, the CRF and the e-diary.
- j. Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian in order to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day that the electronic diary (e-diary) was completed.
- k. For additional reporting period details for AEs, SAEs, newly diagnosed chronic medical conditions (NDCMCs) and medically attended events (MAEs), see Section 8.
- 1. Occurring within 48 hours after blood draw.
- m. Checklist includes questions regarding NDCMC and MAEs/AEs.
- n. If required.
- o. An end-of-Stage 1 telephone call will take place after the subject has completed Visit 9 and following sponsor release of randomization codes.

 Abbreviations: AE = adverse event; e-diary = electronic diary; MAE = medically attended event; NDCMC = newly diagnosed chronic medical condition; SAE = serious adverse event.

Schedule of Activities for Stage 2 Duration of MnB-Specific Immune Response (Bivalent rLP2086 Subjects Only)						
Visit Identifier	11	12	13			
Time Period	Month 30	Month 42	Month 54			
Visit Description (Time After Vaccination 3)	Immunogenicity 1 (24 Months)	Immunogenicity 2 (36 Months)	Immunogenicity 3 (48 Months)			
Visit Window	±30 Days	±30 Days	±30 Days			
Confirm continued eligibility	X	X	X			
Obtain 5-mL blood sample	X	X	X			
Record AEs, and, any research-related injury occurring within 48 hours after blood draw	X	X	X			
Record any nonstudy vaccinations	X	X	X			
Issue memory aid	X	X				

Abbreviations: AE = adverse event; bivalent rLP2086 = bivalent recombinant lipoprotein 2086 vaccine; MnB = *Neisseria meningitidis* serogroup B.

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

The development program for the Pfizer investigational *Neisseria meningitidis* serogroup B bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086; subfamily A and B; *Escherichia coli*) aims for international licensure with an indication for active immunization to prevent invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroup B (MnB) in adolescents and young adults, aged 10 through 25 years.

This study will provide additional data on the safety, tolerability, and immunogenicity of bivalent rLP2086 in toddlers aged 12 months to 24 months.

1.2. Background and Rationale

1.2.1. Neisseria meningitidis Disease Background

Neisseria meningitidis is a leading cause of bacterial meningitis in infants, adolescents, and young adults in developed countries. In particular, MnB is responsible for approximately two-thirds of the cases of observed meningococcal infections in Europe, with an overall case-fatality rate of 6% to 8% from 1999 to 2006. MnB disease accounts for approximately one-third of meningococcal cases seen in North America. There is substantial morbidity among survivors, including neurologic disability, limb loss, and hearing loss.

While incidence rates of IMD vary with age, incidence is often highest during infancy from age 1 month to 1 year, with a second peak in incidence during adolescence. In the United States, during 1998 to 2007, the overall rate of meningococcal disease in infants aged less than 2 years was 3.9 per 100,000. In children aged 2 to 10 years, the incidence was 0.68 per 100,000, with 41% of cases in this age group occurring in children aged 2 to 3 years. National surveillance data from Australia show the peak incidence of disease in children aged 4 years or less, with a secondary peak in adolescents and young adults; approximately 85% of all cases are attributed to serogroup B disease. The high carriage rates in adolescents and young adults are believed to be due to a number of factors, including social behavior and crowding of susceptible individuals in classrooms and dormitories. 5,6

A number of countries worldwide have included vaccination against meningococcal disease in their routine immunization schedules, in accordance with recommendations of the World Health Organization—target groups for vaccination vary by country and may include infants, children, and/or young adults. ^{7,8,9} In addition, the composition of the vaccine(s) recommended may also vary according to the epidemiology of the particular country. Until recently, meningococcal vaccines have been directed against the organism's capsular polysaccharide and are available to prevent invasive disease caused by serogroups A, C, W, and Y. However, vaccine candidates aimed at producing antibodies to the capsular polysaccharide of serogroup B *N meningitidis* are unlikely to be useful, because they are poorly immunogenic. The serogroup B capsular polysaccharide is composed of polysialic acid repeating units that are chemically similar to molecules found on human neuronal cells; the poor immunogenicity is probably a result of cross-reactive epitopes between the serogroup B capsular polysaccharide and similar epitopes found on neuronal cells. ¹⁰

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Vaccines produced from outer membrane vesicles (OMVs) prepared from MnB strains have been shown to have clinical efficacy against homologous strains in children older than 4 years, but not against heterologous strains. A recombinant, multicomponent MnB vaccine (Bexsero) is licensed in Europe, Canada, Australia, Chile, and the United States. Trumenba® (bivalent rLP2086), developed by Pfizer, is approved in the United States for use in individuals 10 through 25 years of age for active immunization to prevent IMD caused by MnB. Recommendations for MnB vaccination are under consideration in various countries. However, to date, no broadly effective vaccine against MnB disease is available worldwide. General availability of a safe and immunogenic MnB vaccine remains an unmet medical need, and a successful vaccine will provide substantial improvement in prevention of meningococcal infection and a reduction in the burden of disease.

1.2.2. Bivalent Recombinant Lipoprotein 2086 Vaccine (Bivalent rLP2086)

Bivalent rLP2086 is a subcapsular protein vaccine based on major surface components that are antigenically invariant and expressed in most disease-associated meningococci. Bivalent rLP2086 is targeted to a conserved, surface-exposed lipoprotein, lipoprotein 2086 (LP2086), a meningococcal virulence factor that binds human factor H. The *LP2086* gene is present in 100% of *N meningitidis* serogroup B strains in Pfizer's strain collection of more than 1800 strains isolated from patients with invasive disease in the United States and Europe. The LP2086 protein is divided into 2 subfamilies. Subfamily B proteins are expressed in approximately 70% of isolates, and subfamily A proteins are expressed in approximately 30% of isolates. TLP2086 has been expressed in *Escherichia coli* and formulated in a bivalent vaccine composed of 1 subfamily A strain and 1 subfamily B strain of rLP2086. The recombinant proteins have been characterized biochemically and, in several animal species, have elicited bactericidal antibodies effective against subfamily A and B strains. Subfamily A and B

1.2.3. Functional Antibody Assay as a Surrogate of Efficacy

MnB clearance from the bloodstream is primarily by complement-mediated bacteriolysis, and an effective complement system is critical for resistance against infections caused by MnB. Individuals with complement deficiencies have an increased risk of developing MnB disease. The in vivo complement-mediated bacteriolysis of MnB is mimicked by the in vitro serum bactericidal assay using human complement (hSBA), a functional serological assay shown to be the correlate of protection against IMD and recognized as the surrogate marker of vaccine efficacy. ¹⁸

Disease incidence of MnB is approximately 1 in 100,000, meaning that extremely large numbers of subjects (400,000 to over 6 million) would be required to support a statistically significant assessment.

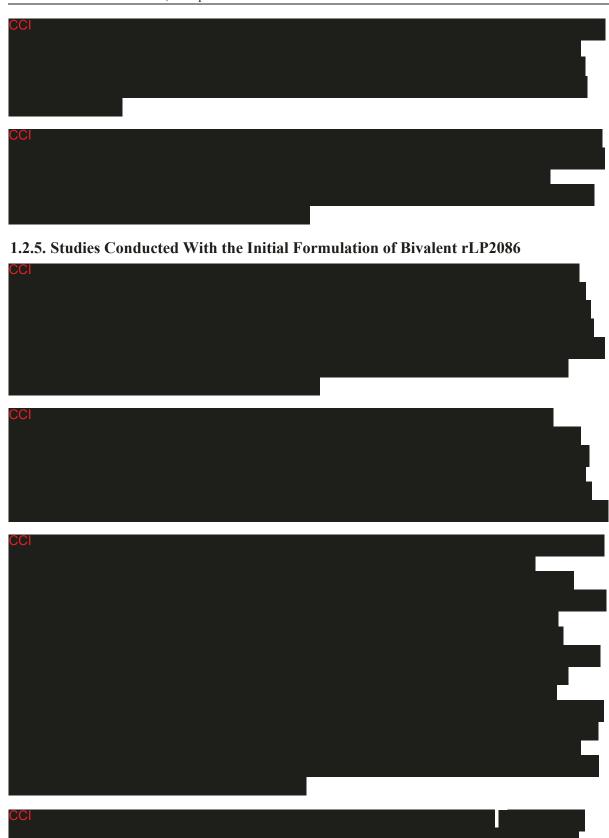
Pfizer has built an extensive MnB strain collection (N=1263) comprising IMD-causing isolates from Years 2000 to 2006. The isolates were systematically collected from the United States (US) Centers for Disease Control and Prevention (CDC) and health and reference laboratories from European countries.¹⁹ OCI



The 4 primary MnB test strains for hSBA, representative for LP2086 subfamily A and B variants, were selected from the clinically relevant strain pool of 1263 MnB isolates, ¹⁹ taking into account the population distribution of LP2086 surface expression.

1.2.4. Clinical Experience







1.2.6. Studies Conducted With the Final Formulation of Bivalent rLP2086



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1.2.7. Study Rationale

This will be 1 of 2 studies (B1971035 and B1971017) that will together explore the immunogenicity and safety of bivalent rLP2086 in toddlers and children aged 12 months to 10 years.

This 2-stage study (B1971035) will seek to evaluate the safety, tolerability, and immunogenicity of bivalent rLP2086 at 2 dose levels (60 μ g and 120 μ g) in healthy toddlers aged 12 to <24 months. Stage 1 will be composed of a sentinel-enrollment phase with 2 sentinel cohorts and an expanded-enrollment phase. Selection of dose level for the expanded-enrollment phase will be based on an internal review committee (IRC) review of the safety profile of the 2 dose levels.

- Should the IRC determine that safety data for both dose levels demonstrate a satisfactory safety profile, the 120-µg dose level will be selected for the expanded-enrollment phase.
- Should the IRC determine that safety data for the 60-µg dose level demonstrate a satisfactory safety profile, and the 120-µg dose level does not demonstrate a satisfactory safety profile, the 60-µg dose level will be selected for the expanded-enrollment phase.

Stage 2 will assess the duration of the immune response.

Risks/Benefits

Complete information on risks/benefits for this compound may be found in the SRSD, which for this study is the most recent version of the bivalent rLP2086 IB.

Refer to the most recent version of the licensed pediatric HAV vaccine USPI for a summary of the known and potential risks and benefits, if any, to human subjects.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Immunogenicity Objectives

• To describe the immune response as measured by hSBA performed with 4 primary MnB strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy toddlers aged 12 to <18 months at study entry.

• To describe the immune response as measured by hSBA performed with 4 primary MnB strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy toddlers aged 18 to <24 months at study entry.

2.1.2. Primary Safety Objective

• To evaluate the safety profile of bivalent rLP2086 compared to a control (HAV vaccine), as measured by local reactions, systemic events, AEs, SAEs, newly diagnosed chronic medical conditions (NDCMCs), medically attended events (MAEs), and immediate AEs in healthy toddlers 12 to <18 months and 18 to <24 months of age at study entry, and in both age strata combined.

2.1.3. Secondary Immunogenicity Objectives

- To describe the immune response 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 third vaccination with bivalent rLP2086, in healthy toddlers aged 12 to <24 months at study entry (ie, both age strata combined).
- To describe the immune response 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 and 6, 12, 24, 36, and 48 months after the third vaccination in healthy toddlers aged 12 to <18 months and 18 to <24 months at study entry, and in both age strata combined.

2.1.4. CCI CCI

2.2. Endpoints

It is anticipated that the volume of serum from individual study subjects may not be adequate for performance of hSBA with all 4 primary MnB test strains. Therefore, the study design designates randomization of sera from individual study subjects for initial testing with 2 of the 4 primary hSBA test strains. At a minimum, approximately 50% of subjects from each

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age group will be randomly selected to test for hSBA on strains (B24), and the other 50% of subjects from each age group will be tested for hSBA on strains (A56) and (B44). Serum bactericidal assay (SBA) with all 4 primary MnB test strains will be performed with individual serum specimens when the volume of the sample permits.

The lower limit of quantitation (LLOQ) for CCl (A22) is 1:16. The LLOQ for the other 3 primary test strains is 1:8.

2.2.1. Primary Immunogenicity Endpoints

- Proportions of subjects achieving an hSBA titer ≥ LLOQ 1 month after the third vaccination, for each of the 4 primary MnB test strains in healthy toddlers aged 12 to <18 months at study entry.
- Proportions of subjects achieving an hSBA titer ≥ LLOQ 1 month after the third vaccination, for each of the 4 primary MnB test strains in healthy toddlers aged 18 to <24 months at study entry.

2.2.2. Primary Safety Endpoints

The following endpoints will be applied to results in healthy toddlers aged 12 to <18 months and in healthy toddlers aged 18 to <24 months at study entry, and in both age strata combined:

- Percentages of subjects reporting local reactions (tenderness, redness, and swelling) and by severity after each vaccination visit.
- Percentages of subjects reporting systemic events (fever, decreased sleep, increased sleep, decreased appetite, and irritability) by severity after each vaccination visit.
- Percentages of subjects reporting the use of antipyretic medication after each vaccination visit.
- Percentages of subjects with at least 1 SAE during the following time periods:
 - 30 Days after each vaccination.
 - 30 Days after any vaccination.
 - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 7]).
 - During the follow-up phase (from 1 month after the last study vaccination [Visit 7] through 6 months after the third study vaccination [Visit 8]).

