



**A PHASE 2, RANDOMIZED, CONTROLLED, OBSERVER-BLINDED STUDY TO  
DESCRIBE THE IMMUNOGENICITY, SAFETY, AND TOLERABILITY OF  
*NEISSERIA MENINGITIDIS* SEROGROUP B BIVALENT RECOMBINANT  
LIPOPROTEIN 2086 VACCINE (BIVALENT rLP2086) IN HEALTHY SUBJECTS  
AGED ≥24 MONTHS TO <10 YEARS**

<b>Compound:</b>	PF-05212366
<b>Compound Name:</b>	<i>Neisseria meningitidis</i> Serogroup B Bivalent Recombinant Lipoprotein 2086 Vaccine (Bivalent rLP2086)
<b>United States (US) Investigational New Drug (IND) Number:</b>	13812
<b>European Clinical Trials Database (EudraCT) Number:</b>	2014-000933-21
<b>Universal Trial Number:</b>	Not Applicable
<b>Protocol Number:</b>	B1971017
<b>Phase:</b>	2



### Document History

Document	Version Date	Summary of Changes
Protocol Amendment 1	03 Feb 2015	<ul style="list-style-type: none"><li>• Updated description of control hepatitis A vaccine.</li><li>• Updated the Introduction with current information.</li><li>• Clarified text in Section 5.4.2 that investigational product will be administered to subjects who are blinded.</li></ul>
Original protocol	12 May 2014	Not applicable

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
CRF	case report form
CTA	clinical trial application
DAI	dosage and administration instructions
DTaP	diphtheria, tetanus, and acellular pertussis
DU	dispensable unit
EC	ethics committee
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	enzyme-linked immunosorbent assay
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
HPV	human papillomavirus
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
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ISC	independent statistical center
IUD	intrauterine device
LFT	liver function test
LLOQ	lower limit of quantitation

LOD	limit of detection
LP2086	lipoprotein 2086
LSLV	last subject last visit
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measurement
MnB	<i>Neisseria meningitidis</i> serogroup B
NIP	national immunization program
OMV	outer membrane vesicle
PCD	primary completion date
PRP-OMP	polyribosylribitol phosphate oligosaccharide of <i>Haemophilus influenzae</i> type b conjugated to outer membrane protein
PT	prothrombin time
rLP2086	recombinant lipoprotein 2086
RRI	research-related injury
SAE	serious adverse event
SAP	statistical analysis plan
SRSD	single reference safety document
SRM	study reference manual
ULN	upper limit of normal
USPI	United States package insert

## PROTOCOL SUMMARY

### Background and Rationale

*Neisseria meningitidis* is a leading cause of bacterial meningitis in infants, adolescents, and young adults. In particular, *N meningitidis* serogroup B (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-quarter of meningococcal cases seen in North America in the areas participating in the Active Bacterial Core surveillance program. There is substantial morbidity among survivors, including neurological disability, limb loss, and hearing loss.

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 assess the immunogenicity, safety, and tolerability of bivalent rLP2086 (final formulation) administered as a Month 0, 2, and 6 schedule in healthy subjects aged  $\geq 24$  months to  $< 10$  years. Randomization will be stratified to ensure that equal numbers of subjects are included in the  $\geq 24$ -month to  $< 4$ -year age group and the  $\geq 4$ -year to  $< 10$ -year age groups.

### Objectives:

#### Primary Immunogenicity Objectives

- To describe the immune response as measured by serum bactericidal assay using human complement (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 subjects aged  $\geq 24$  months to  $< 4$  years at study entry.
- 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 subjects aged  $\geq 4$  years to  $< 10$  years at study entry.

### **Primary Safety Objective**

- To evaluate the safety profile of bivalent rLP2086 compared to a control (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 AEs, and immediate AEs in healthy subjects aged  $\geq 24$  months to  $< 4$  years at study entry, in healthy subjects aged  $\geq 4$  years to  $< 10$  years at study entry, and in both age strata combined.

### **Secondary 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 subjects aged  $\geq 24$  months to  $< 10$  years at study entry (ie, in 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 months after the third vaccination with bivalent rLP2086, in healthy subjects aged  $\geq 24$  months to  $< 4$  years at study entry,  $\geq 4$  years to  $< 10$  years at study entry, and in both age strata combined.

CCI [REDACTED]

- CCI [REDACTED]

### **Endpoints:**

Because of the possibility of limited volumes of sera, for all primary and secondary immunogenicity endpoints, approximately 50% of subjects randomly selected from each age stratum/group will be tested for hSBA on strain CCI (variant A22) and CCI (B24), and the remaining 50% of subjects from each age stratum/group will be tested for hSBA on CCI (A56) and CCI (B44). CCI [REDACTED]

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

### **Primary Immunogenicity Endpoints**

- Proportion of subjects aged  $\geq$ 24 months to  $<$ 4 years (at study entry) with hSBA titer  $\geq$  LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.
- Proportion of subjects aged  $\geq$ 4 years to  $<$ 10 years (at study entry) with hSBA titer  $\geq$  LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.

### **Primary Safety Endpoints**

In healthy subjects aged  $\geq$ 24 months to  $<$ 4 years and in healthy subjects aged  $\geq$ 4 years to  $<$ 10 years at study entry and in both age strata combined:

- Percentage of subjects reporting local reactions (pain, redness, and swelling) and by severity after each vaccination visit.
- Percentage of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, muscle pain other than muscle pain at any injection site, and joint pain) and by severity after each vaccination visit.
- Percentage of subjects reporting the use of antipyretic medication after each vaccination visit.
- Percentage of subjects with at least 1 SAE during the following time periods:
  - 30 Days after each vaccination.
  - 30 Days after any vaccination.
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).
  - During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).
  - Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).

- Percentage of subjects with at least 1 medically attended AE occurring during the following time periods:
  - 30 Days after each vaccination.
  - 30 Days after any vaccination.
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).
  - During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).
  - Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).
- Percentage of subjects with at least 1 newly diagnosed chronic medical condition occurring during the following time periods:
  - 30 Days after each vaccination.
  - 30 Days after any vaccination.
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).
  - During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).
  - Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).
- Percentage of subjects with at least 1 AE occurring during the following time periods:
  - 30 Days after each vaccination.
  - 30 Days after any vaccination.
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).
- Percentage of subjects reporting at least 1 immediate AE after each vaccination.
- For subjects at school, days of school missed because of AEs during the vaccination phase (Visit 1 through Visit 6).

## Secondary Immunogenicity Endpoints

In healthy subjects aged  $\geq 24$  months to  $< 10$  years at study entry:

- Proportion of subjects with hSBA titer  $\geq$  lower limit of quantitation (LLOQ) for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086 vaccine.

In healthy subjects aged  $\geq 24$  months to  $< 4$  years at study entry,  $\geq 4$  years to  $< 10$  years at study entry, and in both age strata combined:

- Proportion of subjects with hSBA titer  $\geq$  lower limit of quantitation (LLOQ) for each of the 4 primary MnB test strains 1 month after the second vaccination and 1 and 6 months after the third vaccination with bivalent rLP2086 vaccine.
- Proportions of subjects achieving hSBA titers of  $\geq 1:4$ ,  $\geq 1:8$ ,  $\geq 1:16$ ,  $\geq 1:32$ ,  $\geq 1:64$ , and  $\geq 1:128$  for each of the 4 primary test strains at baseline, 1 month after the second vaccination, and 1 and 6 months after the third vaccination with bivalent rLP2086 vaccine.
- hSBA GMTs for each of the 4 primary test strains at baseline, 1 month after the second vaccination, and 1 and 6 months after the third vaccination with bivalent rLP2086 vaccine.

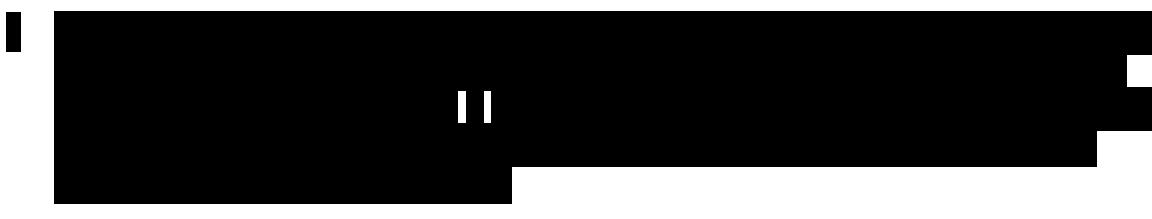
CCI



CCI









- CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

### Study Design:

This is a Phase 2, randomized, controlled, observer-blinded, multicenter study in which approximately 400 healthy subjects will be randomized in a 3:1 ratio to receive either bivalent rLP2086 at Months 0, 2, and 6, or HAV vaccine at Months 0 and 6 and saline at Month 2. Subjects will be stratified equally into 2 age groups:  $\geq 24$  months to  $< 4$  years or  $\geq 4$  years to  $< 10$  years.

The study is designed to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 at the 120- $\mu$ g dose level.

Subjects will have vaccination visits at Months 0, 2, and 6. Follow-up visits will be conducted 1 month after each vaccination and 6 months after the third vaccination to collect safety data and/or a blood sample.

	Vaccination (Vax) 1	Post-Vax 1 Follow-up	Vax 2	Post-Vax 2 Blood Draw	Vax 3	Post-Vax 3 Blood Draw	Month 12 Follow-up and Blood Draw
Visit number	1	2	3	4	5	6	7
Approx month	0	1	2	3	6	7	12
Group 1 (300)	Bivalent rLP2086		Bivalent rLP2086		Bivalent rLP2086		
Group 2 (100)	HAV vaccine		Saline		HAV vaccine		
Blood draw	5-10 mL			5-10 mL		5-10 mL	5-10 mL

Abbreviations: HAV = hepatitis A virus; Vax = vaccination.

