A PHASE 3 STUDY TO ASSESS THE PERSISTENCE OF hSBA RESPONSE UP TO 48 MONTHS AFTER COMPLETION OF A PRIMARY SERIES OF BIVALENT rLP2086, AND THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A BOOSTER DOSE OF BIVALENT rLP2086

Compound:	PF-05212366
Compound Name:	*Neisseria meningitidis* Serogroup B Bivalent Recombinant Lipoprotein 2086 Vaccine (Bivalent rLP2086; subfamily A and B; *E coli*)
United States (US) Investigational New Drug (IND) Number:	13812
European Clinical Trials Database (EudraCT) Number:	2011-005697-31
Universal Trial Number:	Not Applicable
Protocol Number:	B1971033
Phase:	3

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Protocol Amendment 4	18 Apr 2017	• Extended the booster stage follow-up duration from 12 months to 26 months to assess the longevity of immune responses after the booster dose. • Added an additional blood draw visit (Visit 11) to assess immune response 26 months after the booster dose. • CCI [redacted] • Updated the primary safety endpoint relating to the booster stage follow-up at 26 months. • Updated the duration of the subject participation, duration of the study, and number of subjects to reflect the extension of the booster stage up to 26 months after the booster dose. • Updated the inclusion criteria for the booster stage to include subject eligibility criteria for the additional blood draw 26 months after the booster dose. • Updated the Study Procedures section to include an additional informed consent process required for Visit 11 and the study procedures at Visit 11. • Updated Table 2 and the Investigational Product section to reflect administrative changes made after protocol amendment 3 (protocol administrative change letter dated 26 Mar 2015). • Added the current US Centers for Disease Control and Prevention's recommendation for *Neisseria meningitidis* serogroup B (MnB) vaccination to keep it up to date. • Replaced the study rationale for protocol amendment 3 with the study rationale for the current protocol amendment 4 (Section 1.2.5).

Document	Version Date	Summary of Changes and Rationale
		• Updated the risks and benefits sections to refer to the most recent version of the bivalent rLP2086 investigator's brochure instead of the outdated version (Section 1.2.6 and Section 7.7) and removed the text about unknown risks and benefits of a booster dose of bivalent rLP2086 to reflect the status change from unknown to known (Section 1.2.6). • CCI [redacted] • Added Visit 11 to the adverse event reporting information. • Added Visit 11 to data analysis for immunogenicity and safety endpoints.
Protocol Amendment 3	08 Jan 2015	• Added a booster dose (booster stage). • The title has been updated to capture the vaccine booster component design. • Updated to comply with the "interventional" protocol template. • Primary objective and corresponding endpoint added relating to the assessment of immunogenicity following a booster vaccination. • Added hSBA testing of sera from subjects who did not receive bivalent rLP2086 in the primary study. Updated Stage 1 objective to reflect this. • CCI [redacted] • Added primary safety objective/endpoints describing the safety profile of bivalent rLP2086 booster vaccination. • Up to 2 interim analyses incorporated into the study (1 and 12 months after the booster vaccination).

Document	Version Date	Summary of Changes and Rationale
		• Testing on the Luminex assay for antigen detection of MCV4 (previously Section 7.1.2) now removed. • Updated safety reporting requirements to reflect receipt of the booster dose. • Added booster stage inclusion/exclusion criteria.
Protocol Amendment 2	19 Dec 2013	• CCI [redacted] • Inclusion criteria updated to allow enrollment of subjects where subject vaccine assignment is blinded at the time of study entry. • Exclusion criterion 8 added to ensure subjects who were not compliant with the primary study's eligibility criteria will not be enrolled. • Subject selection updated from 800 to up to 1200 subjects participating in the study. • Addition of collection of newly diagnosed chronic medical conditions. • Updated the requirement to report serious adverse events back to the primary studies after the active reporting phase, in line with current Pfizer policy. • Interim analysis section amended to confirm that no analysis is planned. • Added the definition of the end of the trial. • Updated the abbreviated vaccine name (ie, "bivalent rLP2086"). • CCI [redacted] • Updated to comply with the current protocol template.

Document	Version Date	Summary of Changes and Rationale
		• Added Section 7.1.2 on the Luminex assay for antigen detection for MCV4. • Added a confirmation that subjects' consent should be obtained after they are no longer minors.
Protocol Amendment 1	21 Mar 2012	The purpose of this amendment is to add the benefit-risk assessment in the protocol. Wording on biological samples has also been added.
Original protocol	14 Dec 2011	N/A

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

This is a list of abbreviations that may or may not be used in the protocol.

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
$Al3^+$	aluminum
$ALPO_4$	aluminum phosphate
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
CSA	clinical study agreement
CTA	clinical trial application
EC	ethics committee
e-diary	electronic diary
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act of 2007
fHBP	factor H binding protein
GCP	Good Clinical Practice
GMC	geometric mean concentration
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 Council for Harmonisation
IgG	immunoglobulin G
IMD	invasive meningococcal disease
INR	international normalized ratio

IRB	institutional review board
ISC	independent statistical center
IUD	intrauterine device
IVRS	interactive voice response system
IWRS	interactive Web-based response system
LFT	liver function test
LLOQ	lower limit of quantitation
LP2086	lipoprotein 2086
LSLV	last subject last visit
MCV4	quadrivalent meningococcal polysaccharide conjugate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MnB	*Neisseria meningitidis* serogroup B
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
OMV	outer membrane vesicle
PCD	primary completion date
PS80	polysorbate 80
PT	prothrombin time
RCDC	reverse cumulative distribution curve
rLP2086	recombinant lipoprotein 2086
RRI	research-related injury
SAE	serious adverse event
SAP	statistical analysis plan
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
Tdap	tetanus, diphtheria, and acellular pertussis
ULN	upper limit of normal
US	United States

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 a case-fatality rate of 6% to 8% from 1999 to 2006. MnB disease accounts for approximately one-third of meningococcal cases seen in North America.

A recombinant, multicomponent MnB vaccine (Bexsero) is licensed in the European Union (EU), Canada, Australia, and Chile; and recommendations for use are under consideration in various countries. Trumenba® (bivalent recombinant lipoprotein 2086 vaccine), developed by Pfizer, has recently (October 2014) been approved in the United States for active immunization to prevent invasive disease caused by *N meningitidis* serogroup B, for use in individuals 10 through 25 years of age. The US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) has assigned a Category B recommendation for administration of MnB vaccines for adolescents and young adults aged 16 to 23 years, with particular focus on the 16- to 18-year age group. A Category A recommendation was assigned for MnB vaccination of certain groups of persons at increased risk for serogroup B meningococcal disease, including for persons aged ≥10 years during outbreaks of serogroup B meningococcal disease. Broad implementation of a safe and immunogenic vaccine against diverse MnB strains is anticipated to provide substantial improvement in prevention of this uncommon but severe bacterial infection and a reduction in the burden of disease.