- Throughout the SAE collection period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 8]).
- Percentages of subjects with at least 1 MAE occurring during the following time periods:
 - 30 Days after each vaccination.
 - 30 Days after any vaccination.
 - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 7]).
 - During the follow-up phase (from 1 month after the last study vaccination [Visit 7] through 6 months after the third study vaccination [Visit 8]).
 - Throughout the AE collection period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 8]).
- Percentages of subjects with at least 1 NDCMC occurring during the following time periods:
 - 30 Days after each vaccination.
 - 30 Days after any vaccination.
 - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 7]).
 - During the follow-up phase (from 1 month after the last study vaccination [Visit 7] through 6 months after the third study vaccination [Visit 8]).
 - Throughout the AE collection period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 8]).
- Percentages 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 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 7]).
- Percentages of subjects reporting at least 1 immediate AE after each vaccination.

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2.2.3. Secondary Immunogenicity Endpoints

The LLOQ for CCI (A22) is 1:16. The LLOQ for the other 3 primary test strains is 1:8.

The following endpoint will be applied to results in healthy subjects aged 12 months to <24 months (ie, both age strata combined) at study entry:

• Proportion of subjects with hSBA titers ≥ LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.

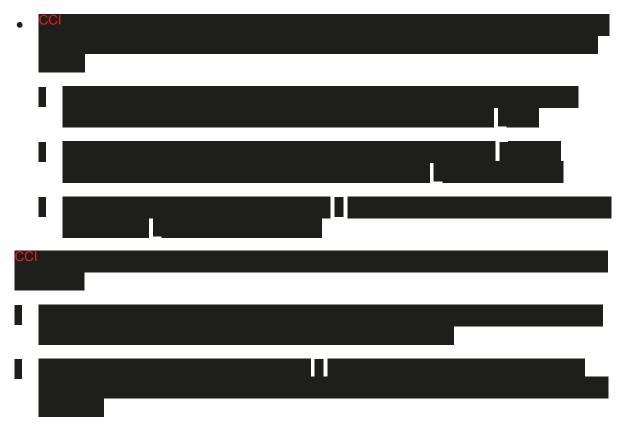
The following endpoints will be applied to results in healthy subjects aged 12 to <18 months and 18 to <24 months at study entry, and in both age strata combined:

- Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary MnB test strains at 1 month after the second vaccination with bivalent rLP2086 and 6, 12, 24, 36, and 48 months after the third vaccination with bivalent rLP2086.
- Proportions of subjects with hSBA titers \geq LLOQ, \geq 1:4, \geq 1:8, \geq 1:16, \geq 1:32, \geq 1:64, and \geq 1:128 for each of the 4 primary MnB strains at each applicable blood sampling visit.
- hSBA GMTs for each of the 4 primary test strains at each applicable blood sampling visit.



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3. STUDY DESIGN

3.1. Description

The study is a Phase 2, randomized, active-controlled, observer-blinded, sponsor-unblinded, multicenter study in which approximately 396 healthy toddlers stratified by age, 12 to <18 months or 18 to <24 months old, will be randomly assigned in a 2:1 ratio to receive either 1 of 2 dose levels (60 μ g or 120 μ g) of bivalent rLP2086 or a licensed pediatric HAV vaccine (0.5 mL)/sterile saline solution for injection (0.85% sodium chloride) in a 0.5-mL dose.

The study will be conducted in 2 stages:

Stage 1 will assess vaccine immunogenicity, safety, and tolerability across 2 phases: a sentinel-enrollment phase and an expanded-enrollment phase. Within the sentinel-enrollment phase, 2 sentinel cohorts will be enrolled: one composed of subjects aged 12 to <15 months and the other of subjects aged 18 to <24 months. The expanded-enrollment phase will be open to subjects in 2 cohorts, one aged 12 to <18 months and the other aged 18 to <24 months.

Within the study age cohort of 12 to <18 months, an additional subset of subjects aged 12 to <15 months is identified for the sentinel phase of the study. The designation of a subset of subjects aged 12 to <15 months aims to ensure that the sentinel cohort includes adequate

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enrollment of this youngest age cohort to support assessment of postvaccination reactions and AEs prior to the start of enrollment of the expanded-enrollment phase.

Stage 2 will assess the duration of the immune response to bivalent rLP2086; hence, only those subjects randomly assigned to bivalent rLP2086 (irrespective of dose level) will be eligible for Stage 2.

Bivalent rLP2086 will be administered on a Month 0, 2, and 6 schedule.

Pediatric HAV vaccine is administered at Months 0 and 6 and has been selected as the vaccine control so that subjects randomly assigned to the control group receive a benefit from participating in the study. HAV vaccine has a well-established tolerability profile and will provide protection to subjects who may become at increased risk for hepatitis A viral infection either during future travel or during other exposures. As the recommended schedule for HAV vaccine is 2 doses 6 months apart, saline will be given at Month 2 to maintain the study blind.

3.2. Sentinel- and Expanded-Enrollment Plan, Stage 1

3.2.1. Sentinel Enrollment, Stage 1

Two (2) sentinel cohorts, one aged 12 to <15 months and the other aged 18 to <24 months, will each simultaneously and independently enroll approximately 33 subjects. Stopping rules apply for sentinel cohorts (see Section 7.9 Stopping Rules).

60-µg Sentinel Cohort

For each 60-µg dose-level sentinel cohort, approximately 33 subjects will be randomly assigned in a 2:1 ratio to receive either 60 µg of bivalent rLP2086 or HAV vaccine/saline. Stopping rules apply for sentinel cohorts (see Section 7.9 Stopping Rules).

Within the 60-µg sentinel cohort of each age group, when the last subject has received Vaccination 1 and has attended the Day 7 follow-up visit, all post–Vaccination 1, 7-day electronic diary (e-diary) and AE data (summary safety data) will be tabulated for review by the sponsor's IRC.

Following completion of the data review(s) for the 60-µg sentinel cohort, a decision will be made by the IRC whether to proceed to the 120-µg sentinel cohort.

If the IRC finds the 60-µg summary safety data to be acceptable, and no further review is warranted, the subjects in the 60-µg sentinel cohort will continue through the vaccine series.

If the 60-µg summary safety data are unacceptable for the older-age sentinel cohort, then vaccinations will be halted for both of the 60-µg sentinel cohorts and enrollment into the study will stop.

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If the summary safety data 60-µg dose are acceptable for the older-age sentinel cohort but not the younger-age sentinel cohort, then vaccination and enrollment will cease for the younger-age sentinel cohort only but enrollment may commence for the 120-µg dose-level older-age sentinel cohort only.

120-µg Sentinel Cohort

For each 120-µg dose-level sentinel cohort, approximately 33 subjects will be randomly assigned in a 2:1 ratio to receive either 120 µg of bivalent rLP2086 or HAV vaccine/saline. Stopping rules apply for sentinel cohorts (see Section 7.9 Stopping Rules).

Within the 120-µg sentinel cohort of each age group (if applicable), when the last subject has received Vaccination 1 and has attended the Day 7 follow-up visit, all post–Vaccination 1, 7-day e-diary and AE data (summary safety data) will be tabulated for review by the sponsor's IRC.

Following completion of the sentinel data review(s) of the 120-µg dose, either the 60-µg dose or the 120-µg dose will be selected for each age cohort by the IRC for use in the expanded-enrollment phase of Stage 1.

If the IRC finds the summary safety data for the 120-µg dose to be acceptable, and no further review is warranted, the subjects in the 120-µg sentinel cohort will continue through the vaccine series. Younger-age sentinel subjects will not progress to the 120-µg dose level before the safety data of the 120-µg dose level have been found to be acceptable in the older-age sentinel cohort. If the 120-µg summary safety data are unacceptable in the younger-age sentinel cohort but acceptable in the older-age sentinel cohort, then a) vaccination and enrollment at the 120-µg dose level will cease in the younger-age sentinel cohort, but vaccination and expanded enrollment may continue in the younger-age sentinel cohort at the 60-µg dose level, and b) vaccination and expanded enrollment may continue at the 120-µg dose level for the older-age sentinel cohort.

If the summary data for the 120-µg dose are unacceptable in the older-age sentinel cohort, vaccination and enrollment for the sentinel cohort at the 120-µg dose level will cease. Further expanded enrollment and vaccination, however, may continue at the 60-µg dose level.

3.2.2. Expanded Enrollment, Stage 1

The expanded-enrollment stage will enroll approximately 132 subjects each into 2 age groups (12 to <18 months and 18 to <24 months), randomly assigned in a 2:1 ratio to the selected dose level of bivalent rLP2086 or HAV vaccine/saline. Randomization will be substratified in the younger age group only: 12 to <15 months and 15 to <18 months. The selected dose level in the expanded-enrollment phase may differ between age groups (12 to <18 months and 18 to <24 months), but not within the substratum (12 to <15 months and 15 to <18 months) of the younger age group.

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3.2.3. Enrollment Plan, Stage 2

Those subjects who received all 3 study vaccinations and who were randomly assigned to bivalent rLP2086 at either dose level may progress to the open-label Stage 2. Subjects randomly assigned to HAV vaccine/saline will not enter Stage 2. To facilitate this transition, the subject's parent(s)/legal guardian will be notified of the subject's randomization allocation prior to entry into Stage 2.

3.3. Sentinel Enrollment, Younger Age Stratum

3.3.1. 60-µg Sentinel Cohort Aged 12 to <15 Months

Only subjects aged 12 to <15 months will be enrolled in the 60- μ g and 120- μ g sentinel cohorts in the younger age stratum.

Approximately 33 subjects aged 12 to <15 months will be enrolled in a 60-μg dose-level sentinel cohort, randomly assigned in a 2:1 ratio to receive either 60 μg of bivalent rLP2086 or HAV vaccine/saline.

One or more primary sites will be responsible for enrolling and vaccinating the first 9 subjects in the 12- to <15-months-of-age, 60-µg sentinel cohort, at a rate of no more than 3 subjects per day for the initial days of staggered enrollment. This restriction will not be lifted until 24 hours after the ninth subject has received Vaccination 1. The daily enrollment rate will be limited to no more than 3 subjects per day for the initial days of staggered enrollment, regardless of the number of primary sentinel-cohort sites.

When all subjects in the 12- to <15-months-of-age, 60-µg sentinel cohort have received study Vaccination 1, the post–Vaccination 1, 7-day e-diary and AE data (summary safety data) will be collated for review by the IRC.

Only when the IRC has determined that the summary safety data demonstrate a satisfactory tolerability, reactogenicity, and safety profile will these subjects in the 60-µg sentinel cohort progress to complete their vaccination regimen (Vaccinations 2 and 3).

If the IRC determines that vaccination should not proceed at the 60-µg dose level, this 60-µg sentinel cohort will be discontinued and no further investigational product will be administered for this age group at any dose level. However, follow-up procedures will be performed as described in Section 6.1.11.

A summary of the 60-µg sentinel cohort enrollment and progression for subjects aged 12 to <15 months is illustrated in Table 1.

If the IRC determines that the 60-µg dose level should not continue in the 12- to <15-month sentinel cohort, and contingent upon a satisfactory tolerability, reactogenicity, and safety profile, an additional 165 expanded-enrollment subjects may be recruited into the 18- to <24-month age group at the selected dose level. This will provide a total study enrollment of approximately 396 subjects.

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Table 1. 60-μg Sentinel Cohort, Aged 12 to <15 Months, Enrollment and Progress

	Visit 1	Is Safety Review	Visit 4	Visit 6	Sentinel-Cohort Progression
		Acceptable?			
60	Administer	YES	Administer	Administer	All subjects who received the 3-vaccination
μg	Vaccination 1 ^a		Vaccination 2	Vaccination 3	series of 60 µg of bivalent rLP2086 progress to Stage 2 (Visits 11-13). Subjects who received the 3-vaccination series of HAV vaccine/saline complete the study at Visit 10.
		NO	Discontinue 60-µg sentinel cohort – no further investigational product will be given to these subjects. See Section 6.1.11 for follow-up procedures. Enrollment quota will transfer to expanded-enrollment phase (18 to <24 months old) based on safety profile.		

a. Staggered enrollment applies (see Section 3.3.1).

Abbreviation: HAV = hepatitis A virus.

3.3.2. 120-µg Sentinel Cohort Aged 12 to <15 Months

If the IRC determines that the tolerability, reactogenicity, and safety data collected through 7 days following the first dose of 60 μg of the vaccine are acceptable, then enrollment will be initiated into the 120-μg dose-level sentinel cohort. The younger-age 120-μg dose-level sentinel cohort cannot be initiated, however, until after the safety of older subjects (18 to <24 months) in the 120-μg sentinel cohort has been deemed acceptable by the IRC. Approximately 33 subjects aged 12 to <15 months will be randomly assigned in a 2:1 ratio to receive either 120 μg of bivalent rLP2086 or HAV vaccine/saline.