Subject enrollment will be stratified according to age. The study will enroll approximately 200 subjects aged  $\geq$ 24 months to  $<$ 4 years and approximately 200 subjects aged  $\geq$ 4 to  $<$ 10 years. Age stratification will ensure equal representation of both age groups.

### **Investigational Products:**

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

- Bivalent rLP2086 [REDACTED] in a 0.5-mL dose for injection.
- Sterile saline solution for injection (0.85% sodium chloride) in a 0.5-mL dose.
- A licensed pediatric HAV vaccine in a 0.5-mL dose for injection.

### **Statistical Methods:**

This is not a hypothesis-testing study; thus, an estimation approach will be used to assess the primary, secondary, and exploratory objectives.

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.

## SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the [Study Procedures](#) and [Assessments](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Visit Identifier	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Approximate month	0	1	2	3	6	7	12
Visit description	Vaccination 1	Post–Vaccination 1 Follow-up	Vaccination 2	Post–Vaccination 2 Blood Draw	Vaccination 3	Post–Vaccination 3 Blood Draw	Month 12 Follow-up and Blood Draw
Visit window	Day 1	25 to 35 Days After Visit 1	42 to 70 Days After Visit 1	28 to 42 Days After Visit 3	105 to 126 Days After Visit 3	28 to 42 Days After Visit 5	168 to 196 Days After Visit 5
Informed consent	X						
Review eligibility criteria	X						
Confirm continued eligibility		X	X	X	X	X	X
Demography	X						
Medical history and physical examination	X						
Record previous PRP-OMP vaccinations	X						
Record previous vaccines with any meningococcal, DTaP, or HPV vaccine antigens	X						
Temperature (measured as appropriate for age)	X		X		X		

Visit Identifier	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Approximate month	0	1	2	3	6	7	12
Visit description	Vaccination 1	Post–Vaccination 1 Follow-up	Vaccination 2	Post–Vaccination 2 Blood Draw	Vaccination 3	Post–Vaccination 3 Blood Draw	Month 12 Follow-up and Blood Draw
Visit window	Day 1	25 to 35 Days After Visit 1	42 to 70 Days After Visit 1	28 to 42 Days After Visit 3	105 to 126 Days After Visit 3	28 to 42 Days After Visit 5	168 to 196 Days After Visit 5
Urine pregnancy test (only for female subjects biologically capable of having children)	X		X		X		
Collect blood sample <sup>a</sup>	X			X		X	X
Randomization	X						
Vaccination and observation	X		X		X		
Record nonstudy vaccinations		X	X	X	X	X	
Provide e-diary, thermometer, measuring tape/ruler, and caliper if required	X		X		X		
Review e-diary		X		X		X	
Collect e-diary				X		X	
Assess reactogenicity <sup>b</sup>	Days 1-7		Days 1-7		Days 1-7		
Record the use and type of antipyretic medication	Days 1-7		Days 1-7		Days 1-7		
(S)AE collection appropriate to the visit	X	X	X	X	X	X	X
Provide the parent(s)/legal guardian with a memory aid						X	

Visit Identifier	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Approximate month	0	1	2	3	6	7	12
Visit description	Vaccination 1	Post–Vaccination 1 Follow-up	Vaccination 2	Post–Vaccination 2 Blood Draw	Vaccination 3	Post–Vaccination 3 Blood Draw	Month 12 Follow-up and Blood Draw
Visit window	Day 1	25 to 35 Days After Visit 1	42 to 70 Days After Visit 1	28 to 42 Days After Visit 3	105 to 126 Days After Visit 3	28 to 42 Days After Visit 5	168 to 196 Days After Visit 5
Complete the Study Visit AE Checklist <sup>c</sup>		X	X	X	X	X	X
Record concomitant medications used to treat AEs	X	X	X	X	X	X	X

- a. Target volume: 5 mL for subjects aged  $\geq$ 24 months to  $<$ 4 years at the time of blood draw and approximately 10 mL for those aged  $\geq$ 4 years at the time of blood draw. Collect the blood sample only if the subject is eligible for vaccination on the same day.
- b. Between visits, review the e-diary data online at frequent intervals to ensure the parent(s)/legal guardian is completing the e-diary appropriately. Contact the parent(s)/legal guardian in order to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication (including the type of medication) that was ongoing on the last day that the e-diary was completed.
- c. Checklist includes questions regarding newly diagnosed chronic medical conditions, neuroinflammatory and autoimmune conditions, medically attended AEs, and missed days of school.

Abbreviations: AE = adverse event; DTaP = diphtheria, tetanus, and acellular pertussis; e-diary = electronic diary; HPV = human papillomavirus; PRP-OMP = polyribosyribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein; SAE = serious adverse event.

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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.

### 1.2. Background and Rationale

#### 1.2.1. *Neisseria meningitidis* Disease Background

*N meningitidis* is a leading cause of bacterial meningitis in infants, adolescents, and young adults. 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.<sup>1</sup> MnB disease accounts for approximately one-quarter of meningococcal cases seen in North America in the areas participating in the Active Bacterial Core surveillance program.<sup>2</sup> There is substantial morbidity among survivors, including neurological disability, limb loss, and hearing loss,<sup>1</sup> even when appropriate antibiotic therapy is initiated promptly.

While incidence rates of invasive meningococcal disease (IMD) vary with age, they are 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.<sup>3</sup> The incidence rate in the youngest age groups is likely due to lack of serum bactericidal antibodies,<sup>4</sup> and that in adolescents is due to behavioral risk factors.<sup>5</sup>

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.<sup>6,7,8</sup> 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.<sup>9</sup> 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.<sup>10,11</sup>

### **1.2.2. Bivalent Recombinant Lipoprotein 2086 Vaccine**

Bivalent rLP2086 is a subcapsular protein vaccine based on major, antigenically stable, surface components that are expressed in most meningococci that cause invasive disease.<sup>12</sup> Bivalent rLP2086 is targeted to a conserved, surface-exposed lipoprotein, lipoprotein 2086 (LP2086), a meningococcal virulence factor that binds human factor H.<sup>13</sup> 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. 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. The recombinant proteins have been characterized biochemically and, in several animal species, have elicited bactericidal antibodies effective against subfamily A and B strains.<sup>14</sup>

### **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.<sup>15,16</sup> 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.<sup>17</sup>

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.

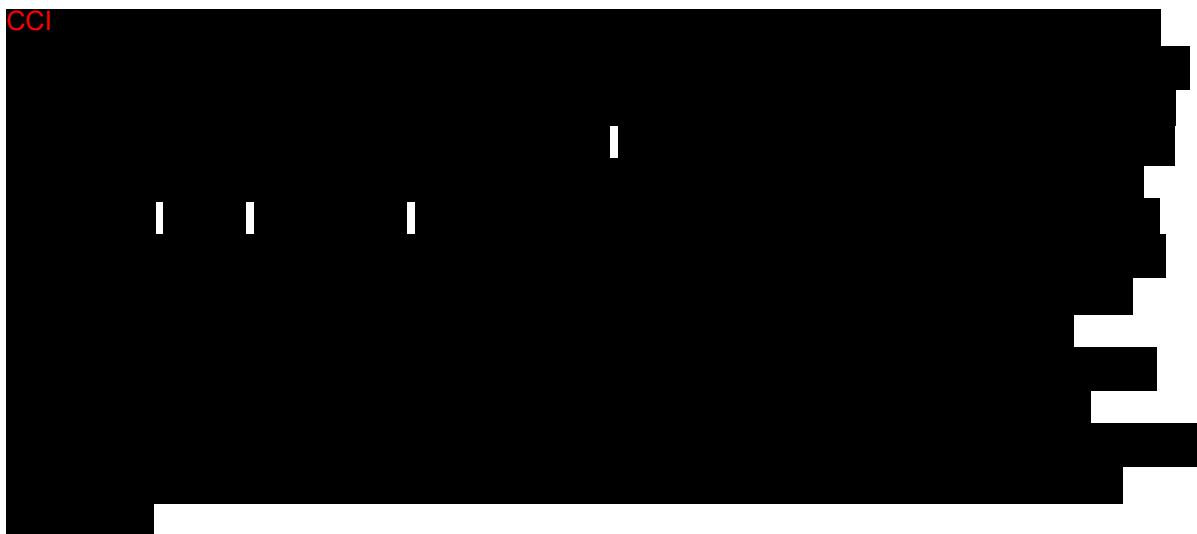
The sponsor has built an extensive MnB strain collection (N=1263) composed of IMD-causing isolates from Years 2000 to 2006. The isolates were systematically collected from the United States (US) Centers for Disease Control and Prevention (CDC) and health and reference laboratories from European countries.<sup>18</sup> The *rLP2086* gene was sequenced from each isolate to determine the sequence heterogeneity of these clinically relevant isolates. *In vitro* surface expression of LP2086 was determined by flow cytometry to assess the surface accessibility of the LP2086 protein and potential susceptibility to killing in hSBA by immune sera to LP2086. Immunity elicited by vaccinating with bivalent rLP2086

(containing subfamily A and subfamily B rLP2086) will be determined using hSBAs against 4 MnB test strains.