Trumenba is targeted to a conserved, surface-exposed lipoprotein, lipoprotein 2086 (LP2086), a meningococcal virulence factor that binds human factor H, and therefore is designated as factor H binding protein (fHBP). The LP2086 gene is present in 100% of MnB strains in Pfizer's strain collection of more than 1800 strains isolated from patients with invasive disease in the United States and Europe. The lipoproteins segregate into 2 antigenically and immunologically distinct subfamilies, A and B. Trumenba is a sterile suspension composed of 2 recombinant lipidated fHBP variants from MnB, 1 from fHBP subfamily A and 1 from subfamily B (A05 and B01, respectively).

This study was initiated in September 2012 to assess the longevity of immune responses in adolescents (aged ≥10 to <19 years at the time of entry into a primary study) following receipt of a vaccination regimen of 2 or 3 doses of bivalent rLP2086 in a primary study (a previously conducted Pfizer study using the final formulation of bivalent rLP2086). This study was amended in January 2015 to add a booster dose of bivalent rLP2086 at approximately 4 years following the final dose of the 2- or 3-dose primary bivalent rLP2086 vaccination series. The study was therefore divided into Stage 1 (4-year persistence of immune responses following receipt of a primary vaccination series) and the booster stage (follow-up through 12 months after booster vaccination).

The study is now amended to further evaluate safety and immune responses up to 26 months following a single booster dose of bivalent rLP2086. The postbooster follow-up through 26 months after booster vaccination is being conducted for a subset of booster stage subjects who previously received bivalent rLP2086 in a primary series of either a 0-, 2-, and 6-month or a 0- and 6-month schedule. The rationale for focusing on this subset of subjects is based on the fact that the 0-, 2-, and 6-month and the 0- and 6-month schedules are the dosing schedules approved by the Food and Drug Administration (FDA).

Objectives:

Primary Objectives

Stage 1

- To describe the immunogenicity of bivalent rLP2086 as determined by serum bactericidal assay using human complement (hSBA) titers to 4 primary test strains at approximately 6, 12, 18, 24, 36, and 48 months after the last dose (second or third dose) of bivalent rLP2086 or saline in the primary study (ie, a previously conducted Pfizer study using the final formulation and dose of bivalent rLP2086).

Booster Stage

- To describe the immune response as measured by hSBA titers to 4 primary test strains 1 month following the last vaccination with bivalent rLP2086 in the primary study, before the booster vaccination, and 1 month, 12 months, and 26 months after a single booster dose of bivalent rLP2086.

Primary Safety Objective (Booster Stage)

- To evaluate the safety profile of bivalent rLP2086 as measured by the incidence of local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended events, and immediate AEs following a booster vaccination of bivalent rLP2086.

Primary Endpoints

Stage 1

- Proportion of subjects with hSBA titers ≥ lower limit of quantitation (LLOQ) for each of the 4 primary strains at each blood draw visit in Stage 1 (Visits 1-6).

Booster Stage

- Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary strains at 1 month following the last vaccination received in the primary study, before the booster vaccination (Visit 6), and 1 month, 12 months, and 26 months (Visits 8, 10, and 11) following booster vaccination.

Primary Safety Endpoints (Booster Stage)

- Percentages of subjects reporting local reactions via the electronic diary (e-diary) by type (pain at the injection site, redness, and swelling) and by severity after a booster vaccination of bivalent rLP2086.

- Percentages of subjects reporting systemic events via the e-diary by type (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain) and by severity after a booster vaccination of bivalent rLP2086.

- Percentage of subjects reporting the use of antipyretic medication via the e-diary after a booster vaccination of bivalent rLP2086.

- Percentages of subjects with at least 1 AE occurring during the following time periods:

    - From Visit 7 to Visit 8

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

    - From Visit 7 to Visit 8

    - From Visit 8 to Visit 9

    - From Visit 7 to Visit 9

- Percentages of subjects with at least 1 NDCMC occurring during the following time periods:

    - From the 6-month safety telephone call in the primary study to Visit 6 (Stage 1)

    - From Visit 7 to Visit 8

    - From Visit 8 to Visit 10

    - From Visit 7 to Visit 10

    - From Visit 8 to Visit 11 (only subjects proceeding to Visit 11)

    - From Visit 7 to Visit 11 (only subjects proceeding to Visit 11)

- Percentages of subjects with at least 1 medically attended event occurring during the following time periods:

    - From Visit 7 to Visit 8

    - From Visit 8 to Visit 9

  - From Visit 7 to Visit 9

- Percentage of subjects reporting at least 1 immediate AE after receiving the booster dose of bivalent rLP2086.

- Number of days subjects miss school or work because of AEs from Visit 7 through Visit 9.

Design

Stage 1 of the study (Visits 1-6) is designed to provide follow-up information on Pfizer Studies B1971010, B1971012, and B1971015, which used the final formulation and dose of bivalent rLP2086 (primary studies). In Stage 1, subjects will attend up to 6 study visits for collection of a 20-mL blood sample at each visit.

The booster stage of the study (Visits 7-11) is optional for eligible subjects at selected sites. Subjects who wish to participate in the booster stage must have completed Stage 1 and received all scheduled doses of bivalent rLP2086 in the primary study.

Subjects will be required to sign a consent form to enter and participate in the booster stage for Visits 7 to 10. Eligible subjects at selected sites will be asked to sign another consent form prior to participating in Visit 11, for a blood draw at 26 months after the booster vaccination.

For consenting booster stage subjects, a booster dose of 120 µg of bivalent rLP2086 will be administered at Visit 7 and blood samples (20 mL per visit) will be collected for immunogenicity analysis 1 month, 12 months, and 26 months after the booster vaccination (Visits 8, 10, and 11).

Design Overview:

	STAGE 1						**BOOSTER STAGE**				
Visit purpose	Blood draw	Blood draw	Blood draw	Blood draw	Blood draw	Blood draw	Booster vaccination	Blood draw	6-Month telephone call	Blood draw	Blood draw
Visit number	1	2	3	4	5	6	7	8	9	10	11
Approximate month	6	12	18	24	36	48	48	1 Month after booster	6 Months after booster	12 Months after booster	26 Months after booster
Vaccination							Bivalent rLP2086				
Blood draw	20 mL	20 mL	20 mL	20 mL	20 mL	20 mL		20 mL		20 mL	20 mL

Investigational Products

The following is defined as the investigational product and will be supplied by the sponsor:

Bivalent rLP2086 is a sterile suspension composed of 2 recombinant lipidated fHBP variants from MnB, 1 from fHBP subfamily A and 1 from subfamily B (A05 and B01, respectively). The proteins are individually produced in *Escherichia coli*. Production strains are grown in defined fermentation growth media to a specific density. The recombinant proteins are extracted from the production strains and purified through a series of column chromatography steps. Polysorbate 80 (PS80) is added to the vaccine substances and is present in the final vaccine product.