One or more primary sites will be responsible for enrolling and vaccinating the first 9 subjects in the 12- to <15-months-of-age, 120-µg sentinel cohort, at a rate of no more than 3 subjects per day for the initial days of staggered enrollment. This restriction will not be lifted until 24 hours after the ninth subject has received Vaccination 1. The daily enrollment rate will be limited to no more than 3 subjects per day for the initial days of staggered enrollment, regardless of the number of primary sentinel-cohort sites.

When all subjects in the 12- to <15-months-of-age, 120-µg sentinel cohort have received study Vaccination 1, the post–Vaccination 1, 7-day e-diary and AE data (summary safety data) will be collated for review by the IRC.

Only when the IRC has determined that the summary safety data demonstrate a satisfactory tolerability, reactogenicity, and safety profile will the subjects in the 120-µg sentinel cohort progress to complete the vaccination regimen with the 120-µg vaccine dose or control as planned (Vaccinations 2 and 3).

If the IRC determines that vaccination should not proceed with the 120-µg dose level, the 120-µg sentinel cohort will be discontinued and no further investigational product will be administered for this age cohort at the 120-µg dose level. However, follow-up procedures will be performed as described in Section 6.1.11.

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A summary of the 120-µg sentinel-cohort enrollment and progression for subjects aged 12 to <15 months is illustrated in Table 2.

Table 2. 120-µg Sentinel Cohort, Aged 12 to <15 Months, Enrollment and Progress

	Visit 1	Is Safety Review Acceptable?	Visit 4	Visit 6	Sentinel-Cohort Progression
120 μg	Administer Vaccination 1 ^a	YES	Administer Vaccination 2		All subjects who received the 3-vaccination series of 120 µg of bivalent rLP2086 progress to Stage 2 (Visits 11-13). Subjects who received the 3-vaccination series of HAV vaccine/saline complete the study at Visit 10.
		NO	Discontinue 120-µg sentinel cohort – no further investigational product will be given to these subjects. See Section 6.1.11 for follow-up procedures.		

a. Staggered enrollment applies (see Section 3.3.2).

Abbreviation: HAV = hepatitis A virus.

3.4. Sentinel Enrollment, Older Age Stratum

3.4.1. 60-µg Sentinel Cohort Aged 18 to <24 Months

Approximately 33 subjects aged 18 to <24 months will be enrolled in a 60-μg dose-level sentinel cohort, randomly assigned in a 2:1 ratio to receive either 60 μg of bivalent rLP2086 or HAV vaccine/saline.

One or more primary sites will be responsible for enrolling and vaccinating the first 9 subjects in the 18- to <24-months-of-age, 60-µg sentinel cohort, at a rate of no more than 3 subjects per day for the initial days of staggered enrollment. This restriction will not be lifted until 24 hours after the ninth subject has received Vaccination 1. The daily enrollment rate will be limited to no more than 3 subjects per day for the initial days of staggered enrollment, regardless of the number of primary sentinel-cohort sites.

When all subjects in the 18- to <24-months-of-age, 60- μ g sentinel cohort have received study Vaccination 1, the post–Vaccination 1, 7-day e-diary and AE data (summary safety data) will be collated for review by the IRC.

Only when the IRC has determined that the summary safety data demonstrate a satisfactory tolerability, reactogenicity, and safety profile will the subjects in the 60-µg sentinel cohort progress to complete the vaccination regimen with the 60-µg vaccine dose or control as planned (Vaccinations 2 and 3).

If the IRC determines that vaccination should not proceed at the 60-µg dose level, the 60-µg sentinel cohort will be discontinued and no further investigational product will be administered for this age group at any dose level. However, follow-up procedures will be performed as described in Section 6.1.11.

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A summary of the 60-µg sentinel-cohort enrollment and progression for subjects aged 18 to <24 months is illustrated in Table 3.

Table 3. 60-µg Sentinel Cohort, Aged 18 to <24 Months, Enrollment and Progress

	Visit 1	Is Safety	Visit 4	Visit 6	Sentinel-Cohort Progression	
		Review				
		Acceptable?				
60 μg	Administer	YES	Administer	Administer	All subjects who received the 3-vaccination series of	
	Vaccination		Vaccination	Vaccination	60 μg of bivalent rLP2086 progress to Stage 2	
	1 ^a		2	3	(Visits 11-13).	
			Subjects who received the 3-vaccination series of HAV			
			vaccine/saline complete the study at Visit 10.			
		NO	Discontinue 60-µg sentinel cohort – no further investigational product will be given to			
			these subjects. See Section 6.1.11 for follow-up procedures.			

a. Staggered enrollment applies (see Section 3.4.1).

Abbreviation: HAV = hepatitis A virus.

3.4.2. 120-µg Sentinel Cohort Aged 18 to <24 Months

If the IRC determines that the tolerability, reactogenicity, and safety data collected through 7 days following the first dose of 60 µg of the vaccine are acceptable, then enrollment will open for the 120-µg dose-level sentinel cohort.

Approximately 33 subjects aged 18 to <24 months will be randomly assigned in a 2:1 ratio to receive either 120 µg of bivalent rLP2086 or HAV vaccine/saline.

One or more primary sites will be responsible for enrolling and vaccinating the first 9 subjects in the 18- to <24-months-of-age, 120-µg sentinel cohort, at a rate of no more than 3 subjects per day for the initial days of staggered enrollment. This restriction will not be lifted until 24 hours after the ninth subject has received Vaccination 1. The daily enrollment rate will be limited to no more than 3 subjects per day for the initial days of staggered enrollment, regardless of the number of primary sentinel-cohort sites.

When all subjects in this 120- μ g sentinel cohort have received Vaccination 1, the post-Vaccination 1, 7-day e-diary and AE data (summary safety data) will be collated for review by the IRC.

Only when the IRC has determined that the summary safety data demonstrate a satisfactory tolerability, reactogenicity, and safety profile will the subjects in the 120-µg sentinel cohort progress to complete the vaccination regimen with the 120-µg vaccine dose or control as planned (Vaccinations 2 and 3).

If the IRC determines that vaccination should not proceed at the 120-µg dose level, the 120-µg sentinel cohort will be discontinued and no further investigational product will be administered for this age group at the 120-µg dose level. However, follow-up procedures will be performed and are described in Section 6.1.11.

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A summary of the 120-µg sentinel cohort enrollment and progression for subjects aged 18 to <24 months is illustrated in Table 4.

Table 4. 120-µg Sentinel Cohort, Aged 18 to <24 Months, Enrollment and Progress

	Visit 1	Is Safety	Visit 4	Visit 6	Sentinel-Cohort Progression	
		Review				
		Acceptable?				
120 μg	Administer	YES	Administer	Administer	All subjects who received the 3-vaccination series of	
	Vaccination 1 ^a		Vaccination	Vaccination	120 μg of bivalent rLP2086 progress to Stage 2	
			2	3	(Visits 11-13).	
			Subjects who received the 3-vaccination series of			
			HAV vaccine/saline complete the study at Visit 10.			
		NO	Discontinue 120-µg sentinel cohort – no further investigational product will be given to these subjects. See Section 6.1.11 for follow-up procedures.			

a. Staggered enrollment applies (see Section 3.4.2).

Abbreviation: HAV = hepatitis A virus.

3.5. Expanded-Enrollment Phase

3.5.1. 12- to <18-Month Age Stratum

The IRC will review all post–Vaccination 1, 7-day e-diary and AE data obtained from sentinel subjects aged 12 to <15 months. Based on the review, the IRC will select the bivalent rLP2086 dose level to be studied in the Stage 1 expanded-enrollment phase. Younger-age sentinel subjects cannot participate in the 120-µg dose level before the safety data of the 120-µg dose level have been found to be acceptable in the 120-µg older-age sentinel cohort.

The expanded-enrollment phase for this age group will enroll approximately 132 subjects: 66 aged 12 to <15 months and 66 aged 15 to <18 months. Within each of these substratified age groups, subjects will be randomly assigned in a 2:1 ratio to the selected dose level of bivalent rLP2086 or HAV vaccine/saline.

In the event that neither dose level is considered to exhibit a satisfactory safety profile for the 12- to <15-month age group sentinel cohort, expanded enrollment will not commence in the 12- to <18-month age group. So that the study may meet its enrollment numbers, additional enrollment will be permitted in the 18- to <24-month age group.

3.5.2. 18- to <24-Month Age Stratum

The IRC will review all post–Vaccination 1, 7-day e-diary and AE data obtained from sentinel subjects aged 18 to <24 months. Based on the review, the IRC will select the bivalent rLP2086 dose level to be studied in the Stage 1 expanded-enrollment phase.

Once the dose level is selected, an additional approximately 132 subjects aged 18 to <24 months will be enrolled. Subjects will be randomly assigned in a 2:1 ratio to the selected dose level of bivalent rLP2086 or HAV vaccine/saline.

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3.6. Progression to Stage 2

For all subjects completing Stage 1, a telephone contact will occur at Visit 10 to notify the parent(s)/legal guardian of their child's randomization allocation. Only those subjects who received the 3-vaccination series of bivalent rLP2086 (irrespective of dose level) will continue through Stage 2 to study completion. Subjects who received the 3-vaccination series of HAV vaccine/saline will conclude the study with the Visit 10 telephone contact (Section 6.1.10).

Pfizer will release unblinding information to the investigator when subjects have completed Visit 8 and before subjects reach Visit 10. Subjects will receive their randomization allocation at Visit 10. Additional information is included in the study reference manual (SRM).

Stage 2 will evaluate the duration of the MnB-specific immune response as measured by hSBA at 2, 3, and 4 years after Vaccination 3 with bivalent rLP2086.

3.7. Approximate Duration of Subject Participation

All subjects will participate in Stage 1 for approximately 18 months, will attend 8 clinic visits, and will receive 2 scheduled telephone contacts.

Subject participation in Stage 2 will last for approximately 2 years. Over this period, subjects will be asked to attend 3 scheduled clinic visits.

The total study duration for subjects who complete Stage 2 will be approximately 4.5 years (54 months).

3.8. Approximate Duration of Study

The approximate duration of each stage is anticipated to be as follows.

Stage 1: Approximately 2 years 10 months (34 months)

Stage 2: Approximately 3 years 4 months (40 months)

Total duration of the study is anticipated to be 5 years 10 months (70 months)

3.9. Approximate Number of Subjects

Approximately 396 subjects will participate in Stage 1. Approximately 264 Stage 1 subjects are expected to continue to Stage 2.

4. SUBJECT SELECTION

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

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4.1. Inclusion Criteria

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

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 parent(s)/legal guardian has been informed of all pertinent aspects of the study (parent[s]/legal guardian must be over 18 years old to consent for the child to be considered for inclusion in this study).
- 2. Subject must have received all vaccinations in the relevant national immunization program (NIP) for his or her age group.
- 3. Male or female subject aged
 - 12 to <15 months or 18 to <24 months during sentinel-cohort enrollment
 - 12 to <24 months during expanded-cohort enrollment
- 4. Subject is determined to be in good health by medical history, physical examination, and judgment of the investigator.
- 5. Subject's parent(s)/legal guardian is willing and able to comply with the child's scheduled visits, vaccination regimen, laboratory tests, and other study procedures.
- 6. Subject is available for the entire study period and his or her parent(s)/legal guardian can be reached by telephone.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

- 1. Previous vaccination with any meningococcal serogroup B vaccine.
- 2. Previous vaccination with HAV vaccine, or requirement to receive nonstudy HAV vaccine during Stage 1 of the study.
- 3. Contraindication to vaccination with any HAV vaccine or known latex allergy.
- 4. Receiving any allergen immunotherapy.
- 5. A previous anaphylactic reaction to any vaccine or vaccine-related component.
- 6. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection.

- 7. A known or suspected disorder 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 or those receiving systemic immunosuppressive therapy. Subjects with terminal complement deficiency may be included. Please refer to the SRM for additional details.
- 8. History of microbiologically proven disease caused by *N meningitidis* or *Neisseria gonorrhoeae*.
- 9. Significant neurologic 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 until the end of Stage 1.
- 11. Current chronic use of systemic antibiotics.
- 12. Current participation in another investigational study. Participation in purely observational studies is acceptable.
- 13. Received any investigational drugs, vaccines or devices within 28 days before administration of the first study vaccination and/or during study participation.
- 14. Any neuroinflammatory or autoimmune condition, including but not limited to transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
- 15. Other severe acute or chronic medical or psychiatric condition 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.
- 16. Subjects who are children of investigational site staff members or relatives of those site staff members or subjects who are children of Pfizer employees directly involved in the conduct of the study.