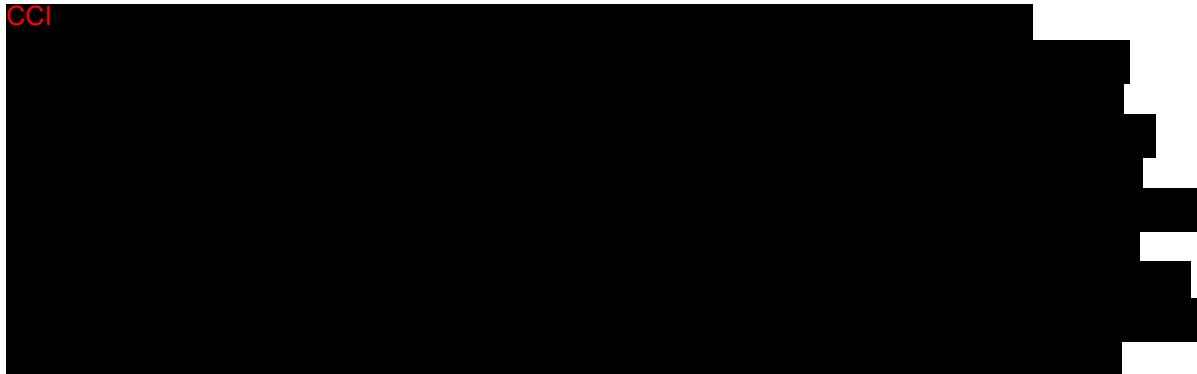
Briefly, the 4 primary MnB test strains for hSBA representative for LP2086 subfamily A and B variants were selected from the clinically relevant strain pool of N=1263 MnB isolates, taking into account the population distribution of LP2086 surface expression.<sup>18</sup> It was known from earlier studies that in vitro surface expression of LP2086 is an important predictor of hSBA susceptibility. Thus, only MnB strains with LP2086 surface-expression levels above that threshold (majority of isolates) were candidates for random selection of primary MnB test strains to be used in hSBAs supporting late-phase clinical studies. This approach, coupled with identification of epidemiologically prevalent (circulating) strains in the United States and Europe, was used to select the 4 Phase 3 primary MnB test strains: 2 each from subfamilies A and B. Two (2) MnB test strains (ie, 1 from subfamily A [CC1] and 1 from subfamily B [CC1] were selected in an unbiased fashion, while the other 2 test strains (i.e., 1 from subfamily A [CC1] and 1 from subfamily B [CC1] were selected based on epidemiological prevalence. These 4 test strains will be used for determination of the primary immunogenicity endpoints. A similar approach was used to select the 10 Phase 3 secondary MnB test strains for evaluation.

#### 1.2.4. Clinical Experience

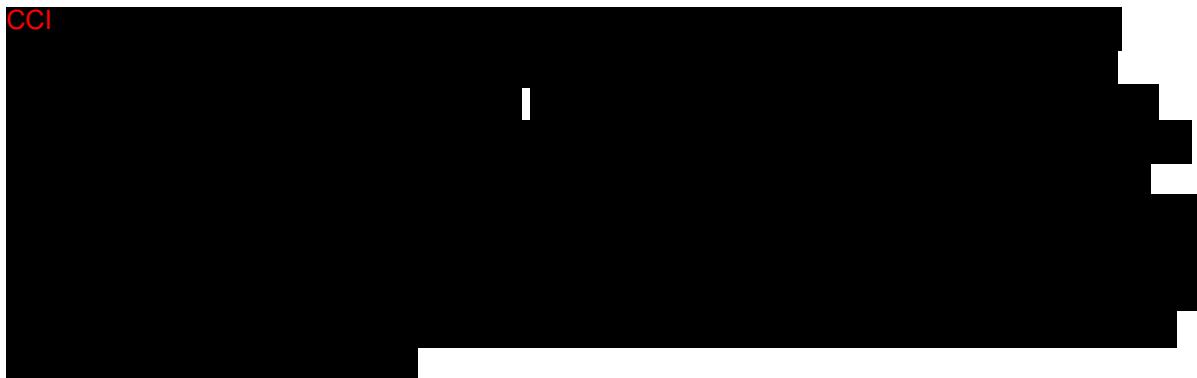
CC1



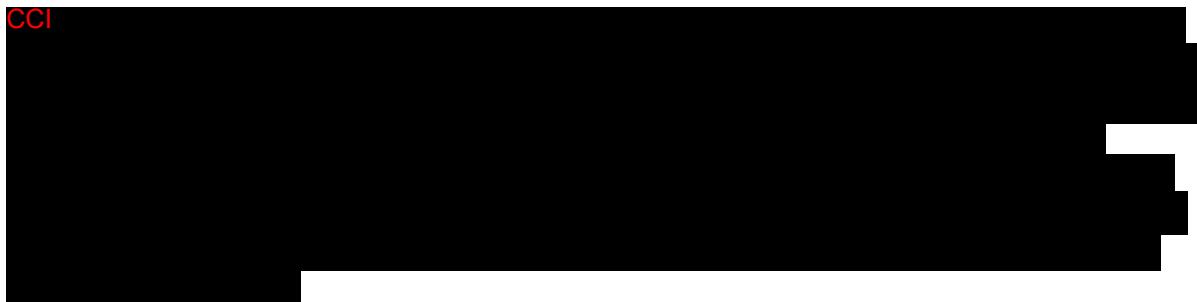
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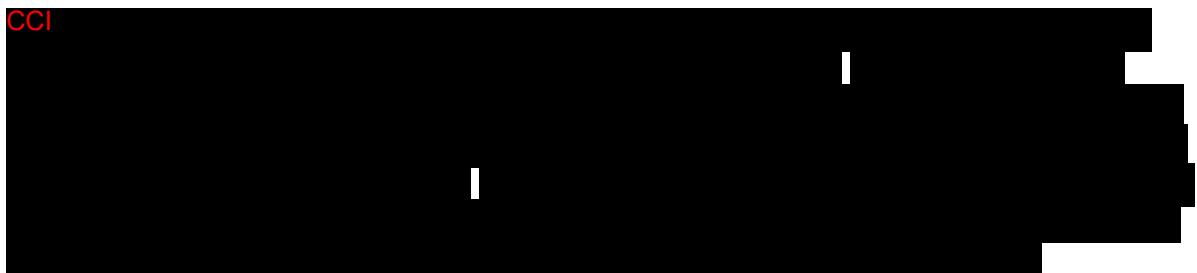
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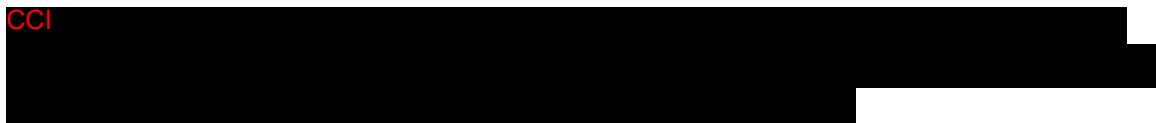
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### 1.2.5. Study Rationale

The target population for the initial vaccine indication is subjects aged 10 to 25 years. Two (2) studies (B1971017 and B1971035) will together explore the immunogenicity and safety of the vaccine in children from 12 months up to 10 years of age. This study will assess the immunogenicity, safety, and tolerability of bivalent rLP2086 at the 120- $\mu$ g dose level (final formulation) administered to healthy subjects aged  $\geq$ 24 months to <10 years as part of a Month 0, 2, and 6 schedule. Approximately 400 subjects will be randomized to 1 of 2 groups in a 3:1 ratio. Group 1 will receive bivalent rLP2086 at Month 0 (Visit 1) followed by subsequent vaccinations at Months 2 and 6. Group 2 will receive HAV vaccine at Month 0 (Visit 1) and Month 6 and an injection with saline at Month 2. Randomization will be stratified to ensure that equal numbers of subjects are included in the  $\geq$ 24-month to <4-year and  $\geq$ 4-year to <10-year age groups.

## Risk/Benefits

Refer to the most recent version of the bivalent rLP2086 IB for a summary of findings from nonclinical studies that potentially have clinical significance and from clinical studies that are relevant to this study. Also refer to the most recent version of the bivalent rLP2086 IB for a summary of the known and potential risks and benefits, if any, to human subjects.

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

There may be pain and/or bruising with blood collections or with vaccine injection.

Any newly identified risks to the subjects must be reported promptly by the sponsor to the investigators.

## **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 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 subjects aged  $\geq 24$  months to  $< 4$  years at study entry.
- 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 subjects aged  $\geq 4$  years to  $< 10$  years 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, medically attended AEs, and immediate AEs in healthy subjects aged  $\geq 24$  months to  $< 4$  years and in healthy subjects aged  $\geq 4$  years to  $< 10$  years at study entry, and in both age strata combined.

#### **2.1.3. Secondary 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 subjects aged  $\geq 24$  months to  $< 10$  years at study entry (ie, in 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 months after the third vaccination with bivalent rLP2086, in healthy subjects aged  $\geq 24$  months to  $< 4$  years at study entry, in healthy subjects aged  $\geq 4$  years to  $< 10$  years at study entry, and in both age strata combined.

#### 2.1.4. **CC1**



### 2.2. Endpoints

Because of the possibility of limited volumes of sera, for all primary and secondary immunogenicity endpoints, approximately 50% of subjects randomly selected from each age stratum/group will be tested for hSBA on strain **CC1** (variant A22) and **CC1** (B24), and the remaining 50% of subjects from each age stratum/group will be tested for hSBA on **CC1** (A56) and **CC1** (B44). **CC1**



The lower limit of quantitation (LLOQ) for **CC1** (A22) is 1:16. The LLOQ for the other 3 primary test strains is 1:8.

#### 2.2.1. Primary Immunogenicity Endpoints

- Proportion of subjects aged  $\geq 24$  months to  $< 4$  years (at study entry) with hSBA titer  $\geq$  LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.
- Proportion of subjects aged  $\geq 4$  years to  $< 10$  years (at study entry) with hSBA titer  $\geq$  LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.