CCI [redacted]

Statistical Methods

This is a descriptive study; therefore, an estimation approach will be utilized to address the immunogenicity objectives. All binary endpoints (including the Stage 1 and booster stage primary endpoints) will be analyzed by presenting 2-sided exact 95% confidence intervals (CIs). Geometric mean titers (GMTs) and 2-sided 95% CIs based on Student's t distribution will be estimated. A mixed model with repeated measures adjusted with covariates will also be used to estimate the GMTs at different time points. Safety endpoints will be descriptively summarized via proportions of subjects with each event and the associated 2-sided exact 95% CIs.

SCHEDULE OF ACTIVITIES

The schedule of activities (Table 1 to Table 3) 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.

Table 1. Schedule of Activities – Stage 1

Visit Identifier	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Visit Window	**6 Months (150-240 Days) After Last Dose of Bivalent rLP2086, or After Last Injection of Investigational Product in Primary Study[a]**	**12 Months (330-390 Days) After Last Dose of Bivalent rLP2086, or After Last Injection of Investigational Product in Primary Study[a]**	**18 Months (510-570 Days) After Last Dose of Bivalent rLP2086, or After Last Injection of Investigational Product in Primary Study[a]**	**24 Months (676-764 Days) After Last Dose of Bivalent rLP2086, or After Last Injection of Investigational Product in Primary Study[a]**	**36 Months (1036-1124 Days) After Last Dose of Bivalent rLP2086, or After Last Injection of Investigational Product in Primary Study[a]**	**48 Months (1396-1484 Days) After Last Dose of Bivalent rLP2086, or After Last Injection of Investigational Product in Primary Study[a]**
Informed consent	X	X[b]				
Confirm continued eligibility	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X
Record any nonstudy vaccination	X	X	X	X	X	X
Blood samples for hSBA[d]	X	X	X	X	X	X
NDCMCs	X	X	X	X	X	X
AEs and RRIs	48 Hours after visit	48 Hours after visit	48 Hours after visit	48 Hours after visit	48 Hours after visit	48 Hours after visit

a. If the subject's primary study vaccine assignment is known at the time of consent for Study B1971033, the visits in Study B1971033 should be scheduled relative to the last dose of bivalent rLP2086 in the primary study. If the subject's primary study vaccine assignment is blinded at the time of consent for Study B1971033, the visits in Study B1971033 should be scheduled relative to the last injection of investigational product in the primary study.
b. Consent may be obtained at Visit 2 if subjects are enrolled at Visit 2.
c. Vital signs will include blood pressure, pulse rate, and temperature (oral).
d. Amount of blood collected is approximately 20 mL.

Abbreviations: AE = adverse event; hSBA = serum bactericidal assay using human complement; NDCMC = newly diagnosed chronic medical condition; RRI = research-related injury.

Table 2. Schedule of Activities – Booster Stage

Visit Identifier	Visit 7 Booster Vaccination	Visit 8 Postvaccination Blood Draw 1	Visit 9 6-Month Telephone Contact	Visit 10 Postvaccination Blood Draw 2	Visit 11 Postvaccination Blood Draw 3
Visit Window	**48 Months After Last Dose of Bivalent rLP2086 in Primary Study[a] (1396-1484 Days After Last Dose of Bivalent rLP2086, and Within 42 Days After Visit 6)**	**1 Month After Booster (28-42 Days After Visit 7)**	**6 Months After Booster (168 to 196 Days After Visit 7)**	**12 Months After Booster (330-390 Days After Visit 7)**	**26 Months After Booster (750-810 Days After Visit 7)**
Informed consent[b]	X				X
Review eligibility criteria[c]	X				X
Confirm continued eligibility[c]		X	X	X	
Vital signs[d]	X[e]	X		X	X
Medical history	X				
Physical examination	X				
Urine pregnancy test (all female subjects)	X				
Record any nonstudy vaccination and allergen immunotherapy[f]	X[e]	X	X	X	X
Blood sample[g]		X		X	X
IVRS/kit assignment	X				
Investigational product administration and observation	X				
Provide subject or parent/legal guardian with e-diary, caliper, measuring tape/ruler, and thermometer	X				
Record concomitant medications used to treat AEs	X	X	X	X	X
Review e-diary		X			

Table 2. Schedule of Activities – Booster Stage

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Collect e-diary		X			
Record use of antipyretic medication in the e-diary	Day 1 to 7				
Assess reactogenicity	Day 1 to 7				
Provide the subject with a memory aid		X			
Complete study visit/AE checklist	X	X	X	X	X
(S)AE collection appropriate for the visit[h]	X	X	X	X	X

a. Visit 7 may occur a maximum of 42 days after Visit 6.
b. If a subject reaches the age at which he or she is able to provide legal consent during the study, the subject's consent must be obtained.
c. Subjects must satisfy all eligibility criteria for Stage 1 and the booster stage. In addition, subjects participating in Visit 11 must meet eligibility criteria for Visit 11.
d. Vital signs will include blood pressure, pulse rate, and temperature (oral).
e. If Visits 6 and 7 do not occur on the same day, ensure that vital sign measurements and recording of nonstudy vaccinations are performed again at Visit 7.
f. Nonstudy vaccination occurring from the final blood draw in the primary study until Visit 11. From Visit 7, this also includes allergen immunotherapy.
g. Amount of blood collected is approximately 20 mL.
h. Subject or subject's parent(s)/legal guardian to report any AEs within 48 hours following Visit 10 and Visit 11.

Abbreviations: AE = adverse event; e-diary = electronic diary; IVRS = interactive voice response system; RRI = research-related injury; SAE = serious adverse event.