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 antipyretic medication on the planned day of vaccination.
- 3. Subject has received any nonstudy meningococcal vaccines or any vaccine containing all or individual antigens included in DTaP (ie, diphtheria, tetanus, and acellular pertussis [DTaP]) vaccines within the previous 28 days (see Section 5.7.3).

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- 4. Subject has received a nonlive vaccine other than described in delay criterion #3 (or intramuscular/sublingual allergen immunotherapy) within 14 days, or a live vaccine within 28 days, prior to investigational product administration.
- 5. Subject is less than 5 days into a course of systemic antibiotics.
- 6. 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.
- 2. Subject has received any blood products, including immunoglobulin, within 6 months before any blood draw during Stage 2.

4.5. 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' parent(s)/legal guardian are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another health care professional not involved in the subject's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject's parent(s)/legal guardian directly, and if a parent(s)/legal guardian calls that number, he or she will be directed back to the investigational site.

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5. INVESTIGATIONAL PRODUCT

5.1. Allocation to Investigational Product

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) that is accessible 24 hours a day, 365 days a year. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the project and protocol number, the investigator site number, the subject number, and the date of birth of the subject. The site personnel will then be provided with a subject randomization number and dispensable unit (DU) or kit 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 will provide a confirmation report containing the subject randomization number and DU or kit number assigned. The confirmation report must be stored in the site's files.

There is a 24-hour-a-day, 365-days-a-year IRT help desk available for any questions or issues. The study-specific IRT reference manual will provide contact information and further details on the use of the IRT.

5.2. Blinding

5.2.1. Maintaining the Blind

5.2.1.1. Unblinded Study Personnel

As the physical appearances of bivalent rLP2086, HAV vaccine, and saline differ, dispensing and administration of the investigational product will be performed by an unblinded dispenser/administrator. The unblinded dispenser/administrator will at all times (other than as described in Section 5.2.2) keep the identity of the randomized, allocated vaccination concealed from parent(s)/legal guardian/other family members and blinded study staff. Unblinded study staff will not take part in any subject assessments/interviews/data collection or CRF data entry; however, investigational product dispensing and administration should be noted in the study/medical record (while maintaining the blind) and accountability logs.

So that subject safety and stopping rule criteria can be closely monitored and responded to in a timely fashion, a subset of sponsor representatives will be unblinded (see the IRC charter). These include the medical clinicians, clinical scientists, and statisticians. In addition, an investigational product monitor(s) will be required to monitor the pharmacy dispensing records.

5.2.1.2. Blinded Study Personnel

All other site personnel, including the investigator, investigator staff, subjects, and subjects' parent(s)/legal guardian, will be blinded to investigational product assignments until randomization allocations are made available. Pfizer will release unblinding information to the investigator when subjects have completed Visit 8 and before subjects reach Visit 10.

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Subjects will receive their randomization allocation at Visit 10. Additional information is included in the SRM.

Stage 2 will be unblinded.

All immunogenicity assays will be performed in a central laboratory by blinded laboratory staff.

5.2.2. 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 the case of a medical emergency, or when knowledge of the investigational product assignment is required, for the medical management of an individual subject, the individual's randomization assignment may be revealed. Whenever possible, the investigator or subinvestigator should consult with a member of the study team prior to breaking any blind. When this is not possible, the investigator should proceed with breaking the blind and notify the sponsor as soon as practically possible that the blind has been broken. When the blinding code is broken, the date and reason must be fully documented in the source notes and in the CRF. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

5.3. Subject Compliance

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

5.4. Investigational Product Supplies

5.4.1. Dosage Forms and Packaging

The bivalent rLP2086 formulation is described in Table 5 below.

 Table 5.
 Bivalent rLP2086 Investigational Product Formulation

Ingredient	Component Grade	Function	Dose Level	
			60-µg	120-μg
CCI				

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Table 5. Bivalent rLP2086 Investigational Product Formulation

Ingredient	Component Grade	Function	Dose Level	
			60-µg	120-µg
CCI				

A licensed pediatric HAV vaccine to be administered at Visit 1 (Vaccination 1) and Visit 6 (Vaccination 3) will be provided in a 0.5-mL dose for injection. Information on which licensed pediatric HAV vaccine is to be used is contained in the investigational product manual.

A placebo (sterile saline for injection containing 0.85% sodium chloride in a 0.5-mL dose) will be administered at Visit 4 (Vaccination 2).

The investigational products (bivalent rLP2086 and HAV vaccine/saline) will be provided by the sponsor to each study site. Study vaccines will be packed and labeled as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. Each investigational product will be labeled with a unique kit number.

HAV vaccine (at Months 0 and 6) has been chosen as the control in this study. In comparison to other recommended vaccines for this age group, HAV vaccine has a better tolerability profile. In addition, HAV vaccine will confer a benefit to subjects who may become at increased risk for hepatitis A viral infection either during future travel or during other exposures. The generally recommended regimen for HAV vaccine is 2 doses at Months 0 and 6. In this study, saline is given at Month 2 to maintain the study blind.

5.4.2. Preparation and Dispensing

See the dosage and administration instructions (DAI) for bivalent rLP2086 and saline or the licensed pediatric HAV vaccine package insert for instructions in how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by 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 products will be administered to blinded subjects.

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5.4.3. 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, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. In this observer-blinded study, the study staff dispensing and administering the vaccine will be unblinded, but all other site personnel, including the principal investigator (PI), will be blinded.

Only a third-party unblinded medically qualified member of the study staff will administer the investigational product. Investigational product administration details (ie, date of administration, kit number, volume, route, and site of administration) will be recorded on the CRF. Investigational product accountability will be documented as per Section 5.6.

As shown in Table 6, bivalent rLP2086 will be administered 3 times over the course of the study: the first vaccination at Visit 1 (Month 0), second vaccination at Visit 4 (Month 2), and third vaccination at Visit 6 (Month 6). Bivalent rLP2086 will be administered as an intramuscular injection into either the deltoid muscle or anterolateral thigh muscle. If muscle mass in the deltoid is not adequate for intramuscular injection, then the thigh is the preferred injection site. Site of administration (eg, left/right arm/thigh) should be noted in the source notes and the CRF.

HAV vaccine will be administered twice over the course of the study: the first vaccination at Visit 1 (Month 0) and third vaccination at Visit 6 (Month 6). Saline will be administered at the second vaccination (Month 2) time point. HAV vaccine/saline will be administered as an intramuscular injection into either the deltoid muscle or anterolateral thigh muscle. If muscle mass in the deltoid is not adequate for intramuscular injection, then the thigh is the preferred injection site. Site of administration (eg, left/right arm/thigh) should be noted in the source notes and the CRF.

The schedule of vaccine administration is shown in Table 6 and the Schedule of Activities.

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Table 6. Investigational Product Administration Schedule

Sentine	l Enrollment, Stage 1			
		Visit 1	Visit 4	Visit 6
		Month 0	Month 2	Month 6
uo (60 μg of bivalent rLP2086	60 μg of bivalent rLP2086	60 μg of bivalent rLP2086	60 μg of bivalent rLP2086
Randomization Cohort (2:1)	HAV vaccine	Pediatric HAV vaccine	Saline placebo	Pediatric HAV vaccine
andon Cohor	120 μg of bivalent rLP2086	120 μg of bivalent rLP2086	120 μg of bivalent rLP2086	120 μg of bivalent rLP2086
R.	HAV vaccine	Pediatric HAV vaccine	Saline placebo	Pediatric HAV vaccine
Expand	ed Enrollment, Stage 1			
		Visit 1	Visit 4	Visit 6
		Month 0	Month 2	Month 6
Randomization Cohort (2:1)	Selected dose level (60 µg or 120 µg) of bivalent rLP2086 (dose level may differ between age groups)	Selected dose level of bivalent rLP2086	Selected dose level of bivalent rLP2086	Selected dose level of bivalent rLP2086
Ran Cc	HAV vaccine	Pediatric HAV vaccine	Saline placebo	Pediatric HAV vaccine

Abbreviation: HAV = hepatitis A virus.

5.5. Investigational Product Storage

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

The investigational product(s) should be stored in its original container and in accordance with the product label. For storage, the preferred orientation of the vaccines is horizontal. See the DAI or package insert for storage conditions of the product.

Storage conditions stated in the bivalent rLP2086 IB or the pediatric HAV vaccine USPI will be superseded by the investigational product kit label storage instructions. All vaccines will be shipped at +2°C to +8°C to each study site upon request. Upon receipt at the study site, the vaccines should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

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

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vaccination phase of the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Specific details regarding temperature monitoring, procedures for the review of temperature deviations, and information the site should report for each excursion will be provided to the site in the investigational product manual.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions.

5.6. Investigational Product Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

The investigator/designee must maintain a complete and current accountability record. Investigational product accountability applies to such products when they are required by the protocol and supplied (shipped) by the sponsor (including diluents such as sterile water for injection). The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). 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 are discarded at the point of use. Investigational product return must be documented on the accountability log.

5.7. Concomitant Treatment(s)

The product name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD to study completion will be recorded in 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 an e-diary) from the signing of the ICD to Visit 8 (Month 12; 6-month follow-up visit) will be recorded in the CRF.

Non-AE-related concomitant medications (other than vaccinations) will not be collected. A study visit AE checklist will be used as a guide, completed at each scheduled study visit, and included in the source documentation. Please refer to the SRM for details.

5.7.1. Prohibited During the Study

The following medications and treatments are prohibited or restricted:

- For the duration of the vaccination phase of Stage 1 (through Visit 7), prophylactic use of antipyretic and other pain medications to prevent symptoms that might occur as a result of study vaccination is not permitted.
- On the day of planned vaccination, if the subject has received antipyretic medications and/or other pain medications, vaccination should be temporarily delayed as specified in Section 4.3.
- Nonstudy meningococcal vaccines and any vaccines containing all or individual antigens included in DTaP vaccines are not permitted before Visit 5 (1 month after the second vaccination visit) and within 28 days of any study vaccination (Visit 1, Visit 4, or Visit 6).
- Other nonlive or live nonstudy vaccines are not permitted within 14 and 28 days, respectively, of any study vaccination.
- Any child receiving nonstudy HAV vaccine during Stage 1 must be withdrawn from the study.
- Intramuscular/sublingual allergen immunotherapy is not permitted within 14 days of any study vaccination.
- Systemic (oral, intravenous, or intramuscular) corticosteroid therapy is not permitted within 28 days of any study vaccination.

5.7.2. Permitted During the Study

The following medications and treatments are permitted:

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed at any time, and while standard clinical care should be prioritized, efforts should be made to administer nonstudy vaccines as follows:
- Nonstudy vaccines (other than any meningococcal vaccines and vaccines containing all
 or individual antigens included in DTaP vaccines) that are part of recommended
 immunization schedules are allowed anytime during the study but should not be
 administered within 14 days (for nonlive vaccines) and 28 days (for live vaccines) of
 study vaccine administration.

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- Nonstudy vaccines containing all or individual antigens included in DTaP vaccines and meningococcal vaccines (excluding meningococcal serogroup B vaccines) are permitted at any time after Visit 5 (1 month after the second vaccination visit).
- Antipyretic and other pain medication to treat symptoms following investigational product administration is permitted.
- A local/topical anesthetic may be applied before blood draw.
- Topical antibiotics are permitted.
- Topical and inhaled corticosteroids are permitted.

5.7.3. Prior Treatment

If the subject is known to have ever received a vaccine with a polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein (PRP-OMP), the name of the vaccine and date of administration will be recorded on the CRF. PRP-OMP—containing vaccines that are or have been commercially available are Comvax, Procomvax, and PedvaxHIB. These are also listed in the SRM.

All nonstudy vaccines received since birth and administered during the study period will be captured. The trade name (if known) and date of administration (dd/mmm/yyyy) for each of these will be recorded on the CRF. Verbal vaccination history is acceptable and should be supplemented with written confirmation if possible.

5.7.4. Prohibited Prior Treatment(s)

The following are prohibited:

- Receipt of any blood products, including immunoglobulin, within 6 months of the first study vaccination until the end of Stage 1.
- During Stage 2, blood products or immunoglobulin may be administered, but blood draws for immunogenicity analysis should not be taken within 6 months after administration. Blood draws should be delayed as appropriate.

6. STUDY PROCEDURES

Before enrollment and before any study-specific procedures are performed, voluntary, written study-specific informed consent will be obtained from the subject's parent(s)/legal guardian, who must be, at the time of consent, at least 18 years of age. Each signature on the ICD must be personally dated by the signatory. A copy of the signed and dated ICD must be given to the subject's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained prior to participation in the study.