#### 2.2.2. Primary Safety Endpoints

The following endpoints will be applicable in healthy subjects aged  $\geq 24$  months to  $< 4$  years and in healthy subjects aged  $\geq 4$  years to  $< 10$  years at study entry, and in both age strata combined:

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

- Percentage of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, muscle pain other than muscle pain at any injection site, and joint pain) and by severity after each vaccination visit.
- Percentage of subjects reporting the use of antipyretic medication after each vaccination visit.
- Percentage of subjects with at least 1 SAE during the following time periods:
  - 30 Days after each vaccination.
  - 30 Days after any vaccination.
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).
  - During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).
  - Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).
- Percentage of subjects with at least 1 medically attended AE occurring during the following time periods:
  - 30 Days after each vaccination.
  - 30 Days after any vaccination.
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).
  - During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).
  - Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).
- Percentage of subjects with at least 1 newly diagnosed chronic medical condition occurring during the following time periods:
  - 30 Days after each vaccination.
  - 30 Days after any vaccination.
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).

- During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).
- Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).
- Percentage of subjects with at least 1 AE occurring during the following time periods:
  - 30 Days after each vaccination.
  - 30 Days after any vaccination.
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).
- Percentage of subjects reporting at least 1 immediate AE after each vaccination.
- For subjects at school, days of school missed because of AEs during the vaccination phase (Visit 1 through Visit 6).

### **2.2.3. Secondary Immunogenicity Endpoints**

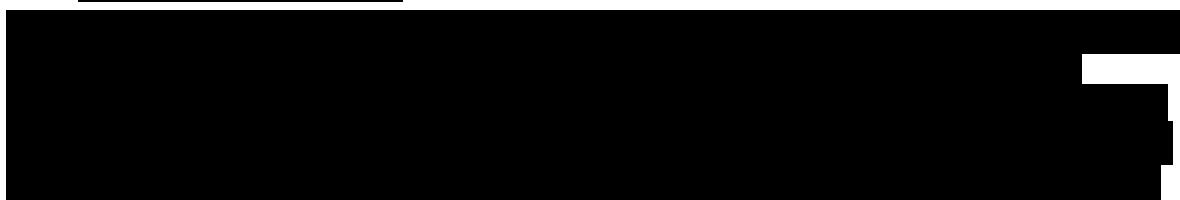
In healthy subjects aged  $\geq 24$  months to  $< 10$  years at study entry:

- Proportion of subjects with hSBA titer  $\geq$  LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.

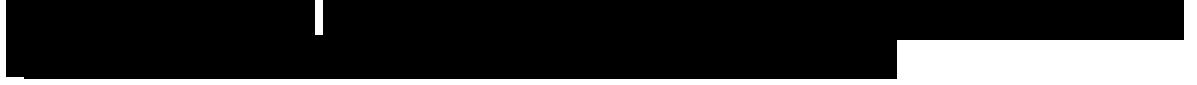
In healthy subjects aged  $\geq 24$  months to  $< 4$  years at study entry, in healthy subjects aged  $\geq 4$  years to  $< 10$  years at study entry and in both age strata combined:

- Proportion of subjects with hSBA titer  $\geq$  LLOQ for each of the 4 primary MnB test strains 1 month after the second vaccination and 1 and 6 months after the third vaccination with bivalent rLP2086.
- Proportions of subjects achieving hSBA titers of  $\geq 1:4$ ,  $\geq 1:8$ ,  $\geq 1:16$ ,  $\geq 1:32$ ,  $\geq 1:64$ , and  $\geq 1:128$  for each of the 4 primary test strains at baseline, 1 month after the second vaccination, and 1 and 6 months after the third vaccination with bivalent rLP2086.
- hSBA GMTs for each of the 4 primary test strains at baseline, 1 month after the second vaccination, and 1 and 6 months after the third vaccination with bivalent rLP2086.

### **2.2.4. CCI**



CCI



### 3. STUDY DESIGN

#### 3.1. Description

This is a Phase 2, randomized, controlled, observer-blinded, multicenter study in which approximately 400 subjects will be randomly assigned to 1 of 2 groups in a 3:1 ratio. Group 1 will receive bivalent rLP2086 at Month 0 (Visit 1) followed by subsequent vaccinations at Months 2 and 6. Group 2 will receive a licensed pediatric HAV vaccine at Month 0 (Visit 1) and Month 6 and an injection with saline at Month 2. Randomization will be stratified to ensure that equal numbers of subjects are included in the  $\geq 24$ -month to  $< 4$ -year age group and the  $\geq 4$ -year to  $< 10$ -year age group.



This study is designed to assess the immunogenicity, safety, and tolerability of bivalent rLP2086 at the 120- $\mu$ g dose level administered to healthy subjects aged  $\geq$ 24 months to  $<$ 10 years as part of a Month 0, 2, and 6 schedule. Follow-up visits will be conducted 1 month after each vaccination and 6 months after the third vaccination to collect safety data and/or a blood sample.

**Table 1. Study Design**

	Vax 1	Post-Vax 1 Follow-up	Vax 2	Post-Vax 2 Blood Draw	Vax 3	Post-Vax 3 Blood Draw	Month 12 Follow-up and Blood Draw
<b>Visit number</b>	1	2	3	4	5	6	7
<b>Approx month</b>	0	1	2	3	6	7	12
<b>Group 1 (300)</b>	Bivalent rLP2086		Bivalent rLP2086		Bivalent rLP2086		
<b>Group 2 (100)</b>	HAV vaccine		Saline		HAV vaccine		
<b>Blood draw</b>	5-10 mL			5-10 mL		5-10 mL	5-10 mL

Abbreviations: HAV = hepatitis A virus; Vax = vaccination.

Subject enrollment will be stratified according to age. The study will enroll approximately 200 subjects aged  $\geq$ 24 months to  $<$ 4 years and approximately 200 subjects aged  $\geq$ 4 to  $<$ 10 years. Age stratification will ensure equal representation of both age groups.

HAV vaccine administered at Months 0 and 6 has been chosen as the control in this study in order that those randomized to the control group receive a personal benefit from participating in the study. In comparison to other recommended vaccines for this age group, HAV vaccine has a well-established tolerability profile. In addition, HAV vaccine will provide protection to subjects who may become at increased risk for hepatitis A viral infection either during future travel or 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.

### **3.2. Approximate Duration of Subject Participation**

Subjects will participate in the study for up to 13 months. The duration of subject participation is calculated using the last day of each of the visit windows.

### **3.3. Approximate Duration of the Study**

This study will be completed in approximately 20 months.

### **3.4. Approximate Number of Subjects**

Approximately 400 subjects will participate in this study. Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal.

## **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.

### **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 subject's parent(s)/legal guardian has been informed of all pertinent aspects of the study.
2. Parent(s)/legal guardian and subject who are willing and able to comply with scheduled visits, vaccine regimen, laboratory tests, and other study procedures.
3. Male or female subjects aged  $\geq 24$  months and  $< 10$  years at time of randomization, stratified equally by age ( $\geq 24$  months to  $< 4$  years or  $\geq 4$  years to  $< 10$  years).
4. Subject is available for the entire study period and subject's parent(s)/legal guardian can be reached by telephone.
5. Healthy subject as determined by medical history, physical examination, and judgment of the investigator.
6. Subject must have received all vaccinations in the relevant national immunization program (NIP) for their age group.
7. Male and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active. Refer to [Section 4.5](#) for further information.
8. Negative urine pregnancy test for all female subjects who are biologically capable of having children.

#### **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. Subjects who have received prior HAV vaccination.
3. Contraindication to vaccination with any HAV vaccine or known latex allergy.
4. Subjects receiving any allergen immunotherapy with a nonlicensed product or subjects receiving allergen immunotherapy with a licensed product and who are not on stable maintenance doses.
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 defect of the immune system that would prevent an immune response to the vaccine, such as subjects with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, intravenous, or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy. Subjects with terminal complement deficiency may be included. Additional details will be provided in the study reference manual (SRM).
8. History of microbiologically proven disease caused by *N meningitidis* or *Neisseria gonorrhoeae*.
9. Significant neurological disorder or history of seizure (excluding simple febrile seizure).
10. Receipt of any blood products, including immunoglobulin, within 6 months before the first study vaccination.
11. Current chronic use of systemic antibiotics.
12. Participation in other studies involving investigational product(s)/device(s) (Phases 1-4) within 28 days before administration of the first study vaccination. Participation in purely observational studies is acceptable.
13. Any neuroinflammatory or autoimmune condition, including but not limited to transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
14. 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.

15. Pregnant female subjects, breastfeeding female subjects, male subjects with partners who are currently pregnant, or male and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study.
16. Subjects who are children of investigational site staff members directly involved in the conduct of the study and their family members, subjects who are children of site staff members otherwise supervised by the investigator, 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  $\geq 38.0^{\circ}\text{C}$  [ $100.4^{\circ}\text{F}$ ]) or other acute illness within 48 hours before investigational product administration.
2. Subject has received prophylactic antipyretic medication or other pain medication to prevent symptoms associated with investigational product on the planned day of vaccination.
3. Subject has received a nonlive vaccine (or intramuscular/sublingual allergen immunotherapy) within 14 days, or live vaccine within 28 days, before investigational product administration.
4. Subject has received any nonstudy meningococcal vaccines or any vaccine containing all or individual antigens included in diphtheria, tetanus, and acellular pertussis (DTaP) or human papillomavirus (HPV) vaccines within the previous 28 days. See [Section 5.9](#).
5. Subject is less than 5 days into a course of systemic antibiotic therapy.
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.

#### **4.5. Lifestyle Guidelines**

All male and female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the study. The investigator, or his/her designee, in consultation with the subject and parent(s)/legal guardian, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator, or his/her designee, will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

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

1. Established use of oral, inserted, injected, or implanted hormonal methods of contraception are allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used with a spermicide (ie, foam, gel, film, cream, suppository).
4. Male sterilization with absence of sperm in the postvasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

#### **4.6. Sponsor's Qualified Medical Personnel**

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subject and 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 healthcare 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 subject's parent(s)/legal guardian calls that number, he/she will be directed back to the investigational site.