Table 3. Adverse Event Reporting Schedule

Stage 1							Booster Stage				
AE Type	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
SAE[a]	Nonactive reporting of SAEs to the primary study						From booster stage ICD to Visit 9			Nonactive reporting of SAEs to the B1971033 study	
NDCMC[b]	From 6-month telephone call in the primary study to Visit 11										
MAE							From booster stage ICD to Visit 9				
RRI[c]	48 Hours after blood draw	48 Hours after blood draw	48 Hours after blood draw	48 Hours after blood draw	48 Hours after blood draw	48 Hours after blood draw				48 Hours after blood draw	48 Hours after blood draw
AE[d]	48 Hours after blood draw	48 Hours after blood draw	48 Hours after blood draw	48 Hours after blood draw	48 Hours after blood draw	48 Hours after blood draw	All AEs from booster stage ICD to Visit 8	48 Hours after blood draw		48 Hours after blood draw	48 Hours after blood draw
Reactogenicity events							1-7 Days				

a. Events with an onset during Stage 1 will be reported under the primary study number. Events with an onset during the booster stage will be reported under Study B19710133.
b. Events with an onset after the 6-month follow-up telephone call in the primary study.
c. Events reportable only within the first 48 hours following a blood draw.
d. Events with an onset in Stage 1, or from Visit 8 to Visit 11, are reportable only within the first 48 hours following a blood draw. From Visit 7 to Visit 8, all AEs are reportable.

Abbreviations: AE = adverse event; ICD = informed consent document; MAE = medically attended event; NDCMC = newly diagnosed chronic medical condition; RRI = research-related injury; 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 (MnB) bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086; subfamily A and B; *Escherichia coli*) is in support of licensure with an indication for active immunization to prevent invasive meningococcal disease (IMD) caused by MnB expressing either subfamily A or subfamily B factor H binding protein (fHBP) 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 a case-fatality rate of 6% to 8% from 1999 to 2006.[1] MnB disease accounts for approximately one-third of meningococcal cases seen in North America.[2] There is substantial morbidity among survivors, including neurological disability, limb loss, and hearing loss.[1]

The incidence rate of IMD varies with age, with a peak in infants and a peak in adolescents and young adults.[3] The increased risk of disease in adolescents and young adults is believed to be due to a number of factors, including social behavior and crowding of susceptible individuals in classrooms and dormitories.[4,5] Carriage rates are high in adolescents, and this age group may serve as a reservoir for transmission to younger age groups.[6]

After licensure of the first quadrivalent meningococcal conjugate vaccine (MCV4, MenACWY vaccine) in the United States in 2005, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) prioritized vaccination for persons aged 11 or 12 years, persons entering high school, and first-year college students living in residence halls. This recommendation was expanded in 2007 to include routine vaccination with MCV4 for all adolescents in the United States. In 2010, following recognition of waning immunity after a single dose of MCV4, the ACIP revised their recommendation to provide for routine vaccination of adolescents, preferably at age 11 or 12 years, with a booster dose at age 16 years.[7]

In the United States in 2011, the incidence of meningococcal disease was 0.06 and 0.15 per 100,000 population for 11- to 17-year-olds and 18- to 22-year-olds, respectively, higher than that seen for the general population.[8] Incidence rates of MnB disease during recent outbreaks at college campuses in the United States have, however, been as high as 134 per 100,000 among undergraduates at Princeton University during a 2013/2014 outbreak and 21.1 per 100,000 among 17- to 22-year-olds at the University of California Santa Barbara during a 2013 outbreak.[9,10]

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 given the chemical similarity between the serogroup B capsular polysaccharide and molecules found on human neuronal cells.[11] Vaccines produced from outer membrane vesicles (OMVs) prepared from MnB strains have been shown to have clinical efficacy against homologous strains but not against heterologous strains.[12,13] A recombinant, multicomponent MnB vaccine (Bexsero) is licensed in the European Union (EU), Canada, Australia, and Chile, and recommendations for use are still under consideration in various countries. Trumenba® (bivalent rLP2086), developed by Pfizer, has recently (October 2014) been approved in the United States for use in individuals 10 through 25 years of age for active immunization to prevent IMD caused by MnB. The US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) has assigned a Category B recommendation for administration of MnB vaccines for adolescents and young adults aged 16 to 23 years, with particular focus on the 16- to 18-year age group. A Category A recommendation was assigned for MnB vaccination of certain groups of persons at increased risk for serogroup B meningococcal disease, including for persons aged ≥10 years during outbreaks of serogroup B meningococcal disease.[14] Broad implementation of a safe and immunogenic vaccine against diverse MnB strains is expected to provide substantial improvement in prevention of this uncommon but severe bacterial infection and a reduction in the burden of disease.

1.2.2. Bivalent Recombinant Lipoprotein 2086 Vaccine

Trumenba is a subcapsular protein vaccine based on major surface components that are antigenically invariant and expressed in most disease-associated meningococci.[15] Trumenba utilizes a conserved, surface-exposed lipoprotein, lipoprotein 2086 (LP2086), as a vaccine target.[16] In the meningococcus, LP2086 is a virulence factor that binds human factor H. The LP2086 gene is present in 100% of MnB strains in Pfizer's strain collection of more than 1800 strains isolated from patients with invasive disease in the United States and Europe. The lipoproteins segregate into 2 antigenically and immunologically distinct subfamilies, A and B. 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 *E 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 have elicited bactericidal antibodies effective against subfamily A and B strains in nonclinical studies.[17]

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.[18,19] 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[20] and recognized as the surrogate marker of vaccine efficacy.[21,22,23]

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 of vaccine efficacy determined by a clinical disease endpoint.

The company 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 CDC and health and reference laboratories from European countries.[24] CCI

[redacted]

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,[24] taking into account the population distribution of LP2086 surface expression. CCI

[redacted]