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6.1. Study Visits

6.1.1. Visit 1 (Month 0), Vaccination 1 (Day 1)

- Obtain written informed consent from the subject's parent(s)/legal guardian before performing any study-specific procedures. Informed consent should be obtained by the PI or delegate of the PI. Record the date of consent in the CRF.
- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met. In the case where temporary delay criteria are met, all assessments and procedures noted below should be delayed, reperformed, or reconfirmed, as applicable, on the rescheduled date of vaccination. Randomization, however, should only ever occur on the day of and prior to the subject's first study vaccination.
- 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 allergies (drug/nondrug).
- Measure height (or length for nonwalking subjects) and weight. Perform a physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, neurologic, 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 physical examination must be performed on the day of vaccination to document that no change in health has occurred in the interim.
- Record the subject's complete vaccination history. Record trade name (if known) and date (dd/mmm/yyyy) of all previously administered vaccines.
- On the day of and prior to vaccination, measure and record in the source document the subject's axillary temperature, heart rate, and respiratory rate. Record the route by which the temperature was taken.
- After all eligibility criteria are confirmed, the investigator or designee will enter the subject into the CRF system and obtain a subject number.
- Prior to and always on the day of vaccination, collect a blood sample (approximately 5 mL) from the subject. Collect the blood sample only if the subject is eligible for vaccination on the same day. Local/topical anesthetic may be used to numb the skin prior to the blood draw.

- Vaccination cannot occur until all prerequisite procedures, including the prevaccination blood draw, have occurred. Using the IRT, obtain the randomization number and vaccine assignment. On receipt of the randomization allocation, and provided no vaccination delay criteria are met, the unblinded dispenser prepares the assigned investigational product ready for administration.
- The unblinded administrator administers a single intramuscular injection of investigational product (bivalent rLP2086 or HAV vaccine) into the deltoid muscle or anterolateral thigh muscle. Kit and randomization numbers, site of administration, and time of administration are recorded for CRF entry.
- Following investigational product administration, the blinded observer will observe the subject for at least 30 minutes (or longer as per local practice) for any acute reactions. Any events observed within 30 minutes after vaccine administration will be recorded on the AE CRF. These AEs are defined as immediate AEs. Date and time of vaccination and date and time of onset of the event will be captured in the CRFs. Record AEs as described in the AE reporting section (Section 8) and the Schedule of Activities. The time of onset will be recorded for any AE that occurs on the same day as investigational product administration.
- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4).
- Issue the e-diary and provide instructions on the collection and recording of local reactions and systemic events and on the use and type of antipyretic medication. Ask the subject's parent(s)/legal guardian to complete the e-diary from Day 1 to Day 7 after vaccination, with Day 1 being the day of vaccination. Instructions on daily transfer of data and charging the battery should also be provided.
- Issue a caliper, a measuring tape, and a digital thermometer and provide verbal and written instructions on their use. Ask the parent(s)/legal guardian to use the caliper to measure the maximum diameter of redness and swelling at the injection site each day for 7 days after study vaccination and record in the e-diary.
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if the child experiences severe redness or swelling at the injection site (>14 caliper units) or an axillary temperature ≥39.0°C (102.2°F), within 7 days after vaccination, as an unscheduled visit should be arranged (see Section 6.3).
- If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units, Section 7.4.1), the parent(s)/legal guardian should also use the measuring tape 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 to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤14 caliper units.
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Remind the subject's parent(s)/legal guardian that nonstudy vaccinations should not be administered within a 28-day window (live vaccines) or 14-day window (nonlive vaccines or intramuscular/sublingual allergen immunotherapy) either before or after a study vaccine administration.
- Schedule an appointment for the next study visit within the time window per protocol.
- Remind the subject's parent(s)/legal guardian to bring the e-diary to the next study visit.
- Complete the source documents.
- Complete the CRFs and the investigational product accountability records.

Between visits, review the e-diary data online at frequent intervals. For sentinel-cohort subjects, following Vaccination 1 online review must be performed daily (see Section 7.9 Stopping Rules). Contact the parent(s)/legal guardian in order to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information should be entered into the CRF at the next study visit of the subject.

For sentinel-cohort subjects only:

- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if the child experiences any MAE or SAE during the active safety period (Day 1 to Day 7) (see Section 7.9 Stopping Rules).
- The investigator must contact the Pfizer study physician immediately in the event of a subject's experiencing an MAE or SAE during the active safety period (Day 1 to Day 7). See Section 7.9 Stopping Rules for further detail on safety reporting requirements for sentinel-cohort subjects. All AEs should be promptly captured in the CRF and/or SAE reports as applicable (see Section 8 Safety for reporting requirements).

6.1.2. Visit 2 (Week 1), Follow-up Visit (7 to 10 Days After Visit 1)

• Confirm that the subject continues to be eligible for the study and does not meet any withdrawal criteria (Section 6.4).

- Record nonstudy vaccinations.
- Review the subject's e-diary data and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Collect the e-diary.
- Using the study visit AE checklist as a guide:
 - Inquire whether the subject had any NDCMCs 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, and medication use. Please refer to the SRM for additional details.
 - Inquire about neuroinflammatory conditions 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 section (Section 8) and the Schedule of Activities. The time of onset will be recorded for any AE that occurs 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 ongoing.
- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4).
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if any illness requiring medical attention or hospitalization occurs between visits.
- Notify the subject's parent(s)/legal guardian that he or she will receive a phone call (Visit 3) in approximately 3 weeks (25 to 35 days after Visit 1) to follow up on the child's health, any ongoing AEs, and new concomitant medications and nonstudy vaccinations.
- Schedule an appointment for the next study visit within the time window per protocol.
- Remind the subject's parent(s)/legal guardian that nonstudy vaccinations should not be administered within a 28-day window (live vaccines) or 14-day window (nonlive vaccines or intramuscular/sublingual allergen immunotherapy) either before or after a study vaccine administration.
- Complete the source documents and CRF.

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For sentinel-cohort subjects only:

- Review the e-diary data and discuss with the subject's parent(s)/legal guardian if the child experienced any MAE or SAE during the active safety reporting period (Day 1 to Day 7). See Section 7.9 Stopping Rules for further details on the safety reporting requirements for sentinel-cohort subjects.
- The investigator must contact the Pfizer study physician immediately in the event of a subject's experiencing an MAE or SAE during the active safety reporting period (Day 1 to Day 7). See Section 7.9 Stopping Rules for further details on safety reporting requirements for sentinel-cohort subjects.

6.1.3. Visit 3 (Month 1), Day 30 Telephone Contact (25 to 35 Days After Visit 1)

Approximately 1 month after Vaccination 1, contact the subject's parent(s)/legal guardian and perform the following:

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.4).
- Record nonstudy vaccinations.
- Using the study visit AE checklist as a guide:
 - Inquire whether the subject had any NDCMC s 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, and medication use. Please refer to the SRM for additional details.
 - Inquire about neuroinflammatory conditions 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 section (Section 8) and the Schedule of Activities. The time of onset will be recorded for any AE that occurs 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 ongoing.
- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4). Ask the subject's parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs between visits.
- Confirm the subject's next clinic appointment.
- Complete the source documents and the CRF.

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6.1.4. Visit 4 (Month 2), Vaccination 2 (42 to 70 Days After Visit 1)

Note that any sentinel subject who has been withdrawn from the study on IRC/external data monitoring committee (EDMC) recommendations will complete a modified Visit 4. Procedures to be followed are detailed in Section 6.1.11.

Visit 4 must not be performed on any sentinel subject until the IRC has completed the post-Vaccination 1 safety review (specific to the subject's sentinel cohort) and has given its recommendations to proceed with the study. For sentinel-cohort subjects who are unable to receive Vaccination 2 within the protocol-specified window because of availability of the IRC recommendation, the visit window may be extended for individual subjects by up to 14 days from the receipt of the positive IRC recommendation, at the discretion of the sponsor.

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal or temporary delay criteria (Section 4.3, Section 4.4, and Section 6.4). In the case where temporary delay criteria are met, all assessments and procedures noted below should be delayed, reperformed, or reconfirmed, as applicable, on the rescheduled date of vaccination.
- Perform a brief physical examination comprising general appearance, ears, throat, heart, and lungs.
- On the day of and prior to vaccination, measure and record in the source document the subject's axillary temperature, heart rate, and respiratory rate. Record the route by which the temperature was taken.
- Record nonstudy vaccinations.
- The unblinded administrator administers a single intramuscular injection of investigational product (bivalent rLP2086 or saline) into the deltoid muscle or anterolateral thigh muscle. Kit number, site of administration, and time of administration are recorded for CRF entry.
- Following investigational product administration, the blinded observer will observe the subject for at least 30 minutes (or longer as per local practice) for any acute reactions. Any events observed within 30 minutes after vaccine administration will be recorded as immediate AEs on the AE CRF. Date and time of vaccination and date and time of onset of the event will be captured in the CRFs.
- Using the study visit AE checklist as a guide:
 - Inquire whether the subject had any NDCMC s 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, and medication use. Please refer to the SRM for additional details.

- Inquire about neuroinflammatory conditions 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 section (Section 8) and the Schedule of Activities. The time of onset will be recorded for any AE that occurs 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 ongoing.
- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4).
- Issue the e-diary and provide instructions on the collection and recording of local reactions and systemic events (reactogenicity) and on the use and type of antipyretic medication. Ask the subject's parent(s)/legal guardian to complete the e-diary from Day 1 to Day 7 after vaccination, with Day 1 being the day of vaccination. Instructions on daily transfer of data and charging the battery should also be provided.
- If required, reissue a caliper, a measuring tape, and a digital thermometer and provide verbal and written instructions on their use. Ask the parent(s)/legal guardian to use the caliper to measure the maximum diameter of redness and swelling at the injection site each day for 7 days after study vaccination and record in the e-diary.
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if their child experiences severe redness or swelling at the injection site (>14 caliper units) or an axillary temperature ≥39.0°C (102.2°F), within 7 days after vaccination, as an unscheduled visit should be arranged (Section 6.3).
- If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units, Section 7.4.1), the parent(s)/legal guardian should also use the measuring tape 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 to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤14 caliper units.
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Remind the subject's parent(s)/legal guardian that nonstudy vaccinations should not be administered within a 28-day window (live vaccines) or 14-day window (nonlive vaccines or intramuscular/sublingual allergen immunotherapy) before or after a study

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

- Remind the subject's parent(s)/legal guardian to bring the e-diary to the next study visit.
- Complete the source documents.
- Complete the CRF and update the investigational product accountability records.

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

6.1.5. Visit 5 (Month 3) (28 to 42 Days After Visit 4) Blood Collection

- Confirm that subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.4) and none of the temporary delay criteria for the blood draw (Section 4.4).
- Obtain a 5-mL blood sample. Local anesthetic may be applied prior to the blood draw.
- Record nonstudy vaccinations.
- Review the subject's e-diary data and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Collect the e-diary.
- Using the study visit AE checklist as a guide:
 - ➤ Inquire whether the subject had any NDCMC 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, and medication use. Please refer to the SRM for additional details.
 - Inquire about neuroinflammatory conditions 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 section (Section 8) and the Schedule of Activities. The time of onset will be recorded for any AE that occurs 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 ongoing.

- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4).
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs between visits.
- Remind the subject's parent(s)/legal guardian that nonstudy vaccinations should not be administered within a 28-day window (live vaccines) or 14-day window (nonlive vaccines or intramuscular/sublingual allergen immunotherapy) either before or after a study vaccine administration.
- Schedule an appointment for the next study visit within the time window per protocol.
- Complete the source documents and CRF.

Between visits, contact the subject's parent(s)/legal guardian in order to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information should be entered into the CRF.

6.1.6. Visit 6 (Month 6), Vaccination 3 (105 to 126 Days After Visit 4)

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal or temporary delay criteria (Section 4.3, Section 4.4, and Section 6.4). In the case where temporary delay criteria are met, all assessments and procedures noted below should be delayed, reperformed, or reconfirmed, as applicable, on the rescheduled date of vaccination.
- Perform a brief physical examination comprising general appearance, ears, throat, heart, and lungs.
- On the day of and prior to vaccination, measure and record in the source the subject's axillary temperature, heart rate, and respiratory rate. Record the route by which the temperature was taken.
- Record nonstudy vaccinations.
- The unblinded administrator administers a single intramuscular injection of investigational product (bivalent rLP2086 or HAV vaccine) into the deltoid muscle or anterolateral thigh muscle. Kit number, site of administration, and time of administration are recorded for CRF entry.
- Following investigational product administration, the blinded observer will observe the subject for at least 30 minutes (or longer as per local practice) for any acute reactions. Any events observed within 30 minutes after vaccine administration will be recorded as an immediate AE on the AE CRF. Date and time of vaccination and date and time of onset of the event will be captured in the CRFs.