## **5. INVESTIGATIONAL PRODUCTS**

Subjects will receive 1 dose of 120 µg of bivalent rLP2086 or HAV vaccine/saline/HAV vaccine at Months 0, 2, and 6 according to the [Schedule of Activities](#).

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.

Only an unblinded, medically qualified member of the study staff will administer the investigational products. Investigational product administration details (ie, date of administration, kit number, volume, route, and site of administration) will be recorded on the case report form (CRF). Investigational product accountability will be documented as per [Section 5.7](#).

For the purpose of vaccine administration, a medically qualified member of the study staff is a study physician or a study nurse, as applicable to the investigator's local practice.

In the event of a product quality complaint, which is defined as a report regarding a physical, chemical, microbiologic, or other alleged defect of a Pfizer Vaccine Research investigational product, the investigator or designee will telephone the appropriate person as detailed in the SRM and follow the instructions therein.

### **5.1. Allocation to Investigational Product**

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) system that is accessible 24 hours a day, 365 days a year. Having logged in, the site personnel (study coordinator or specified designee) will be required to enter or select certain information including but not limited to the user's identification (ID) and password, protocol number, the subject number, 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 container number. The randomization number and the date on which the randomization number was assigned will be recorded on the CRF. Once subject numbers, DU numbers, and randomization numbers have been assigned, they cannot be reassigned. The IRT system will provide a confirmation report containing the subject randomization number and DU or container number assigned. The confirmation report must be stored in the site's files.

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. 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 this observer-blinded study, the study staff dispensing and administering the vaccine will be unblinded, but all other study personnel, including the principal investigator and the sponsor, will be blinded. In particular, the individuals who evaluate subject safety as well as the subject will be blinded. Because the study vaccines are different in physical appearance, the study vaccine syringes will be labeled in a manner that prevents the study subjects from identifying the vaccine type based on its appearance.

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

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

## **5.3. 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 Form(s) and Packaging**

Bivalent rLP2086 (containing 60 µg each of a purified subfamily A and subfamily B rLP2086 protein, adsorbed to aluminum in a sterile buffered isotonic suspension) is provided in a 0.5-mL dose for injection.

The bivalent rLP2086 final formulation is described in Table 2.

**Table 2. Bivalent rLP2086 Investigational Product Formulation**

The investigational products (bivalent rLP2086, HAV vaccine, and 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 dispensable unit (DU) or container number.

A licensed pediatric HAV vaccine 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.

The placebo consists of sterile saline solution for injection (0.85% sodium chloride) supplied as a 0.5-mL dose.

### 5.4.2. Preparation and Dispensing

See the dosage and administration instructions (DAI) or package insert for instructions on 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 product will be administered to subjects who are blinded.

## 5.5. 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 study personnel, including the principal investigator and the sponsor, will be blinded.

Investigational product administration details (ie, date of administration, container number, volume, route, and site of administration, administration errors) will be recorded on the CRF.

During the study, subjects in Group 1 will be administered bivalent rLP2086 by intramuscular injection at Months 0, 2, and 6 into the upper deltoid muscle of the arm.

Subjects in Group 2 will be administered HAV vaccine/saline/HAV vaccine at Months 0, 2, and 6 into the upper deltoid muscle of the arm.

### **5.6. 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.

Investigational product should be stored in its original container and in accordance with the vaccine label. For storage, the preferred orientation of the vaccine is horizontal. See the DAI or package insert for storage conditions of the product.

Storage conditions stated in the SRSD will be superseded by the storage conditions stated in the labeling.

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 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.

### **5.7. Vaccine Accountability**

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

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.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

### **5.8. Concomitant Treatment**

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

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

### **5.9. Prohibited During the Study**

- Prophylactic antipyretics and other pain medications to prevent symptoms associated with investigational product are not permitted. If the subject has received such medications prior to a planned administration of investigational product, vaccination should be temporarily delayed as specified in [Section 4.3](#).
- Receipt of any blood products, including immunoglobulin.
- Nonstudy meningococcal vaccines or vaccines containing all or individual antigens included in DTaP or HPV vaccines are not permitted before Visit 3 and within 28 days of any study vaccination.

- Receipt of any other serogroup B meningococcal vaccine is prohibited throughout the course of the study.
- Other nonlive or live nonstudy vaccines are not permitted within 14 and 28 days, respectively, of any study vaccination.
- Intramuscular/sublingual allergen immunotherapy is not permitted within 14 days of any study vaccination.
- Systemic (oral, intravenous, or intramuscular) corticosteroid therapy within 28 days of any study vaccination.

#### **5.10. Permitted During the Study**

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed. However, while prioritizing standard clinical care, efforts should be made not to administer nonstudy vaccines within 14 days (for nonlive vaccines) or 28 days (for live vaccine) as specified below.
- Nonstudy vaccines (other than any meningococcal vaccines and vaccines containing all or individual antigens included in DTaP and HPV 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. Please refer to [Section 5.9](#) regarding restrictions on administration other serogroup B meningococcal vaccines and vaccines containing all or individual antigens included in the DTaP and HPV vaccines.
- Antipyretics and other pain medications to treat symptoms associated with investigational product are permitted.
- A local anesthetic may be used at the site of the blood draw.
- Topical antibiotics are permitted.
- Topical and inhaled corticosteroids are permitted.

#### **5.11. Prior Treatment**

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

If the subject has received any meningococcal vaccines and any vaccines containing all or individual antigens included in DTaP or HPV vaccines prior to the study, the trade name (if known) and date of administration (mm/yyyy) of the most recent vaccination for each of these will be recorded on the CRF. Verbal vaccination history is acceptable and should be supplemented with written confirmation if possible.

### **5.11.1. Prohibited Prior Treatments**

The following are prohibited:

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

## **6. STUDY PROCEDURES**

### **6.1. Informed Consent Process**

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

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

### **6.2. Visit 1 (Day 1): Vaccination 1**

- In the case of temporary delay of vaccination, procedures and assessments below will be reperformed or reconfirmed, as applicable, on the day of vaccination.
- Obtain written informed consent before performing study-specific procedures. The date of informed consent will be recorded on the CRF.
- Record the subject's demographic information (including date of birth, sex, race, and ethnicity).
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.
- Record previous PRP-OMP vaccinations as described in the Prior Treatment section ([Section 5.11](#)).
- Record trade name (if known) and date (mm/yyyy) of previous receipt of any meningococcal vaccine and any vaccine containing all or individual antigens included in DTaP and HPV vaccines as described in the [Prior Treatment](#) section.

- Perform a physical examination including height, weight, and vital signs, evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, neurological, musculoskeletal, and lymph nodes, including worsening of medical history conditions. Results must be recorded on source documents and the CRF. Findings from a physical examination conducted as part of standard routine care and before informed consent may be used for purposes of the study only if the examination was performed no more than 2 days before vaccination. A brief examination must be performed on the day of vaccination to document that no change in health has occurred in the interim.
- On the day of vaccination, perform a urine pregnancy test on all female subjects who are biologically capable of having children. A negative pregnancy test result is required before the subject may receive the investigational product.
- On the day of and before vaccination, measure and record the subject's temperature (measured as appropriate for age, according to routine practice) and route by which temperature was taken.
- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- If a subject is eligible for the study, enroll and randomize the subject to 1 of the 2 groups using the IRT system.
- Before vaccination, collect a blood sample (approximately 5 mL for subjects aged  $\geq 24$  months to  $< 4$  years at the time of blood draw and approximately 10 mL for those aged  $\geq 4$  years at the time of blood draw) from the subject. Collect the blood sample only if the subject is eligible for vaccination on the same day.
- Investigational product will be administered by intramuscular injection, by an unblinded dispenser, into the upper deltoid muscle of the arm. The time of administration will be recorded on the CRF.
- Observe the subject for at least 30 minutes after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs ([Section 7.2](#)).
- Record AEs as described in the AE [Reporting Requirements](#) section and the [Schedule of Activities](#). The time of onset will be recorded for any AEs that occur on the same day as investigational product administration.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment section ([Section 5.8](#)).

- Issue a subject e-diary and provide instructions on the collection and recording of local reactions, systemic events (reactogenicity), and 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.
- Ask the parent(s)/legal guardian to complete the e-diary from Day 1 to Day 7 after vaccination.
- Issue a caliper, measuring tape/ruler, and a digital thermometer and provide verbal and written instructions on their use.
  - Agree with the parent(s)/legal guardian, and record in the CRF, which route will be used to measure the subject's temperature using the thermometer provided during the 7 days after study vaccination.
  - 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 the 7 days after study vaccination and record in the e-diary as described in [Section 7.6.1](#).
  - Ask the parent(s)/legal guardian to contact the investigator immediately if the subject experiences a severe redness or swelling (>14 caliper units) at the injection site, a fever  $\geq 39.0^{\circ}\text{C}$  ( $102.1^{\circ}\text{F}$ ), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged ([Section 6.9](#)).
    - If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units [[Section 7.6.1](#)]), the parent(s)/legal guardian should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator. These measurements will be recorded in the CRF.
    - 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  $\leq 14$  caliper units.
  - Ask the 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) either before or after a study vaccine administration.
  - Schedule an appointment for the next study visit within the time window per protocol.
  - Remind the parent(s)/legal guardian to bring the e-diary to the next study visit.

- Complete the source documents.
- Complete the CRFs 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 entered into the CRF at the next study visit of the subject.

### **6.3. Visit 2 (25 to 35 Days After Visit 1): Post–Vaccination 1 Follow-up**

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria ([Section 6.10](#)).
- Review the subject's e-diary data and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Complete the Study Visit AE Checklist to:
  - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school (if appropriate). Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE [Reporting Requirements](#) section 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 continuing.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment section ([Section 5.8](#)).
- Record nonstudy vaccinations as described in the Concomitant Treatment section ([Section 5.8](#)).
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.