1.2.4. Clinical Experience

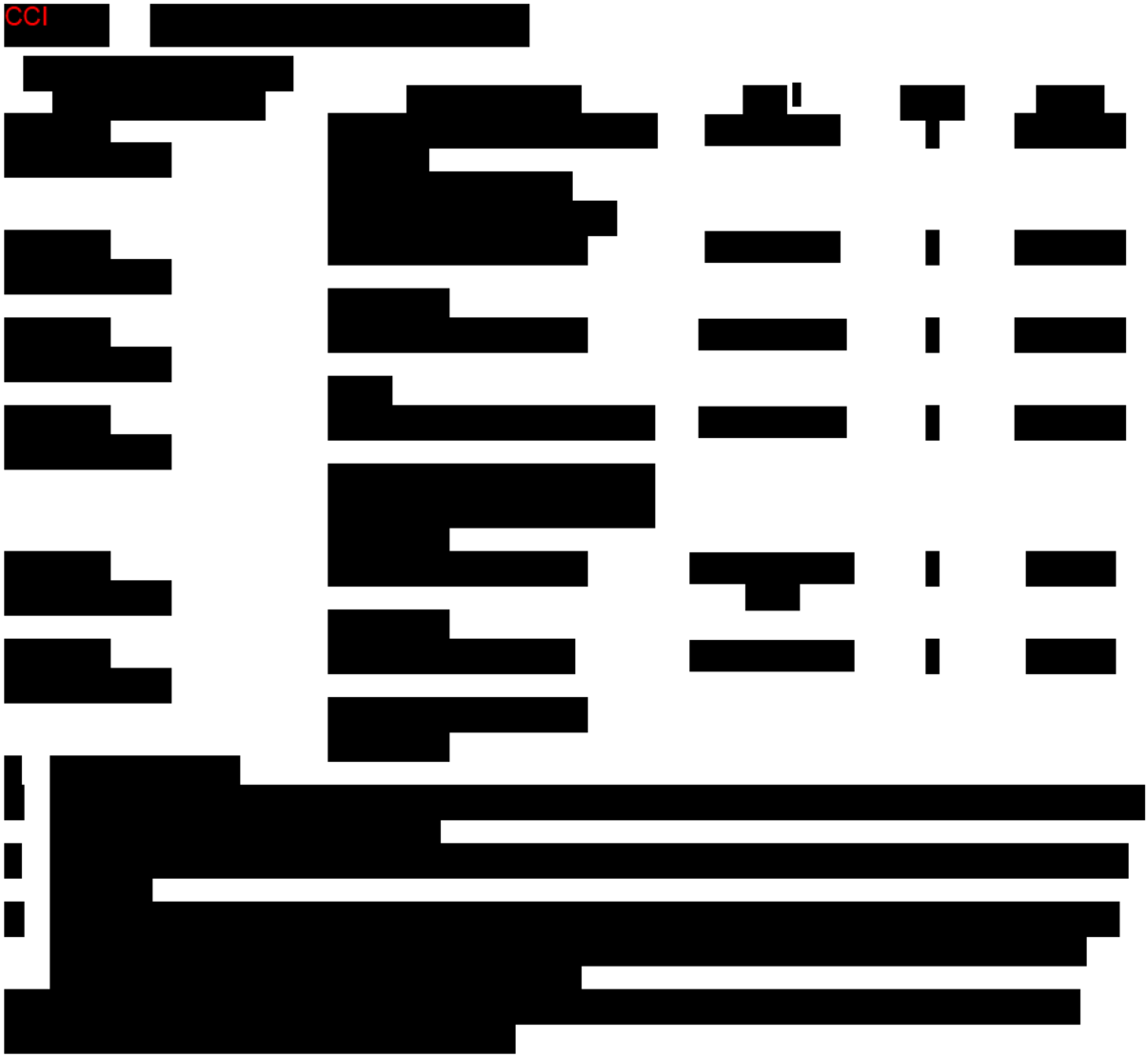
CCI

[redacted]

CCI

CCI

CCI



Safety information is available in the current version of the investigator's brochure (IB). Safety data from adults and adolescents participating in studies with the final formulation of bivalent rLP2086 are consistent with the safety of the initial formulation, which was changed to improve stability.

The safety data from the completed studies using the final formulation support an acceptable safety profile for bivalent rLP2086 in the population(s) studied. Overall, the rates of local reactions and systemic events were higher following administration of bivalent rLP2086 than for saline control, but similar to the active control group. Vaccine-related adverse events (AEs) were infrequent. The incidence of serious adverse events (SAEs) with bivalent rLP2086 was low and mostly considered not related to the study vaccine.

The percentage of subjects who withdrew from studies was low. Concomitant administration of bivalent rLP2086 with other vaccines was well tolerated in the adolescent population.

Studies B1971010 and B1971011 demonstrated an acceptable safety profile when bivalent rLP2086 was administered alone or in combination with Repevax and Gardasil, respectively.

The immunogenicity data from completed Phase 2 clinical studies using the final formulation provide evidence of a robust immune response in adolescent and adult populations. In particular, 3 Phase 2 clinical studies conducted in adolescents (B1971010, B1971011, and B1971012) demonstrated that a substantial proportion of subjects exhibited potentially protective responses after 2 vaccine doses, as assessed by hSBA with test strains that expressed fHBP antigens heterologous to those of vaccine antigens. Further, the proportions of subjects with hSBA responses increased following a third dose of bivalent rLP2086. These 3 studies formed the basis of approval in the United States via an accelerated regulatory pathway.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the IB. The SRSDs for the concomitant vaccines are specified in the primary studies' protocols.

1.2.5. Study Rationale

The purpose of Stage 1 of the study is to assess the longevity of immune responses following receipt of a vaccination course of 2 or 3 doses of bivalent rLP2086.

This study was initiated in September 2012 to assess the longevity of immune responses in adolescents (aged ≥10 to <19 years at the time of entry into a primary study) following receipt of a vaccination regimen of 2 or 3 doses of bivalent rLP2086 in a primary study (a previously conducted Pfizer study using the final formulation of bivalent rLP2086). This study was amended in January 2015 to add a booster dose of bivalent rLP2086 at approximately 4 years following the final dose of the 2- or 3-dose primary bivalent rLP2086 vaccination series. The study was, therefore, divided into Stage 1 (4-year persistence of immune responses following receipt of a primary vaccination series) and the booster stage (follow-up through 12 months after booster vaccination).

The study is now amended to further evaluate safety and immune responses up to 26 months following a single booster dose of bivalent rLP2086. The 26-month postbooster follow-up is being conducted for a subset of booster stage subjects who previously received bivalent rLP2086 in a primary series of either a 0-, 2-, and 6-month or a 0- and 6-month schedule. The rationale for focusing on this subset of subjects is based on the fact that the 0-, 2-, and 6-month and the 0- and 6-month schedules are the dosing schedules approved by the FDA.

1.2.6. Risk and Benefits

Potential risks associated with participation in Stage 1 of this study are limited to those associated with drawing blood (bruising, mild bleeding, momentary discomfort, fainting, and, rarely, infection), as well as any potential long-term side effects (later-emerging events) that may be associated with bivalent rLP2086, administered previously in the primary studies.

Refer to the most recent version of the bivalent rLP2086 IB for a summary of the known and potential risks and benefits to human subjects after primary and booster vaccinations.

It is considered that, based on the currently available safety and efficacy data for bivalent rLP2086, the benefit-risk profile of the vaccine remains favorable.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

Stage 1

- To describe the immunogenicity of bivalent rLP2086 as determined by hSBA titers to 4 primary test strains at approximately 6, 12, 18, 24, 36, and 48 months after the last dose (second or third dose) of bivalent rLP2086 or saline in the primary study (ie, a previously conducted Pfizer study using the final formulation and dose of bivalent rLP2086).

Booster Stage

- To describe the immune response as measured by hSBA titers to 4 primary test strains 1 month after the last dose (second or third dose) of bivalent rLP2086 in the primary study, before the booster vaccination, and 1 month, 12 months, and 26 months after a single booster dose of bivalent rLP2086.