- Using the study visit AE checklist as a guide:
 - ➤ Inquire whether the subject had any NDCMC 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, and medication use. Please refer to the SRM for additional details.
 - Inquire about neuroinflammatory conditions 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 section (Section 8) and the Schedule of Activities. The time of onset will be recorded for any AE that occurs 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 ongoing.
- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4).
- Issue the e-diary and provide instructions on the collection and recording of local reactions and systemic events (reactogenicity) and on the use and type of antipyretic medication. Ask the subject's parent(s)/legal guardian to complete the e-diary from Day 1 to Day 7 after vaccination, with Day 1 being the day of vaccination. Instructions on daily transfer of data and charging the battery should also be provided.
- If required, reissue a caliper, a measuring tape, and a digital thermometer and provide verbal and written instructions on their use.
- Ask the parent(s)/legal guardian to use the caliper to measure the maximum diameter of redness and swelling at the injection site, each day for 7 days after study vaccination, and record in the e-diary.
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if the child experiences severe redness or swelling at the injection site (>14 caliper units) or an axillary temperature ≥39.0°C (102.2°F), within 7 days after vaccination, as an unscheduled visit should be arranged (Section 6.3).
- If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units, Section 7.4.1), the parent(s)/legal guardian should also use the measuring tape 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 to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤14 caliper units.

- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Remind the subject's parent(s)/legal guardian that nonstudy vaccinations should not be administered within a 28-day window (live vaccines) or 14-day window (nonlive vaccines or intramuscular/sublingual allergen immunotherapy) before or after a study vaccine administration.
- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Remind the subject's parent(s)/legal guardian to bring the e-diary to the next study visit.
- Complete the source documents.
- Complete the CRF and update the investigational product accountability records.

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

6.1.7. Visit 7 (Month 7) (28 to 42 Days after Visit 6) Blood Collection

- Confirm that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.4) and none of the temporary delay criteria for the blood draw (Section 4.4).
- Obtain a 5-mL blood sample. Local anesthetic may be applied prior to the blood draw.
- Record nonstudy vaccinations.
- Review the subject's e-diary data and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Collect the e-diary.
- Using the study visit AE checklist as a guide:
 - Inquire whether the subject had any NDCMCs 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, and medication use. Please refer to the SRM for additional details.

- ➤ Inquire about neuroinflammatory conditions 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 section (Section 8) and the Schedule of Activities. The time of onset will be recorded for any AE that occurs 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 ongoing.
- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4).
- Issue a memory aid.
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs between visits.
- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents and CRF.

Between visits, contact the subject's parent(s)/legal guardian in order to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information should be entered into the CRF.

6.1.8. Visit 8 (Month 12) (168 to 196 Days After Visit 6) 6-Month Blood Draw

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.4) and none of the temporary delay criteria for the blood draw (Section 4.4).
- Obtain a 5-mL blood sample. Local anesthetic may be applied prior to the blood draw.
- Record nonstudy vaccinations.
- Using the study visit AE checklist as a guide:
 - Inquire whether the subject had any NDCMCs 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, and medication use. Please refer to the SRM for additional details

- Inquire about neuroinflammatory conditions 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 section (Section 8) and the Schedule of Activities. Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still ongoing.
- ➤ Record concomitant medications used to treat SAEs, NDCMCs or MAEs (see Section 5.7 and Section 7.6.4).
- Ask the subject's parent(s)/legal guardian to contact the investigator if any AEs or research-related injuries (RRIs) occur within 48 hours after the blood draw as described in Section 8.
- Issue a memory aid if required.
- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents and CRF.

6.1.9. Visit 9 (Month 18) (337 to 365 Days After Visit 6) Antibody Persistence Blood Draw

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.4) and none of the temporary delay criteria for the blood draw (Section 4.4).
- Obtain a 5-mL blood sample. Local anesthetic may be applied prior to the blood draw.
- Record any AEs and RRIs occurring within 48 hours after the blood draw as described in Section 8 and the Schedule of Activities
- Record nonstudy vaccinations.
- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still ongoing.
- Notify the subject's parent(s)/legal guardian that he or she will receive a phone call
 (Visit 10) to follow up on his or her child's health, any ongoing AEs, and new nonstudy
 vaccinations. In addition, the subject's parent(s)/legal guardian can expect to receive
 notification of the child's randomization group (bivalent rLP2086 or HAV
 vaccine/saline).
- Issue a memory aid if required.

• Complete the source documents and CRFs.

6.1.10. Visit 10 (End of Stage 1) Telephone Contact

Only when the randomization codes have been released by the sponsor/designee to the investigator may Visit 10 occur. The procedures and order to be followed at the Visit 10 telephone contact are as follows:

Upon receipt of randomization codes from sponsor, contact the subject's parent(s)/legal guardian and perform the following:

- Record nonstudy vaccinations.
- Complete the source documents and CRFs.
- Notify the parent(s)/legal guardian of the child's randomization group, and manage as follows:
 - Bivalent rLP2086-vaccinated subjects (sentinel- and expanded-enrollment cohorts, irrespective of dose level) who completed Stage 1 are eligible to progress to Stage 2 (Section 6.2). Schedule an appointment for the next clinic visit in approximately 12 months (24 months [±1 month] after Visit 6).
 - All subjects randomly assigned to HAV vaccine who complete Stage 1 will finish the study requirements with this contact.

6.1.11. Discontinued Sentinel Subjects/Cohorts

For any sentinel subject/cohort that is discontinued from the study on IRC/EDMC recommendations, the following procedures will be performed at Visit 4 or within 2 weeks after receiving notification of discontinuance if Visit 4 has been attended:

- Perform a brief physical examination comprising general appearance, ears, throat, heart, and lungs. Measure heart rate, respiratory rate, and temperature.
- Record nonstudy vaccinations.
- Where applicable, review the subject's e-diary data and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Collect the e-diary.
- Using the study visit AE checklist as a guide:
 - Inquire whether the subject had any NDCMCs since the last visit. Inquire whether the subject had any of the following related to the AE since the last visit:

hospitalizations, visits to other medical facilities and medication use. Please refer to the SRM for additional details.

- Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Refer to the SRM for additional details.
- ➤ Record AEs as described in the AE reporting section (Section 8.14) and the Schedule of Activities. The time of onset will be recorded for any AE that occurred 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 ongoing.
- Record any AE-related hospitalizations or visits to medical facilities or healthcare practitioners. See SRM for additional details.
- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4).
- Ask the subject's parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Notify the subject's parent(s)/legal guardian that a telephone contact (Section 6.1.10) will occur approximately 6 months following the last study vaccination for safety follow-up.
- Complete the source documents.
- Complete the CRFs.

6.1.12. Subjects Who Withdraw Prior to Visit 8

For those subjects who withdraw before Visit 8, a telephone contact will occur approximately 6 months after the subject's last study vaccination:

- Using the study visit AE checklist as a guide:
 - ➤ Inquire whether the subject had any NDCMCs 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, and medication use. Please refer to the SRM for additional details.
 - Inquire about neuroinflammatory conditions 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 section (Section 8) and the Schedule of Activities. The time of onset will be recorded for any AE that occurred 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 ongoing.
- Record any AE-related hospitalizations or visits to medical facilities or health care practitioners. Refer to the SRM for additional details.
- Record concomitant medications used to treat AEs (see Section 5.7 and Section 7.6.4).
- Record nonstudy vaccinations.
- Complete the source documents and CRFs.
- Notify the parent(s)/legal guardian of the child's randomization group and manage as follows:
 - Bivalent rLP2086-vaccinated subjects will complete the study requirements with this contact
 - Subjects randomly assigned to receive HAV vaccine/saline will complete the study requirements with this contact.
 - Parent(s)/legal guardian of any subject randomly assigned to the HAV vaccine/saline cohort who did not complete Stage 1 should be informed to make arrangements to have the subject receive a booster vaccination of HAV vaccine using commercially available product.

6.2. Stage 2

Visit 11 should only be conducted for subjects who were randomly assigned and received 3 doses of bivalent rLP2086 at either dose level (60 µg or 120 µg).

6.2.1. Visit 11, Study Month 30, Immunogenicity 1 (24 Months After Vaccination 3 ± 30 Days)

- Confirm that the subject continues to be eligible for the study and does not meet any withdrawal criteria (Section 6.4).
- Confirm that the subject has not received a dose of systemic antibiotics less than 5 days before blood collection (Section 4.4). If the subject has received such a dose, delay the visit to meet the 5-day exclusionary period.

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- Confirm that the subject has not received blood products or immunoglobulin within the last 6 months. If the subject has received such products, discuss delaying the visit with the sponsor.
- Obtain a 5-mL blood sample. Local anesthetic may be applied prior to the blood draw.
- Record any AEs and RRIs occurring within 48 hours after the Visit 11 blood draw as described in Section 8 and the Schedule of Activities.
- Record nonstudy vaccinations received since the last study visit.
- Issue a memory aid.
- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents and CRFs.

6.2.2. Visit 12, Study Month 42, Immunogenicity 2 (36 Months After Vaccination 3 ± 30 Days)

- Confirm that the subject continues to be eligible for the study and does not meet any withdrawal criteria (Section 6.4).
- Confirm that the subject has not received a dose of systemic antibiotics less than 5 days before blood collection (Section 4.4). If the subject has received such a dose, delay the visit to meet the 5-day exclusionary period.
- Confirm that the subject has not received blood products or immunoglobulin within the last 6 months. If the subject has received such products, discuss delaying the visit with the sponsor.
- Obtain a 5-mL blood sample. Local/topical anesthetic may be applied prior to the blood draw.
- Record any AEs and RRIs occurring within 48 hours after the Visit 12 blood draw as described in Section 8 and the Schedule of Activities.
- Record nonstudy vaccinations received since the last study visit.
- Issue a memory aid.
- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents and CRFs.

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6.2.3. Visit 13, Study Month 54, Immunogenicity 3 (48 Months After Vaccination 3 ± 30 Days)

- Confirm that the subject continues to be eligible for the study and does not meet any withdrawal criteria (Section 6.4).
- Confirm that the subject has not received a dose of systemic antibiotics less than 5 days before blood collection (Section 4.4). If the subject has received such a dose, delay the visit to meet the 5-day exclusionary period.
- Confirm that the subject has not received blood products or immunoglobulin within the last 6 months. If the subject has received either of these products, discuss delaying the visit with the sponsor.
- Obtain a 5-mL blood sample. Local anesthetic may be applied prior to the blood draw.
- Record any AEs and RRIs occurring within 48 hours after the Visit 13 blood draw as described in Section 8 and the Schedule of Activities.
- Record nonstudy vaccinations received since the last study visit.
- Complete the source documents and CRFs.

6.3. Unscheduled Visits

The parent(s)/legal guardian will be requested to contact the study staff if the subject experiences a severe redness or swelling at the injection site (>14 caliper units) or a temperature $\geq 39.0^{\circ}$ C (102.2° F) in the 7 days after vaccination. If the parent(s)/legal guardian does not contact the site, the investigator is required to contact the parent(s)/legal guardian as soon as possible. The outcome of any contact will be recorded on the CRF. The investigator should determine if the subject requires an unscheduled visit. If the unscheduled visit does not take place following subject report of fever $\geq 39.0^{\circ}$ C (102.2° F) or severe redness/swelling, the reason must be documented in the CRF (for example, reaction no longer present or e-diary–entry error).

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

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

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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.

6.4. 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 (Section 4.1) and exclusion criteria (Section 4.2) should be taken into consideration when determining if a subject must be withdrawn. The investigator is not required to repeat the physical examination completed at Visit 1, unless clinically indicated.

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, AE (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.

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, returned to baseline, or in case of permanent impairment, until the condition stabilizes.

When a subject discontinues or is withdrawn from the study prior to completion, the investigator will notify the sponsor and, when possible, will perform the procedures indicated in Section 6.1.11 (discontinued sentinel subjects) or Section 6.1.12 (subjects who withdraw prior to Visit 8) if the subject has received at least 1 study vaccination.

Subjects may be withdrawn from the study at any time at the request of their parent(s)/legal guardian, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety 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's parent(s)/legal guardian. Details for contacting lost-to-follow-up subjects are provided in the SRM. 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's parent(s)/legal guardian return the e-diary (if applicable), request that the subject return for a final visit, if applicable, and follow up with the subject's parent(s)/legal guardian regarding any unresolved AEs.

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If the parent(s)/legal guardian withdraws the subject 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 fashion.

7.1. Immunogenicity

7.1.1. Blood Draw Volume

Stage 1

To facilitate immunogenicity analysis, subjects will have approximately 5 mL of blood collected at the following time points during Stage 1:

- Immediately before Vaccination 1;
- 1 Month after Vaccination 2;
- 1 Month after Vaccination 3;
- 6 Months after Vaccination 3;
- 12 Months after Vaccination 3.

In total, 25 mL will be collected over the 18-month period. Local/topical anesthetic may be used prior to blood draws.

Stage 2

To determine duration of immune response, Stage 2 subjects will have approximately 5 mL of blood collected at the following time points:

- 2 Years after Vaccination 3;
- 3 Years after Vaccination 3;
- 4 Years after Vaccination 3.

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In total, 15 mL will be collected over approximately 2.5 years. Local/topical anesthetic may be used prior to blood draws.

7.1.2. Serum Sample Storage

All serum samples should be stored in an upright position in a laboratory-grade manual-defrost freezer that does not cycle and forms ice that must be removed (a non-frost-free freezer), and that maintains a temperature of -15° C or lower.