- Complete the source documents.
- Complete the CRFs.

#### **6.4. Visit 3 (42 to 70 Days After Visit 1): Vaccination 2**

- Ensure that the subject continues to be eligible for the study, meets none of the withdrawal criteria ([Section 6.10](#)), and meets none of the temporary delay of vaccination criteria ([Section 4.3](#)).
- In the case of temporary delay of vaccination, procedures and assessments below will be reperformed or reconfirmed, as applicable, on the day of vaccination.
- Complete the Study Visit AE Checklist to:
  - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school (if appropriate). Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE [Reporting Requirements](#) section and the [Schedule of Activities](#). The time of onset will be recorded for any AEs that occur on the same day as investigational product administration.
- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment section ([Section 5.8](#)).
- Record nonstudy vaccinations as described in the Concomitant Treatment section ([Section 5.8](#)).
- On the day of vaccination, perform a urine pregnancy test on female subjects who are biologically capable of having children. A negative pregnancy test result is required before the subject may receive the investigational product.
- On the day of and before vaccination, measure and record the subject's temperature (measured as appropriate for age, according to routine practice) and route by which temperature was taken.

- Investigational product will be administered by intramuscular injection, by an unblinded dispenser, into the upper deltoid muscle of the arm. The time of administration will be recorded on the CRF.
- Observe the subject for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs ([Section 7.2](#)).
- Ask the parent(s)/legal guardian to complete the e-diary from Day 1 to Day 7 after vaccination and provide instructions on the collection and recording of local reactions, systemic events (reactogenicity), and 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, issue a new e-diary, caliper, measuring tape/ruler, or digital thermometer and provide instructions for use.
  - Agree with the parent(s)/legal guardian, and record, which route will be used to measure the subject's temperature during the 7 days after study vaccination.
  - 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 the 7 days after study vaccination and record in the e-diary as described in [Section 7.6.1](#).
  - Ask the parent(s)/legal guardian to contact the investigator immediately if the subject experiences a severe redness or swelling (>14 caliper units) at the injection site, a fever  $\geq 39.0^{\circ}\text{C}$  ( $102.1^{\circ}\text{F}$ ), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged ([Section 6.9](#)).
    - If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units [[Section 7.6.1](#)]), the parent(s)/legal guardian should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator. These measurements will be recorded in the CRF.
    - 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  $\leq 14$  caliper units.
  - Ask the 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) before or after a study vaccine administration.
- Schedule an appointment for the next study visit within the time window per protocol.
- Remind the parent(s)/legal guardian to bring the e-diary to the next visit.
- Complete the source documents.
- Complete the CRFs and update the investigational product accountability records.

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

#### **6.5. Visit 4 (28 to 42 Days After Visit 3): Post–Vaccination 2 Blood Draw**

- Ensure that the subject continues to be eligible for the study, meets none of the withdrawal criteria ([Section 6.10](#)), and meets none of the temporary delay of blood draw criteria ([Section 4.4](#)).
- Collect the subject's e-diary.
- Review the subject's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Complete the Study Visit AE Checklist to:
  - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school (if appropriate). Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE [Reporting Requirements](#) section and the [Schedule of Activities](#).
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment section ([Section 5.8](#)).
- Record nonstudy vaccinations as described in the Concomitant Treatment section ([Section 5.8](#)).
- Collect a blood sample (approximately 5 mL for subjects aged ≥24 months to <4 years at the time of blood draw and approximately 10 mL for those aged ≥4 years at the time of blood draw) from the subject. Collect the blood sample only if the subject meets none of the temporary delay of blood sample collection criteria described in [Section 4.4](#).
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next visit within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

#### **6.6. Visit 5 (105 to 126 Days After Visit 3): Vaccination 3**

- Ensure that the subject continues to be eligible for the study, meets none of the withdrawal criteria ([Section 6.10](#)), and meets none of the temporary delay of vaccination criteria ([Section 4.3](#)).
- In the case of temporary delay of vaccination, procedures and assessments below will be reperformed or reconfirmed, as applicable, on the day of vaccination.
- Complete the Study Visit AE Checklist to:
  - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school (if appropriate). Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE [Reporting Requirements](#) section and the [Schedule of Activities](#). The time of onset will be recorded for any AEs that occur on the same day as investigational product administration.
- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still continuing.

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment section ([Section 5.8](#)).
- Record nonstudy vaccinations as described in the Concomitant Treatment section ([Section 5.8](#)).
- On the day of vaccination, perform a urine pregnancy test on female subjects who are biologically capable of having children. A negative pregnancy test result is required before the subject may receive the investigational product.
- On the day of and before vaccination, measure and record the subject's temperature (measured as appropriate for age, according to routine practice) and route by which temperature was taken.
- Investigational product will be administered by intramuscular injection, by an unblinded dispenser, into the upper deltoid muscle of the arm. The time of administration will be recorded on the CRF.
- Observe the subject for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs ([Section 7.2](#)).
- Ask the parent(s)/legal guardian to complete the e-diary from Day 1 to Day 7 after vaccination and provide instructions on the collection and recording of local reactions, systemic events (reactogenicity), and 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, issue an e-diary, caliper, measuring tape/ruler, and digital thermometer and provide instructions for use.
  - Agree with the parent(s)/legal guardian, and record, which route will be used to measure the subject's temperature during the 7 days after study vaccination.
  - 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 the 7 days after study vaccination and record in the e-diary as described in [Section 7.6.1](#).
  - Ask the parent(s)/legal guardian to contact the investigator immediately if the subject experiences a severe redness or swelling (>14 caliper units) at the injection site, a fever  $\geq 39.0^{\circ}\text{C}$  ( $102.1^{\circ}\text{F}$ ), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged ([Section 6.9](#)).

- If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units [[Section 7.6.1](#)]), the parent(s)/legal guardian should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator. These measurements will be recorded in the CRF.
- 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 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) before or after a study vaccine administration.
- Schedule an appointment for the next study visit within the time window per protocol.
- Remind the parent(s)/legal guardian to bring the e-diary to the next visit.
- Complete the source documents.
- Complete the CRFs and update the investigational product accountability records.

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

#### **6.7. Visit 6 (28 to 42 Days After Visit 5): Post–Vaccination 3 Blood Draw**

- Ensure that the subject continues to be eligible for the study, meets none of the withdrawal criteria ([Section 6.10](#)), and meets none of the temporary delay of blood draw criteria ([Section 4.4](#)).
- Collect the subject's e-diary.
- Review the subject's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.

- Complete the Study Visit AE Checklist to:
  - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school (if appropriate). Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE [Reporting Requirements](#) section and the [Schedule of Activities](#).
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment section ([Section 5.8](#)).
- Record nonstudy vaccinations as described in the Concomitant Treatment section ([Section 5.8](#)).
- Provide the subject's parent(s)/legal guardian with a memory aid. Instruct the parent(s)/legal guardian to use the memory aid between Visits 6 and 7 to remind them to review any significant illnesses, hospitalizations, newly diagnosed medical conditions, or AEs that resulted in evaluation at a medical facility with study site personnel. Please refer to the SRM and [Section 7.2](#) for additional details.
- Collect a blood sample (approximately 5 mL for subjects aged  $\geq$ 24 months to  $<$ 4 years at the time of blood draw and approximately 10 mL for those aged  $\geq$ 4 years at the time of blood draw) from the subject. Collect the blood sample only if the subject meets none of the temporary delay of blood sample collection criteria described in [Section 4.4](#).
- Ask the parent(s)/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next visit within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

## **6.8. Visit 7 (168 to 196 Days After Visit 5) Month 12 Follow-up and Blood Draw**

- Ensure that the subject meets none of the withdrawal criteria ([Section 6.10](#)) and meets none of the temporary delay of blood draw criteria ([Section 4.4](#)).
- Complete the Study Visit AE Checklist to:
  - Inquire whether the subject had any newly diagnosed chronic medical conditions since the last visit. Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school (if appropriate). Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE [Reporting Requirements](#) section and the [Schedule of Activities](#).
- Report any SAEs to the sponsor as defined in [Section 8.15.1](#).
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment section ([Section 5.8](#)).
- Collect a blood sample (approximately 5 mL for subjects aged  $\geq$ 24 months to  $<$ 4 years at the time of blood draw and approximately 10 mL for those aged  $\geq$ 4 years at the time of blood draw) from the subject. Collect the blood sample only if the subject meets none of the temporary delay of blood sample collection criteria described in [Section 4.4](#).
- Complete the source documents.
- Complete the CRFs.

## **6.9. Unscheduled Visits**

If the subject experiences a severe redness or swelling at the injection site ( $>$ 14 caliper units), a temperature  $\geq$ 39.0°C (102.1°F), or a severe headache in the 7 days after vaccination, the subject/parent(s)/legal guardian must be contacted and a study site visit must be scheduled as soon as possible to assess the extent of the event. The subject contact will be documented in the CRF.

If the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units), ensure the subject has measured the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided. Ask the subject 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 temperature should be measured (as appropriate for age, according to routine practice) and the symptom that prompted the visit should be assessed by a medically qualified member of the study staff. Findings will be recorded in the CRF. If the subject experiences any AEs, these should be recorded on the AE CRF.

If the unscheduled visit does not take place following subject report of fever ≥39.0°C (102.1°F), severe redness/swelling or severe headache, the reason must be documented in the CRF (for example, reaction no longer present or e-diary entry error).

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

## **6.10. Subject Withdrawal**

The investigator and/or sponsor may withdraw a subject from the study if deemed appropriate at any time. Eligibility criteria as listed under inclusion criteria (refer to [Section 4.1](#)) and exclusion criteria (refer to [Section 4.2](#)) should be taken into consideration when determining if a subject must be withdrawn. 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. Subjects who have received investigational product will not be replaced.