2.1.2. Primary Safety Objective (Booster Stage)

- To evaluate the safety profile of bivalent rLP2086 as measured by the incidence of local reactions, systemic events, AEs, SAEs, newly diagnosed chronic medical conditions (NDCMCs), medically attended events, and immediate AEs following a booster vaccination of bivalent rLP2086.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

- CCI [redacted]

CCI [redacted]

- CCI [redacted]

[redacted]

[redacted]

2.2. Endpoints

The 4 primary test strains for hSBA testing are CCI [redacted] (A22 variant), CCI [redacted] (A56), CCI [redacted] (B24), and CCI [redacted] (B44). The lower limit of quantitation (LLOQ) for PMB80 (A22) is an hSBA titer equal to 1:16. The LLOQ for the other 3 primary test strains is an hSBA titer equal to 1:8.

hSBA assays using the 4 primary test strains will be conducted using sera obtained at Visits 1 to 6 from all subjects entered into stage 1, including subjects who did not receive bivalent rLP2086 in the primary study (B1971015 Group 2).

2.2.1. Primary Endpoints

Stage 1

- Proportion of subjects with hSBA titers ≥ LLOQ for each of the 4 primary strains at each blood draw visit in Stage 1 (Visits 1-6).

Booster Stage

- Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary strains at 1 month following the last vaccination received in the primary study, before the booster vaccination (Visit 6), and 1 month, 12 months, and 26 months (Visits 8, 10, and 11) following booster vaccination.

2.2.2. Primary Safety Endpoints (Booster Stage)

- Percentages of subjects reporting local reactions via the electronic diary (e-diary) by type (pain at the injection site, redness, and swelling) and by severity after a booster vaccination of bivalent rLP2086.

- Percentages of subjects reporting systemic events via the e-diary by type (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain) and by severity after a booster vaccination of bivalent rLP2086.

- Percentage of subjects reporting the use of antipyretic medication via the e-diary after a booster vaccination of bivalent rLP2086.

- Percentages of subjects with at least 1 AE occurring during the following time periods:

  - From Visit 7 to Visit 8

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

  - From Visit 7 to Visit 8

  - From Visit 8 to Visit 9

  - From Visit 7 to Visit 9

- Percentages of subjects with at least 1 NDCMC occurring during the following time periods:

  - From the 6-month safety telephone call in the primary study to Visit 6 (Stage 1)

  - From Visit 7 to Visit 8

  - From Visit 8 to Visit 10

  - From Visit 7 to Visit 10

  - From Visit 8 to Visit 11 (only subjects proceeding to Visit 11)

  - From Visit 7 to Visit 11 (only subjects proceeding to Visit 11)

- Percentages of subjects with at least 1 medically attended event occurring during the following time periods:

  - From Visit 7 to Visit 8

  - From Visit 8 to Visit 9

- From Visit 7 to Visit 9

- Percentage of subjects reporting at least 1 immediate AE after receiving the booster dose of bivalent rLP2086.

- Number of days subjects miss school or work because of AEs from Visit 7 through Visit 9.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

- CCI [redacted]

3. STUDY DESIGN

3.1. Description

Stage 1 of the study (Visits 1-6) is designed to provide follow-up information on Pfizer Studies B1971010, B1971012, and B1971015 (see Table 4), which used the final formulation and dose of bivalent rLP2086. For the purpose of this study, these 3 studies are referred to as the primary studies. All subjects enrolled in Study B1971033 were originally enrolled in one of these studies. In Stage 1, subjects will attend up to 6 study visits for collection of a 20-mL blood sample at each visit (see Table 5).

The booster stage of the study (Visits 7 to 11) is optional for eligible subjects at selected sites. Subjects who wish to participate in the booster stage must have completed Stage 1 and received all scheduled doses of bivalent rLP2086 in the primary study. Subjects will be required to sign a consent form to enter and participate in the booster stage for Visits 7 to 10. Eligible subjects at selected sites will be asked to sign another consent form prior to participating in Visit 11 for a blood draw at 26 months after the booster vaccination.

For consenting booster stage subjects, a booster dose of 120 µg of bivalent rLP2086 will be administered at Visit 7 and blood samples (20 mL per visit) will be collected for immunogenicity analysis 1 month, 12 months, and 26 months after the booster vaccination (Visits 8, 10, and 11) (see Table 5).

Table 5. Study Design Overview

	STAGE 1						BOOSTER STAGE				
Visit purpose	Blood draw	Blood draw	Blood draw	Blood draw	Blood draw	Blood draw	Booster vaccination	Blood draw	6-Month telephone contact	Blood draw	Blood draw
Visit number	1	2	3	4	5	6	7	8	9	10	11
Approximate month	6	12	18	24	36	48	48	1 Month after booster	6 Months after booster	12 Months after booster	26 Months after booster
Vaccination							Bivalent rLP2086				
Blood draw	20 mL	20 mL	20 mL	20 mL	20 mL	20 mL		20 mL		20 mL	20 mL

3.2. Approximate Duration of Subject Participation

The duration of subject participation will be approximately 3.5 years for Stage 1 of the study, an additional 1 year for those subjects who enroll in the booster stage for Visits 7 to 10 and an additional approximately 1 year for subjects participating in Visit 11. The total duration for subjects participating in both Stage 1 and the booster stage will be approximately 5.5 years.

3.3. Approximate Duration of the Study

Study duration will be approximately 6 years.

3.4. Approximate Number of Subjects

It is anticipated that up to approximately 800 subjects will participate in this study.

The booster stage of the study (Visits 7 to 11) is optional for eligible subjects at selected sites, so the number may be less than 800 for Visits 7 to 10. It is estimated that up to 200 of these subjects will continue to Visit 11.

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.

For the purposes of subject selection into Stage 1, the original planned schedule is as follows:

- If the subject's vaccine assignment is known at the time of subject enrollment in Study B1971033, the bivalent rLP2086 administration schedule detailed in the initially implemented version of the primary study protocol, ±15 days for the third dose of bivalent rLP2086, applies.

- If the subject's vaccine assignment is blinded at the time of enrollment in Study B1971033, the investigational product administration schedule detailed in the initially implemented version of the primary study protocol, ±15 days for the third injection, applies.

Subjects should preferably start the study with Visit 1 but may enter at Visit 2 where circumstances necessitate a measure of flexibility.

Subjects wishing to participate in the booster stage of the study must have completed Stage 1. Only subjects who received bivalent rLP2086 in a primary study on either a 0-, 2-, and 6-month or a 0- and 6-month schedule will be eligible to continue to Visit 11.

4.1. Inclusion Criteria

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

The inclusion criteria listed for Stage 1 are required for enrollment into Stage 1 of the study. The criteria listed for the booster stage are required, in addition to Stage 1 inclusion criteria, in order to be eligible to continue into the booster stage of the study.