It is the responsibility of the investigator(s) (or designee) to record daily freezer temperature readings, 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 sample collection, storage, shipping, temperature monitoring, and procedures for the review of temperature deviations will be provided in the SRM.

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7.1.3. Bivalent rLP2086 Serum Bactericidal Assay-Primary Test Strains

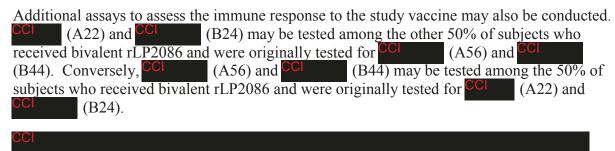
For assessment of the immune response to bivalent rLP2086, functional antibodies will be analyzed in hSBAs with meningococcal serogroup B strains. The hSBA measures antibodies in human sera that result in complement-dependent killing of the target meningococcal strain. Four (4) primary test strains, (A22), (A22), (A36), (B24), and (B24), will be used in the hSBAs for determination of the immunogenicity endpoints in this study. Sera obtained from all subjects prior to the first study vaccination, 1 month after the second vaccination, and 1, 6, and 12 months after the third study vaccination, and for Stage 2 subjects at 24, 36, and 48 months after the third study vaccination, will be used in these assays. The MnB hSBAs will be validated before any testing is performed.

Two (2) of the primary strains (EQ [A22] and EQ [B24]) will be tested at each blood sampling time point for half of the subjects (in both age groups), and the other 2 primary strains (EQ [A56] and EQ [B44]) will be tested at each blood sampling time point for the remaining half of the subjects.

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 provide 2 subject listings (randomly selected, 50% of subjects to be tested for [A22]/[E22]/[E34] and the remaining 50% of subjects to be tested for [A56]/[E34]) to the sponsor's sample management team. Both listings should follow the same randomization ratio (2:1) and age-strata distribution as in the study design. The same strain pair [A22] [B24] or [B24] or [A56]/[CCI] [B44]) will be tested across all visits for the same subjects.

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7.1.4. Additional Assays



7.2. 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 6) and the Schedule of Activities:

7.2.1. Physical Examination

The subject's medical history, physical examination, and vital signs should be obtained and documented at Visit 1 to capture baseline information and should include the following as a minimum:

- Vaccination history, past and present medical and surgical history of significance, and allergies. When taking the medical history, particular care must be taken to note any neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
- Weight, height (or length for nonwalking subjects), general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, neurologic status, musculoskeletal, and lymph nodes will be assessed. Significant observations from the physical examination will be documented in the CRF.

7.2.1.1. Brief Physical Examination

At vaccination Visits 4 and 6, as well as discontinued sentinel subject/cohort visits (Section 6.1.11), a brief physical examination of the subject's general appearance, ears, throat, heart, and lungs should be performed. Temperature, heart rate, and respiratory rate should also be measured and recorded. Record the route by which the temperature was taken.

7.2.2. Reactogenicity (Prompted Diary/E-Diary Events)

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 prospectively collected events are considered prompted diary/e-diary events and include the following:

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

Local reactions, systemic events, and use and type of antipyretic medication will be collected using an e-diary. For events that resolve after Day 7, the end date will be collected on the Symptom Resolved Date CRF. If the diary is not completed for 7 days, the end dates for events ongoing on the last day the diary was completed will be collected on the Symptom Resolved Date CRF.

7.3. Electronic Diary

The subject's parent(s)/legal guardian will be issued an e-diary, based on a personal digital assistant (PDA) or equivalent technology. They will be asked to monitor and record local reactions, systemic events, and the use and type of antipyretic medication on the day of vaccination and for 7 days following each vaccination. 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. Only the most severe rating for any of the local reactions or systemic events each day will be recorded in the e-diary. End dates of local reactions, systemic events, or use of antipyretic medications that was ongoing on the last day the diary was completed by the parent(s)/legal guardian will be collected on the CRF.

The investigator or designee must contact the parent(s)/legal guardian in order to obtain stop dates for any prompted diary/e-diary events or other AE data ongoing on the last day that the e-diary was completed. The stop dates are to be documented in the source documents and the information entered in the CRF. Data reported in the e-diary will be transferred electronically to the e-diary vendor (a trusted third party), where they will be available for review by investigators at all times via an Internet-based portal. At intervals agreed upon between the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator on the CRF.

Investigators will be required to review the e-diary data online at frequent intervals as part of the ongoing safety review and evaluation of subject compliance. For sentinel-cohort subjects, following Vaccination 1 online review must be performed daily (see Section 7.9 Stopping Rules).

7.4. Local Reactions

7.4.1. Injection Site Redness and Swelling

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

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

Table 7. Grading of Redness and Swelling

Mild	0.5 to 2.0 cm (1 to 4 caliper units)	
Moderate	2.5 to 7.0 cm (5 to 14 caliper units)	
Severe	>7.0 cm (>14 caliper units)	

7.4.2. Injection Site Tenderness

The parent(s)/legal guardian will be asked to assess whether tenderness is present at the injection site for the first 7 days following vaccination (Day 1 to Day 7) and grade it using the Grading of Tenderness, Table 8. The assessment will then be recorded in the e-diary.

Table 8. Grading of Tenderness

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

7.5. Systemic Events

7.5.1. Temperature

A digital thermometer will be given to the subject's parent(s)/legal guardian with instructions on how to measure the child's axillary temperature at home. Axillary temperature will be collected at evening bedtime 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 a temperature of ≥38.0°C (100.4°F).

Temperature will be measured and recorded to 1 decimal place and then categorized according to the Scale for Fever, Table 9:

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Table 9. 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 39.4 °C (102.2 °F to 103.0 °F)		
Temperature 39.5°C to 40.0°C (103.1°F to 104.0 °F)		
Temperature >40.0°C (>104.0°F)		

7.5.2. Other Systemic Events

The e-diary will be used to record the presence of other systemic events, including loss of or decreased appetite, drowsiness, and irritability daily for 7 days (Day 1 to Day 7) after each vaccination, using Grading of Other Systemic Events, Table 10.

Table 10. Grading of Other Systemic Events

	GRADE 1	GRADE 2	GRADE 3
	(mild)	(moderate)	(severe)
Loss of appetite	Decreased interest in	Decreased oral intake	Refusal to feed
or decreased appetite	eating		
Drowsiness	Increased or prolonged	Slightly subdued	Disabling not interested in
(synonym with	sleeping bouts	interfering with	usual daily activity
increased sleep)		daily activity	
Irritability (synonym with	Easily consolable	Requiring	Inconsolable;
fussiness, restless sleep;		increased attention	crying cannot
decreased sleep)			be comforted

7.5.3. Use of Antipyretic Medication

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

For the duration of the vaccination phase of Stage 1 (through Visit 7), prophylactic use of antipyretics and other pain medications to prevent symptoms that might occur as a result of study vaccination is not permitted.

On the day of planned vaccination, if the subject has received antipyretics and other pain medications, vaccination should be temporarily delayed as specified in Section 4.3.

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

Please refer to the SRM for further details.

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7.6. Other Safety Monitoring

7.6.1. Adverse Events

AEs and SAEs reported outside of the e-diary are recorded and reported as described in Section 8.

7.6.2. Immediate Adverse Events

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

7.6.3. Medically Attended Events and Newly Diagnosed Chronic Medical Conditions

MAEs and NDCMCs will be assessed throughout the vaccination period and up to Visit 8 (Month 12; 6-month follow-up visit) after the last study vaccination.

A medically attended event 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. This includes conditions that are undiagnosed prior to study entry (diagnosed while on the study) and that are not considered temporary conditions based upon the expected natural history of the condition.

7.6.4. Routine Medical Facility Visits, Elective Hospitalizations, and Routine Concomitant Medication Use Not Associated With Adverse Events

Routine visits to medical facilities and elective hospitalizations not associated with an AE, (ie, health care visits for preventive care, or for routine physical examinations), will not be collected. Non–AE-related concomitant medications other than vaccinations will not be collected. A study visit AE checklist will be used as a guide, completed at each scheduled study visit and telephone visit in Stage 1, and included in the source documentation. Please refer to the SRM for details.

7.6.5. Subject Memory Aid

The parent(s)/legal guardian will be given a memory aid at Visit 7 and as required thereafter. The memory aid will be used as a reminder to review with study site personnel any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility. At Visits 8, 9, 11, and 12, the memory aid will serve as a reminder to review AEs and RRIs occurring within 48 hours following a blood draw. The parent(s)/legal guardian may use the memory aid as needed during subsequent visits 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

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collected by study staff as part of the study visits will be included in the source documents and entered into the CRF.

7.7. Sentinel-Cohort Safety Assessments

Post–Vaccination 1, 7-day e-diary and AE data will be collected for each sentinel cohort receiving the 60-µg dose level of bivalent rLP2086. The sentinel data will be reviewed (independently of the other sentinel cohort) by the sponsor's IRC to determine whether the 60-µg dose level presents satisfactory safety, reactogenicity, and tolerability data in the age stratum under review. Based on the review, the decision to commence enrollment in the 120-µg bivalent rLP2086 sentinel cohort for that age stratum will be made and the investigators will be notified accordingly. Enrollment procedural guidance will be addressed in the SRM.

The EDMC will not participate in the dose-escalation or selected dose-level decision-making processes, but will participate in the stopping rule and overall safety data processes, in line with the remit of the EDMC charter.

7.8. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. Some of the samples may be stored by Pfizer for additional testing. The samples will not be used for any unrelated research, and no genetic testing will be performed. The samples will be stored for up to 15 years after the end of the study and then destroyed.

The parent(s)/legal guardian may request that his or her 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.

7.9. Stopping Rules

The study stopping rules (excluding deaths) apply to bivalent rLP2086–vaccinated sentinel-cohort subjects for the post–Vaccination 1, 7-day safety period only.

Post–Vaccination 1, 7-day e-diary and AE (including deaths) data will be monitored daily during the post–Vaccination 1, 7-day safety period (including non–business days) by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any case that potentially contributes to a stopping rule.

Cases that potentially meet stopping rule criteria will be promptly referred to the IRC for rapid evaluation. The IRC will review the case safety data and determine whether or not the case meets a stopping rule. The IRC opinion on study progression will be forwarded to the EDMC.

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In the event that the IRC confirms that a stopping rule has been met, the following criteria will apply:

- The dose level affected by the stopping rule will PAUSE enrollment and vaccination in both sentinel age groups.
- No further study vaccinations will be administered to any subject in the PAUSED sentinel cohorts until directed to do so.
- The EDMC will convene to evaluate all available safety data and provide its recommendations to the IRC.
- For all sentinel subjects affected by a pause, all other routine study conduct activities such as ongoing data entry, reporting of AEs, subject e-diary completion, and subject follow-up, will continue during the pause.

A stopping rule will be met under the following circumstances:

- Where 2 or more subjects within an age-stratified sentinel cohort receiving the same dose level (60 μg or 120 μg) of bivalent rLP2086 develop an MAE that is similar in nature that cannot be attributed to any other cause during the 7 days following Vaccination 1.
 - ➤ E-diary data confirmed to be entered in error will not contribute towards a stopping rule.
 - ➤ Unscheduled per-protocol visits to the investigator do not fulfill this criterion unless the event that triggered an unscheduled visit meets the protocol-specified definition of an MAE.
- If any sentinel subject receiving bivalent rLP2086 develops an SAE that cannot be attributed to any other cause within 7 days following Vaccination 1.
- If death occurs in a bivalent rLP2086 recipient during the vaccination period that cannot be attributed to any other cause, or if an investigator determines that the death is related to vaccination.

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

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

The IRC will also consider if local reactions, systemic events, or related AEs have occurred that may jeopardize subject safety.

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7.9.1. Resuming Enrollment and Vaccination After a Stopping Rule Is Met

If a stopping rule is triggered by an SAE or death, enrollment and vaccination will not proceed before the IRC receives a recommendation from the EDMC. If a stopping rule is triggered by MAEs, enrollment and vaccination may proceed at the discretion of the IRC before the IRC receives a recommendation from the EDMC.

Once the EDMC has reviewed the AE data and has provided a recommendation to the IRC, the IRC will decide whether or not to continue the study as planned, make changes in study conduct, or stop the study based on the EDMC recommendations. Further information on IRC and EDMC responsibilities and procedures is described in Section 9.4.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. 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.

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.

The investigator is required to assess whether the AE may be related to the subject's participation in the study.

The investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an RRI requiring immediate notification to Pfizer or its designated representative as described below.

8.2. Research-Related Injury

Applicable to Visits 8, 9, 11, 12, and 13 only.

Should a subject, in the investigator's opinion, suffer a medically important RRI caused by his or her participation in the protocol, Pfizer or its representative must be informed immediately.

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A medically important RRI 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;
- 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 an RRI.

An investigator may be requested by Pfizer 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 medications, 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.