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

The decision to withdraw a subject from the study should be discussed with the sponsor. Every attempt must be made to collect all AEs or SAEs following each vaccination. Any AEs or SAEs that are continuing at the time of withdrawal from the study must be followed until the events have subsided, until values have returned to baseline, or, in case of permanent impairment, until the condition stabilizes. When a subject discontinues or is withdrawn from the study, the investigator will notify the sponsor and, when possible, will perform the procedures indicated for the next visit and complete the CRFs for Visit 7 (Month 12 Follow-up and Blood Draw) if the subject has received at least 1 study vaccination.

Subjects may withdraw from the study at any time at their own request or parent(s)/legal guardian's request, 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. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record). In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return the e-diary, request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

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

#### **6.10.1. Final Telephone Contact for Withdrawn Subjects (168 to 196 Days After Last Study Vaccination)**

- The final telephone contact should occur approximately 6 months after the last study vaccination for subjects who have withdrawn; this contact should be attempted for all subjects who have withdrawn from the study and who have received at least 1 study vaccination, unless they have withdrawn consent.
- Contact the subject by telephone and complete the Study Visit/Telephone Contact Checklist to:
  - Inquire about SAEs, newly diagnosed chronic medical conditions, and AEs that resulted in evaluation at a medical facility since the last visit. Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.

- Report any SAEs to the sponsor as defined in [Section 8.15.1](#).
- Record AEs as described in the AE [Reporting Requirements](#) section and the [Schedule of Activities](#).
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment section ([Section 5.8](#)).
- Complete the source documents.
- Complete the CRFs.

## 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/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

To facilitate immunogenicity analysis, subjects will have approximately 5 to 10 mL (dependent upon age) of blood collected immediately before Vaccination 1, 1 month after Vaccination 2, and 1 and 6 months after study Vaccination 3. Sample collection, storage, and shipping information can be found in the SRM.

Target volume for blood draw is 5 mL for subjects aged  $\geq 24$  months to  $< 4$  years at the time of blood draw and approximately 10 mL for those aged  $\geq 4$  years at the time of blood draw.

#### 7.1.1. 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  $-20^{\circ}\text{C}$  or lower within the limits specified by the manufacturer.

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

### **7.1.2. Bivalent rLP2086 Serum Bactericidal Assay—Primary Test Strains**

For assessment of the immune response to bivalent rLP2086, functional antibodies will be analyzed in hSBAs using human complement 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, **CCI** [A22], **CCI** [A56], **CCI** [B24], and **CCI** [B44], 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 study vaccination, and 1 and 6 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 (**CCI** [A22] and **CCI** [B24]) will be tested at each blood sampling time points for half of the subjects (in both groups), and the other 2 primary strains (**CCI** [A56] and **CCI** [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 (50% subjects randomly selected to be tested for A22/B24 and the remaining 50% subjects to be tested for A56/B44) to the sponsor's sample management team. Both listings should follow the same randomization ratio (3:1) and age-strata distribution (50% in each stratum) as in the study design.

### **7.1.3. Additional Assays**

Additional assays to assess the immune response to the study vaccine may also be conducted. **CCI** [A22] and **CCI** [B24] may be tested in serum samples from the 50% of subjects who received bivalent rLP2086 and were originally tested for **CCI** [A56] and **CCI** [B44]. Conversely, **CCI** [A56] and **CCI** [B44] may be tested in serum samples from the 50% of subjects who received bivalent rLP2086 and were originally tested for **CCI** [A22] and **CCI** [B24].

The intention, volume of serum permitting, is to obtain data on all 4 primary test strains in as many subjects as possible.

## 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 ([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, relevant medication use, 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, neurological status, musculoskeletal, and lymph nodes. Significant observations from the physical examination will be documented in the CRF.
- In addition, a urine pregnancy test will be performed on all female subjects who are biologically capable of having children.

### 7.2.2. Reactogenicity: E-Diary Events

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

- Local reactions at the site of investigational product administration (redness, swelling, and pain).
- Systemic events (fever, vomiting, diarrhea, headache, fatigue, muscle pain other than muscle pain at the injection site, and joint pain).
- Local reactions, systemic events, and use and type of antipyretic medication will be collected using an e-diary. Stop dates of local reactions, systemic events, or use of antipyretic medication that was ongoing on the last day the diary was completed by the parent(s)/legal guardian will be collected on the Symptom Resolved Date CRF.

### **7.3. Pregnancy Testing**

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

### **7.4. 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. Any remaining sera will be stored, and may be used for additional assays to assess immune response to vaccines given as part of this protocol or for assay development. The sera 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 subject's 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 that sample will still be used for this research. The serum samples will remain the property of the sponsor and may be shared with other researchers as long as confidentiality is maintained.

### **7.5. Electronic Diary**

The subject's parent(s)/legal guardian will be issued an e-diary, based on a personal digital assistant or equivalent technology, and used to monitor and record the subject's local reactions, systemic events, and use and type of antipyretic medication for 7 days after each vaccination. Grading scales for local reactions and systemic events are based on US Food and Drug Administration (FDA) Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers in Preventive Vaccine Clinical Trials.<sup>19</sup> 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; entry updates where the symptom worsens on any day are possible. End dates of local reactions, systemic events, or use of antipyretic medication 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 e-diary events (such as local reactions and systemic events, including fever) or other e-diary events ongoing on the last day that the e-diary was completed.

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

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

## **7.6. Local Reactions**

Local reactions (redness, swelling, and pain) at the site of the study vaccine injection will be recorded daily for 7 days (Day 1 to Day 7) after each vaccination.

### **7.6.1. 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 as mild, moderate, or severe based on the scale given below. Each caliper unit represents 0.5 cm. A caliper will be issued with instructions for measuring any redness or swelling at the injection site. The caliper will be used to measure and to report the largest diameter of a local reaction. In the event that a caliper measurement is between 2 values, the higher value should be reported. The measurements will then be recorded in the e-diary.

In the event the reaction exceeds the maximum size the caliper is able to measure (>14 caliper units), the parent(s)/legal guardian will also measure the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided and report this immediately to the investigator. The parent(s)/legal guardian 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 3. 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)

### **7.6.2. Injection Site Pain**

The parent(s)/legal guardian will be asked to assess whether pain is present at the injection site for the first 7 days following vaccination (Day 1 to Day 7). If the subject experiences injection site pain, the pain will be graded using the following scale:

**Table 4. Grading of Pain**

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

The assessment will then be recorded in the e-diary.

### **7.7. Systemic Events**

#### **7.7.1. Temperature**

A digital thermometer will be given to the parent(s)/legal guardian with instructions on how to measure their child's temperature at home. Temperature will be collected at 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 temperature of  $\geq 38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ). The subject's temperature should be measured using the thermometer provided and using a method appropriate for the age of the child. The route of temperature measurement will be recorded in the CRF.

Temperature will be measured and recorded to 1 decimal place and then categorized according to the following scale:

**Table 5. Scale for Fever**

Temperature $38.0^{\circ}\text{C}$ to $38.4^{\circ}\text{C}$ ( $100.4^{\circ}\text{F}$ to $101.1^{\circ}\text{F}$ )
Temperature $38.5^{\circ}\text{C}$ to $38.9^{\circ}\text{C}$ ( $101.2^{\circ}\text{F}$ to $102.0^{\circ}\text{F}$ )
Temperature $39.0^{\circ}\text{C}$ to $39.4^{\circ}\text{C}$ ( $102.1^{\circ}\text{F}$ to $103.0^{\circ}\text{F}$ )
Temperature $>39.5^{\circ}\text{C}$ to $40.0^{\circ}\text{C}$ ( $103.1^{\circ}\text{F}$ to $104.0^{\circ}\text{F}$ )
Temperature $>40.0^{\circ}\text{C}$ ( $>104.0^{\circ}\text{F}$ )

### **7.7.2. Use of Antipyretic Medication**

Prophylactic antipyretics and other pain medications to prevent symptoms associated with investigational product are not permitted. If the subject has received such medications prior to a planned administration of investigational product, vaccination should be temporarily delayed as specified in [Section 4.3](#).

Antipyretics and other pain medications to treat symptoms associated with investigational product are permitted.

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

### **7.7.3. Other Systemic Events**

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

**Table 6. Grading of Other Systemic Events**

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

Abbreviation: IV=intravenous

## **7.8. Other Safety Monitoring**

### **7.8.1. Adverse Events**

Reporting of AEs and SAEs outside of the e-diary is described in [Section 8](#).

### **7.8.2. 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.

### **7.8.3. Medically Attended Adverse Events and Newly Diagnosed Chronic Medical Conditions**

Medically attended AEs and newly diagnosed chronic medical conditions will be also assessed throughout the study and documented on the appropriate AE CRF. A medically attended AE is defined as a nonserious AE that results in an evaluation at a medical facility.

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

### **7.8.4. Hospitalizations, Concomitant Medication Use, and Medical Facility Visits Associated With Adverse Events**

AEs (serious and nonserious), newly diagnosed chronic medical conditions, and visits to other medical facilities will be assessed at study visits as specified in the [Schedule of Activities](#) and reported as defined in Adverse Event [Section 8](#).

AE-related hospitalizations, visits to other medical facilities, and medication use and days of school (if appropriate) missed will be collected and recorded in the AE CRF.

Hospitalizations and visits to medical facilities not associated with an AE, such as elective hospitalizations, healthcare visits for preventive care, or routine physical examinations, will not be collected. Non-AE-related concomitant medications (other than vaccinations) and days of school missed (if appropriate) not associated with an AE 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. The checklist includes questions regarding newly diagnosed chronic medical conditions, medically attended AEs, and missed days of school.

Please refer to the SRM for details.