4.1.1. Stage 1

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

2. Subjects who are willing and able to comply with scheduled visits, laboratory tests, and other study procedures.

3. Subjects who completed a primary study and received all the scheduled injections within the originally planned schedule, either with bivalent rLP2086 (either 2 or 3 doses) or with investigational product in cases where subject vaccine assignment is blinded at the time of consent for Study B1971033.

4. Subjects who completed the blood draw following the last vaccination and subjects who completed the 6-month follow-up telephone call in the primary study.

4.1.2. Booster Stage

4.1.2.1. Booster Stage Visits 7 to 10

1. Evidence of a personally signed and dated ICD indicating that the subject or subject's parent(s)/legal guardian has been informed of all pertinent aspects for Visits 7 to 10 of the booster stage of the study.

2. Subject continues to meet all Stage 1 inclusion and none of the Stage 1 exclusion criteria.

3. Subject is confirmed as having received bivalent rLP2086 in the primary vaccination study.

4. Subject has completed B1971033 Stage 1 and completed the Visit 6 blood draw.

5. Subject is available for the entire period of the booster stage and the subject or subject's parent(s)/legal guardian can be reached by telephone.

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

7. Male and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception through Visit 10 of the booster stage. 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 on the day of the booster dose.

4.1.2.2. Booster Stage Visit 11

1. For subject participating in Visit 11, evidence of a personally signed and dated ICD indicating that the subject or subject's parent(s)/legal guardian has been informed of all pertinent aspects of Visit 11.

2. Subject continues to meet all Stage 1 inclusion and none of the Stage 1 exclusion criteria.

3. Subject must have received 2 or 3 doses of bivalent rLP2086 in the primary study on a 0-, 2-, and 6-month or a 0- and 6-month schedule.

4. Subject must have completed booster vaccination at Visit 7.

4.2. Exclusion Criteria

The exclusion criteria listed for Stage 1 must not be met for enrollment in Stage 1 of the study. In order to be eligible for enrollment into the booster stage of the study, the exclusion criteria listed for the booster stage must not be met, in addition to not meeting any of the exclusion criteria for Stage 1.

Criteria are listed for Stage 1 and the booster stage of the study:

4.2.1. Stage 1

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

2. With the exception of the primary study of bivalent rLP2086, participation in other studies within the 1-month (30-day) period before study Visit 1 and/or during study participation. Participation in purely observational studies is permitted.

3. Severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation 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.

4. History of culture-proven disease caused by *N meningitidis* or *Neisseria gonorrhoeae*.

5. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate blood draw.

6. Receipt of any blood products, including gamma globulin, in the period from 6 months before any study visit.

7. Vaccination with any licensed or experimental meningococcal serogroup B vaccine since being enrolled in the primary Pfizer-sponsored MnB study (other than study vaccines permitted in the primary study).

8. Subjects who were not compliant with primary study eligibility criteria while enrolled in the primary study.

4.2.2. Booster Stage

1. Subjects who are scheduled to receive 1 or more doses of a human papillomavirus (HPV) vaccine as part of a 3-dose series during the 28 days after the booster vaccination.

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

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

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

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

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

7. Current chronic use of systemic antibiotics.

8. Current participation in another investigational study. Participation in purely observational studies is acceptable.

9. Received any investigational vaccines, drugs, or devices within 28 days before administration of the booster vaccination.

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

11. 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 through Visit 10 of the study.

4.3. Criteria for Temporarily Delaying Vaccine Administration during the Booster Stage

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:

- Current febrile illness (temperature ≥38.0°C [100.4°F]) or other acute illness within 48 hours before study vaccine administration.

- Subject has received a nonlive vaccine (or intramuscular/sublingual allergen immunotherapy) within the previous 14 days or live vaccine within the previous 28 days.

- Subject has received a vaccine containing all or any individual antigens included in MCV4, tetanus, diphtheria, and acellular pertussis (Tdap), or HPV vaccines within the previous 28 days. See Section 5.8.

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

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

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:

- Subject has received a dose of systemic antibiotics less than 5 days before blood collection.

4.5. Lifestyle Guidelines

The following guidelines are relevant only to subjects who participate in the booster stage.

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 through Visit 10 of the study (Month 12 after booster vaccination). Visit 11 (26 months after booster vaccination) is being added to the booster stage of this protocol amendment after subjects have completed Visit 10. Therefore, the contraception requirements do not apply to Visit 11.

The investigator or his/her designee, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below), 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, at each study visit, 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 will instruct the subject to call immediately if the selected birth control 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 the following:

- Established use of oral, injected, or implanted hormonal methods of contraception is 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.

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

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

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

- 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, subjects 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 directly and if a subject calls that number, he or she will be directed back to the investigational site.

5. INVESTIGATIONAL PRODUCT

Subjects participating in the booster stage will receive 1 dose of bivalent rLP2086 at Visit 7.

Standard vaccination practices should 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.

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 5.6.

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 responsible person at Pfizer as detailed in the SRM and follow the instructions therein.

5.1. Allocation to Investigational Product

At enrollment into Stage 1 of the study, the site personnel registered the subjects into the study via the use of an interactive voice response system (IVRS) or interactive Web-based response system (IWRS). The purpose was to allocate a subject number and track subject visits.

At enrollment in the booster stage, allocation of open-label vaccine kits to subjects will proceed through the use of an IVRS, an IWRS, or an equivalent system that is accessible 24 hours a day, 365 days a year. The kit number should be obtained from the IVRS prior to vaccination. The site personnel (study coordinator or specified designee) will be required to enter or select information that will include the user identification and password, the project and protocol number, the investigator site number, the fax number, the subject number, and the date of birth of the subject. The site personnel will then be provided with a subject number and kit number.

Subjects who participate in the booster stage will retain their Stage 1 subject number and investigational product administration details (ie, date of administration, kit number, volume, route and site of administration) will be recorded on the CRF. Once subject numbers and kit numbers have been assigned, they cannot be reassigned. The IVRS, IWRS, or equivalent system will provide confirmation of the subject number and kit number assignment to the site personnel. Site personnel will retain the confirmation reports. Specific instructions for use of the IVRS, IWRS, or equivalent system will be provided under separate cover.

5.2. Compliance

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

5.3. Investigational Product Supplies

5.3.1. Dosage Form and Packaging

The following is defined as the investigational product and will be supplied by the sponsor.

Bivalent rLP2086 is a sterile suspension composed of 2 recombinant lipidated fHBP variants from MnB, 1 from fHBP subfamily A and 1 from subfamily B (A05 and B01, respectively). The proteins are individually produced in *E coli*. Production strains are grown in defined fermentation growth media to a specific density. The recombinant proteins are extracted from the production strains and purified through a series of column chromatography steps. Polysorbate 80 (PS80) is added to the vaccine substances and is present in the final vaccine product.