8.3. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject's parent(s)/legal guardian provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 6 months after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 are to be reported to the sponsor.

A subject's AEs (serious and nonserious) will be reported and recorded on the CRF from the signing of the ICD through Visit 7 (Month 7, 28-42 days after Vaccination 3).

Nonserious AEs that start between Visits 7 and 8 are reported in the CRF only if they either are NDCMCs or required evaluation at a medical facility (MAEs). At Visit 8 (Month 12; 6-month follow-up visit), the site will inquire about SAEs, NDCMCs, or AEs that resulted in evaluation at a medical facility (MAEs) since Visit 7 and record the responses on the CRF.

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For definitions of SAEs, see Section 8.6, and for definitions of NDCMCs and MAEs, see Section 7.6.3.

At Visits 8, 9, 11, 12, and 13, the site will inquire about any AEs, as well as RRIs (Section 8), 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.

At any visit, and where applicable, stop dates for any reported AEs that were ongoing at the previous visit will be recorded in the CRF. The investigator must instruct the parent(s)/legal guardian on the need to report AEs and SAEs during this time period.

8.4. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation 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 symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;

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- Medication error;
- Occupational exposure.

8.4.1. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- 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;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

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

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

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- Test result leads to a change in study dosing 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 reporting as an AE.

8.6. Serious Adverse Events

An SAE 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.
- Lack of efficacy in an approved indication should be reported as an SAE.

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 the section on Medical Device Complaint Reporting Requirements). 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;

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- 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.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

• For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

Concurrent with

• For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN or if the value reaches ≥3 X ULN (whichever is smaller).

The subject should return to the investigational 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, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent health care 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 should be 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 AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, and 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.	

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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 subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, 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 (see the section on Reporting Requirements). 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, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

- 1. 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).
- 2. 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 study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental

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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) 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 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 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 exposure during pregnancy may be requested by the investigator. 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 study 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 Pregnancy Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a health care 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 the drug safety unit within 24 hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study,

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the information is not reported on a CRF; however, a copy of the completed SAE Report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

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

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the Reporting Requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject's parent(s)/legal guardian. In addition, each study subject's parent(s)/legal guardian will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE 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 medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a

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summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

SAEs are to be reported from signing of the ICD up to Visit 8 (Month 12).

At Visit 8 (Month 12), the site will inquire about SAEs, NDCMCs, or MAEs (AEs that resulted in evaluation at a medical facility) since Visit 7.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

Nonserious AEs will be reported from the signing of the ICD up to Visit 7 (post-Vaccination 3 blood draw). Nonserious AEs starting between Visits 7 and 8 will be reported in the CRF only if they are either NDCMCs or MAEs (ie, required evaluation at a medical facility).

At Visits 8, 9, 11, 12, and 13, the site will inquire about any AEs, as well as RRIs (Section 8.2), for events occurring during the 48-hour period after each blood draw. These events must be recorded in the CRF and the events must be followed.

At all AE collection visits, particular care must be taken to note any neuroinflammatory or autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.

At all visits and if applicable, stop dates for any reported AEs that were ongoing at the previous visit will be recorded in the CRF. The investigator must instruct on the need to report AEs during this time period.

The investigator must 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 as described above. Additional information can be found in the SRM.

8.14.3. Medical Device Complaint Reporting Requirements

All medical device complaints (eg, complaints regarding prefilled syringes used to administer study vaccine), regardless of whether the medical device complaint is associated with an AE, will be collected 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 have led to death or serious deterioration in health.

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

8.14.4. 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.

9. DATA ANALYSIS/STATISTICAL METHODS

Data from all sites will be pooled, analyzed, and included in the clinical study report (CSR). Statistical analyses will be the responsibility of Pfizer. Additional details of the analysis will be provided in the statistical analysis plan (SAP), which will be finalized before any analysis, and maintained by the sponsor. This information may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment and SAP amendment. The SAP amendment will follow the protocol amendment.

9.1. Sample Size Determination

Approximately 396 subjects will be enrolled in this study.

Assuming that 20% of subjects are nonevaluable, about 88 or 176 subjects are available for immunogenicity analysis if 110 or 220 subjects are enrolled in the selected dose/age stratum.

The study sample size is not based on hypothesis testing. However, using a 1-sided exact test for 1-sample binomial population, with an alpha level of 5% (2-sided), with true response rate of 65%, 88 evaluable subjects can provide about 80% power to detect at least a 50% response rate for 1 strain. Under the same condition, 176 subjects can provide about 98% power to detect at least a 50% response rate for 1 strain.

9.1.1. Immunogenicity Analysis

The control group and each dose-level group from different cohorts within the same age stratum will be pooled for analysis. All of the immunogenicity analyses will be summarized for each age stratum separately, as well as for the combined group. Subgroup analyses will also be performed by race and sex. Additionally, race and sex subgroup analyses will be performed within age/dose level. The immunogenicity data will be summarized for the dose level with an acceptable safety profile. For the dose level without an acceptable safety profile from the sentinel cohort, the subjects will discontinue from the study without additional vaccination; therefore, no immunogenicity assay will be performed on those subjects.

This is not a hypothesis-testing study; thus, an estimation approach will be used to assess the primary, secondary, and objectives in this study. As assay data are expected to be missing completely at random (MCAR²⁰), the primary analysis for the primary objectives will be based upon the observed, determinate observations. If all subjects have hSBA tested for all of the 4 primary MnB test strains, descriptive summaries will be provided to describe

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the reason the hSBA data are missing and the relationship between the missing data indicator and other design variables or covariates (age, race, sex, center, etc) and the observed hSBA data. Additionally, a sensitivity analysis using a mixed-effects model with repeated measurement (MMRM) will be applied to the primary endpoints. The MMRM uses the maximum likelihood estimation, and it is valid under the assumption that the data are missing at random (MAR).²¹ If only 50% of the subjects will have 2 strains tested and the remaining 50% have the other 2 strains tested, no sensitivity analyses will be planned because the missing assumption is MCAR.

9.1.2. Analysis of the Primary Endpoint

For each age stratum, the proportion of subjects achieving hSBA titers ≥LLOQ at Month 7 (or 1 month after the third dose of bivalent rLP2086) will be computed for each of the 4 primary strains along with 2-sided 95% exact confidence intervals (CIs).

The LLOQ for CCl (A22) is 1:16. The LLOQ for the other 3 primary test strains is 1:8.

9.1.3. Analysis of Secondary Endpoints

The GMTs will be summarized at each blood sampling time point by randomization group for each of the 4 primary strains, along with 2-sided 95% CIs. The CIs will be constructed by back transformation of the confidence limits computed for the mean of the logarithmically transformed assay data based on Student t distribution.

The proportions of subjects with hSBA titers \geq LLOQ, \geq 1:4, \geq 1:8, \geq 1:16, \geq 1:32, \geq 1:64, and \geq 1:128 will be descriptively summarized with 95% exact CIs by randomization group for each strain at each blood sampling time point.

The empirical reverse cumulative distribution curves (RCDCs) will be presented graphically for each of the 4 primary strains, each group, and each sampling time point.

9.1.4. CC

CCI

9.1.5. Immunogenicity Analysis Populations

An evaluable immunogenicity population and a modified intent-to-treat (mITT) population will also be defined for the immunogenicity analyses. The evaluable immunogenicity population will be the primary population for the immunogenicity analyses. For the immunogenicity analysis, subjects will be analyzed according to the investigational product to which they were randomly assigned.

In general, the evaluable population will include all subjects who were randomly assigned to the study group of interest, were eligible, received all investigational products as randomized, had blood drawn for assay testing within the required time frames, had valid and determinate assay results for the proposed analysis, and had no major protocol deviations. A major

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protocol deviation is one 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.

The mITT population will include all randomly assigned subjects who have at least 1 valid and determinate assay result.

9.2. Safety Analysis

Similar to the immunogenicity analysis, the control group and each dose-level group from different cohorts within the same age stratum will be pooled for analysis. All of the safety analyses will be summarized for each age stratum separately as well as for the overall populations. Subgroup analyses on primary safety endpoints will also be performed by race and sex. Additionally, race and sex subgroup analyses will be performed within age/dose level.

The safety population will be used for all safety analyses. The safety population will include all subjects who have received at least 1 dose of an investigational product and for whom safety data available. For the safety analysis, subjects will be analyzed according to the investigational product received.

The proportion of subjects reporting local reactions at the investigational product administration sites, systemic events and the use of antipyretics within the 7-day period after each vaccination will be descriptively summarized by group. Severities of local reactions and systemic events reported after each vaccination will also be descriptively summarized by group. Two (2)-sided 95% CIs based on the Clopper-Pearson method²² will be presented with the proportions.

All of the AEs and SAEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by group. A medically attended event 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. All summaries will show the number and percentage of subjects experiencing at least 1 event and the number of events. Two (2)-sided 95% CIs based on the Clopper-Pearson method will also be presented for the AE and SAE percentages.

Comparisons will be made on the safety endpoints between bivalent rLP2086 and the control. The reactogenicity data (including use of antipyretic medication) and immediate AEs between the vaccine and control will be compared with an unconditional exact test.²³ The Fisher exact test will be used to compare the endpoints related to AEs, SAE, MAEs, and NDCMCs

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

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

9.3. Analysis Timings

The primary analysis will be performed when all of the immunogenicity data for Visit 7 and safety data up to and including Visit 8 are available.

The final analysis will include all data not included in the primary analysis and will be performed separately after all of the subjects finish the study when all of the data are available. As this study is not a hypothesis-testing study, no alpha will be adjusted on these analyses.

Interim summaries of immunogenicity and safety data may be generated.

The safety data will be reviewed on an ongoing basis, and no alpha will be adjusted for these multiple looks at the safety data.

9.4. Internal Review and Data Monitoring Committees

This study will use both an unblinded IRC and an unblinded EDMC.

9.4.1. Internal Review Committee Responsibilities

The responsibilities of the Internal Review Committee (IRC) are as follows:

- 1. Review the sentinel-cohort post–Vaccination 1, 7-day e-diary and AE data (by age stratum and dose level) to determine whether to cease or continue sentinel-cohort study progression.
- 2. Review the 60-μg sentinel-cohort post–Vaccination 1, 7-day e-diary and AE data (by age stratum) to determine whether to allow enrollment in the 120-μg dose-level sentinel cohort.
- 3. Select the dose level(s) of bivalent rLP2086 to be examined in the expanded-enrollment phase.
- 4. Determine whether to open enrollment to the expanded-enrollment phase.
- 5. Review available safety data and potential stopping rule cases to determine whether or not a stopping rule has been met. Where a stopping rule is deemed to have been met, the IRC findings will be presented to the EDMC for formal review and evaluation.

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- 6. Decide whether or not to continue the study as planned, make changes in study conduct, or stop the study based on the EDMC recommendations.
- 7. Detailed information about the IRC and unblinded sponsor personnel is available in the IRC charter maintained by the sponsor.

9.4.2. External Data Monitoring Committee Responsibilities

This study will use an EDMC. The independent statistical center (ISC) will provide the safety reports to the EDMC. Unblinded 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 responsibilities of the EDMC are as follows:

- Reviewing and evaluating safety data in the event that a stopping rule has been invoked.
 The recommendations made by the EDMC regarding the conduct of the study will be forwarded to the IRC for consideration.
- Ongoing monitoring of the safety of subjects in the study. 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. The final decision regarding assessment of stopping rules and continuation
 of the study resides with the IRC. Final decisions will be communicated to the EDMC
 chairperson in writing.

If the EDMC recommendation is to stop the study based on risk-benefit or for **safety-related** reasons, the sponsor will communicate its final decision to the EDMC within 3 working days of receiving the recommendation.

The IRC will complete the sponsor portion of the brief recommendation form, indicating the actions it will take in response to the EDMC recommendation. The completed form will be transmitted by facsimile or e-mail to the EDMC chairperson.

Detailed information about the EDMC is available in the EDMC charter maintained by the sponsor.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits 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.

The study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies

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working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as a source document. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

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

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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 (IRB)/ Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICDs, 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 legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002 [CIOMS]), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

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

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The ICD must be in compliance with ICH GCP, local regulatory requirements, and legal requirements including applicable privacy laws.

The ICD(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and be available for inspection.

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject's parent(s)/legal guardian before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as during recruitment procedures.

12.5. 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 Competent Authority in any area of the world, or if the investigator is aware of any new information which 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 STUDY

13.1. End of Study in a Member State

End of study 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 Study in All Other Participating Countries

The end of the clinical phase of the study will be the last subject last visit (LSLV) in Stage 2. At this time, sites will be closed out, the institutional review board/ethics committee (IRB/EC) will be informed, and no further CIOMS reports will be sent.

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14. SPONSOR DISCONTINUATION CRITERIA

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

If a study is prematurely terminated or discontinued, 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 study 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 for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date 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 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 primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

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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 has no objection to publication by the investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational vaccine. 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 before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are 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 (other than the study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. 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.

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