### **7.8.5. Memory Aid**

The parent(s)/legal guardian will be given a memory aid at Visit 6. The memory aid will be used to remind them to review any significant illnesses, hospitalizations, newly diagnosed medical conditions, or AEs that resulted in evaluation at a medical facility with study site personnel. The parent(s)/legal guardian may use the memory aid as needed during the Month 12 Follow-up and Blood Draw Visit (Visit 7) to prompt recall of events. These may be used to assist in reporting and discussion of events with study staff, but these memory aids will not be considered source documents and will not be collected at study visits. Only information collected by study staff as part of the study visits will be included in the source documents and entered into the CRF.

In addition, AEs and SAEs will be recorded and reported as described in [Section 7.8](#).

## **8. ADVERSE EVENT REPORTING**

### **8.1. Adverse Events**

All observed or volunteered AEs regardless of treatment 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.

### **8.2. Research-Related Injury**

*Applicable to Visit 7 only.*

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

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 and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer 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 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 from the signing of the ICD through Visit 6.

At Month 12 (Visit 7: Follow-up and Blood Draw), the site will inquire about SAEs, newly diagnosed chronic medical conditions, or AEs that resulted in evaluation at a medical facility since Visit 6.

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

At Visit 7, the site will inquire about any AEs, as well as RRIs ([Section 8.2](#)), for events occurring during the 48-hour period after blood draw. These events must be recorded in the CRF for the visit at which the blood was drawn and the event must be followed.

At all visits, 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 vaccine 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 breast feeding;
- Medication error.
- Occupational exposure.

### **8.5. Medication Errors**

Medication errors may result, in this study, from the administration or consumption of the wrong vaccine, 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.
- Administration of an 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 should be captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

## **8.6. 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
- 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.

## **8.7. 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 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;
- 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.

### **8.7.1. 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 [Section 8.15.1](#)).

### **8.7.2. 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  $\geq 3$  times the upper limit of normal (X ULN) concurrent with a total bilirubin value  $\geq 2$  X ULN with no evidence of hemolysis and an alkaline phosphatase value  $\leq 2$  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  $\geq 2$  times the baseline values and  $\geq 3$  X ULN, or  $\geq 8$  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  $\geq 3$  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.

### **8.8. Hospitalization**

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to 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 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.

### **8.9. Severity Assessment**

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

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

### **8.10. 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 serious adverse 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 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 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.

### **8.11. Exposure During Pregnancy**

For investigational products and for marketed products, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male subject has been exposed (eg, because of vaccination 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 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 (ie, induced abortion) 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, 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 neonatal death as related or possibly related to exposure to 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 Pregnant Partner Release of Information Form to provide to his partner.

### **8.12. Occupational Exposure**

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

An occupational exposure is reported to safety 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, the information is not reported on a CRF; however, a copy of the completed SAE Report Form is maintained in the study master file.

### **8.13. Withdrawal Due to Adverse Events (See Also [Section 6.10 Subject Withdrawal](#))**

Withdrawal due to AE 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.

### **8.14. Eliciting Adverse Event Information**

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

### **8.15. 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.

### **8.15.1. 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 and exposure via breastfeeding cases and occupational exposure cases.

If the investigator is aware of an SAE with an onset on the day of investigational product administration or during the calendar day following investigational product administration, the investigator must contact the Pfizer study physician directly immediately after sending the SAE Report Form to Pfizer. These procedures do not replace any of the standard SAE reporting requirements as described above. Additional information can be found in the SRM.

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

SAEs are to be reported throughout the study from signing of the ICD up to the study end (Visit 7: Month 12 Follow-up and Blood Draw).

At Month 12 (Visit 7: Month 12 Follow-up and Blood Draw), the site will inquire about SAEs, newly diagnosed chronic medical conditions, or medically attended events (AEs that resulted in evaluation at a medical facility) since Visit 6.

### **8.15.2. Nonserious Adverse Event Reporting Requirements**

All AEs will be reported on the AE page 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 to up to Visit 6 (Post-Vaccination 3 Blood Draw).

Nonserious AEs starting between Visits 6 and 7 will only be reported in the CRF if they are either a newly diagnosed chronic medical condition or a medically attended event that resulted in evaluation at a medical facility since Visit 6.

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

At all visits, 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.

### **8.15.3. Medical Device Complaint Reporting Requirements**

All medical device complaints 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.

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.

### **8.15.4. Sponsor 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**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be finalized before the start of any analyses and will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will be reflected both in the amended protocol and in the SAP. The SAP amendment will follow the protocol amendment.

## **9.1. Sample Size Determination**

The study sample size is not based on hypothesis-testing criteria. This study will enroll approximately 400 subjects with a randomization ratio of 3:1 (bivalent rLP2086 group: control).

## **9.2. Immunogenicity Analysis**

This is not a hypothesis-testing study; thus, an estimation approach will be used to assess the primary, secondary, and exploratory objectives.

As assay data are expected to be missing completely at random (MCAR) (Scott & Hsu, 2011<sup>20</sup>), 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 the hSBA data missing reason and the relationship between the missing data indicator and other design variables or covariates (age, race, gender, center, etc) and the observed hSBA data. Additionally, a sensitivity analysis using mixed effects model with repeated measurement (MMRM) will be applied to the primary endpoints. The MMRM uses the maximum likelihood estimation, and it is under the assumption that the missing is at random (MAR). If 50% of the subjects or less have 2 strains tested and the remaining have the other 2 strains tested, no sensitivity analyses will be planned because the missing assumption is MCAR.<sup>21</sup>

For the calculation of GMTs, hSBA results below LLOQ will be set as  $\frac{1}{2}$  of LLOQ as primary analysis.

### **9.2.1. Analysis of Primary Endpoints**

The proportion of subjects in each group achieving hSBA titer  $\geq$  LLOQ 1 month after the third vaccination will be computed for each test strain along with 2-sided 95% exact<sup>22</sup> confidence intervals (CIs), for each of the age strata.

All of the binary endpoints (including primary endpoints) will be summarized with 2-sided 95% CIs using the exact method. GMTs on hSBA results will also be summarized with 95% CIs.

### **9.2.2. Analysis of Secondary Endpoints and Exploratory Endpoints**

The hSBA GMTs will be summarized at each blood sampling time point by randomization group for each test strain, 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 titer  $\geq 1:4$ ,  $\geq 1:8$ ,  $\geq 1:16$ ,  $\geq 1:32$ ,  $\geq 1:64$ , and  $\geq 1:128$  will be descriptively summarized with 95% exact CIs for each primary test strain at each blood sampling time point.

The proportion of subjects achieving hSBA titers with at least a 4-fold rise from baseline and the composite response will be summarized similarly.

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

### **9.3. 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 randomized.

In general, the evaluable population will include all subjects who were randomized 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 important protocol deviations. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine.

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

### **9.4. Demographic and Baseline Characteristics**

The following demographic characteristics will be descriptively summarized: sex, race, ethnicity, and age at first vaccination. Medical history and baseline physical examination data will also be descriptively summarized.

### **9.5. Safety Analysis**

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 information is available. For the safety analysis, subjects will be analyzed according to the investigational product received. Missing safety data will not be replaced or imputed.

The proportion of subjects reporting local reactions at the investigational product administration sites and systemic events within the 7-day period after each vaccination will be descriptively summarized by group. 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 method will be presented with the proportions.

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

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 SAE and AE percentages.

Comparisons will be made on the safety endpoints between Group 1 and Group 2. The reactogenicity data and immediate AEs between the vaccine and control will be compared with unconditional exact test. Fisher exact test will be used to compare the endpoints related to AEs, SAE, medically attended AEs, and newly diagnosed medical conditions.

For each subject, the number of days of school missed because of AEs will be aggregated across the vaccination phase. Then summary statistics using mean (standard deviation), median, and range will be descriptively tabulated for the total days by each group.

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 analyses may also be summarized by other demographic variables.

### **9.6. Analysis Timing**

No interim analysis is planned for this study. The study database will be unblinded after all of the data are cleaned. The analyses will then be performed to include all of the data summaries.

### **9.7. Data Monitoring Committee**

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

## **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 will review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors 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 IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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 and 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 source documents. 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/assents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, 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, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

## **12. ETHICS**

### **12.1. Institutional Review Board (IRB)/Ethics Committee (EC)**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICDs/assents, 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), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 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 on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

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 subject. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's 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.

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

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

In addition, a study-specific assent form will be provided to the subject as required by local regulations. It is to be understood as the child's will to participate in a study after having received age-appropriate information and is sometimes also referred to as "knowing agreement."

The investigator must ensure that each study subject, or his/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 or the 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/assent document.

#### **12.4. Subject Recruitment**

Advertisements approved by ECs and investigator databases may be used 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 TRIAL**

End of trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient 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.

## **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 trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov) and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

#### [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Pfizer posts clinical trial Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

- The timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:
- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within 1 year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results 1 year from last subject last visit (LSV);
- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or 1 year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);
- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within 1 year of discontinuation of the program (if there are no plans for outlicensing, or within 2 years if outlicensing plans have not completed).

*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.

[www\(pfizer.com](http://www(pfizer.com)

Pfizer posts clinical trial results on [www\(pfizer.com](http://www(pfizer.com) for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an 'FDA-approved Pfizer product with a LSLV on or after 27 Sep 2007 for which Basic Results were posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

EudraCT

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01 May 2004, regardless of the marketing status of the compound.

## **15.2. Publications by Investigators**

Pfizer has no objection to publication by investigator of any information collected or generated by investigator, whether or not the results are favorable to the investigational product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure 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 clinical study agreement between Pfizer and the institution. In this section entitled **Publications by Investigators**, the defined terms shall have the meanings given to them in the clinical study agreement.

## 16. REFERENCES

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