CCI [redacted]

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

5.3.2. Preparation and Dispensing

Preparation and dosing information will be provided in the SRM. Investigational product should be prepared and dispensed by an appropriately qualified and 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.

5.4. 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.

Investigational product administration details (ie, date of administration, volume, route, and site of administration) will be recorded on the CRF. Investigational product accountability will be documented as per Section 5.6.

Bivalent rLP2086 booster vaccination will be administered intramuscularly at approximately 48 months (Visit 7) following the last dose of bivalent rLP2086 received in the primary study by injecting 0.5 mL into the deltoid muscle.

5.5. Investigational Product Storage

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. For storage, the preferred orientation of the vaccine is horizontal.

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 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.

The refrigerator must be locked and secure and have limited access. It is the responsibility of the investigator(s) (or designee) to record daily refrigerator temperature readings (working days only), to maintain a daily temperature log for the refrigerator, and to alert the sponsor of any deviations. Investigational product must be stored as indicated.

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 information the site should report for each excursion will be provided to the site.

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

In case of temperature deviations, the investigational products cannot be used and should be quarantined until the sponsor provides documentation of permission to use the investigational products. Guidance on temperature monitoring and procedures for the review of temperature deviations will be provided in the SRM.

Storage conditions stated in the bivalent rLP2086 IB will be superseded by the storage conditions stated in the labeling.

Investigators and site staff are required to check refrigerator temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products. Any temperature excursions must be reported immediately.

5.6. Investigational Product Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the vaccine supplies. Investigational product accountability applies to such products when they are required by the protocol and supplied (shipped) by the sponsor.

Unused investigational product must 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).

5.7. Concomitant Treatment(s)

Throughout the study, nonstudy vaccinations occurring from the final blood draw in the primary study until Visit 11 will be recorded in the CRF.

In the booster stage, any allergen immunotherapy occurring from Visit 7 until Visit 11 will also be recorded in the CRF.

In the booster stage, the name, start and stop dates, and route of administration for concomitant medications (prescription and nonprescription) used to treat an AE (excluding events recorded only in the e-diary) from Visit 7 through Visit 11 will be recorded in the CRF.

5.8. Prohibited During the Study

- Receipt of any blood products, including gamma globulin, in the period from 6 months before any study visit.

- Vaccines containing all or any individual antigens included in MCV4, Tdap, and HPV vaccines are not permitted 28 days before or after study vaccination.

- Other nonlive or live nonstudy vaccines are not permitted within 14 and 28 days, respectively, before or after study vaccination.

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

- Systemic (oral, intravenous, or intramuscular) corticosteroid therapy within 28 days before or after study vaccination.

5.9. 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 vaccines) as specified above.

- Nonstudy vaccines (other than vaccines containing all or any individual antigens included in MCV4, Tdap, and HPV vaccines) that are part of recommended immunization schedules are allowed any time during the study but should not be administered within 14 days (for nonlive vaccines) and 28 days (for live vaccines) of study vaccine administration.

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

- Antipyretics and other pain medications to prevent symptoms associated with investigational product are not encouraged.

- Local anesthetic may be applied before blood draw.

- Topical antibiotics are permitted.

- Topical and inhaled corticosteroids are permitted.

5.10. Prior Treatment

5.10.1. Prohibited Prior Treatments

The following are prohibited:

- Receipt of any blood products, including gamma globulin, in the period from 6 months before any study visit.

6. STUDY PROCEDURES

If the subject's primary study vaccine assignment is known at the time of consent for Study B1971033, the visits in Study B1971033 should be scheduled relative to the last dose of bivalent rLP2086 in the primary study. If the subject's primary study vaccine assignment is blinded at the time of consent for Study B1971033, the visits in Study B1971033 should be scheduled relative to the last injection of investigational product in the primary study.

Subjects should preferably start the study with Visit 1 but may enter at Visit 2 where circumstances necessitate a measure of flexibility.

6.1. Informed Consent Process

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, or publications, or in any other disclosures, except where required by law. For further information, please refer to the Subject Information and Consent section (Section 13.3).

6.2. Stage 1

6.2.1. Study Visit 1 – Serology Follow-up (6 Months [150-240 Days] After the Last Dose of Bivalent rLP2086 in the Primary Study, or After the Last Injection of Investigational Product in the Primary Study if Vaccine Assignment Is Blinded)

Before any study procedure takes place, a signed and dated ICD has to be collected for this study. The following information will be collected and the following assessments will be made at Visit 1:

- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).
- Confirm that the subject meets the inclusion criteria and none of the exclusion criteria.
- Draw a blood sample of approximately 20 mL as described in the SRM and the schedule of activities (Table 1).
- Record AEs as described in Section 8 and the AE reporting schedule (Table 3).
    - Record NDCMCs identified from the 6-month telephone call in the primary study.
    - Record RRIs and nonserious AEs occurring during the 48-hour period after the blood draw.
- Record any nonstudy vaccination received since the final blood draw in the primary study.
- Complete the source documents.
- Complete the CRF.

6.2.2. Study Visit 2 – Serology Follow-up (12 Months [330-390 Days] After the Last Dose of Bivalent rLP2086 in the Primary Study, or After the Last Injection of Investigational Product in the Primary Study if Vaccine Assignment Is Blinded)

The following information will be collected and the following assessments will be made at Visit 2:

- If the subject has been enrolled at Visit 2, obtain written informed consent before performing study-specific procedures.
- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).
- Ensure the subject continues to be eligible for the study.
- Draw a blood sample of approximately 20 mL as described in the SRM and the schedule of activities (Table 1).
- Record AEs as described in Section 8 and the AE reporting schedule (Table 3).
    - Inquire whether the subject had any NDCMCs since the last visit.
    - Record RRIs and nonserious AEs occurring during the 48-hour period after the blood draw.
- Record any nonstudy vaccination received since the previous visit or since the final blood draw in the primary study for subjects enrolled at Visit 2.
- Complete the source documents.
- Complete the CRF.

6.2.3. Study Visit 3 – Serology Follow-up (18 Months [510-570 Days] After the Last Dose of Bivalent rLP2086 in the Primary Study, or After the Last Injection of Investigational Product in the Primary Study if Vaccine Assignment Is Blinded)

The following information will be collected and the following assessments will be made at Visit 3:

- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).
- Ensure the subject continues to be eligible for the study.
- Draw a blood sample of approximately 20 mL as described in the SRM and the schedule of activities (Table 1).
- Record AEs as described in Section 8 and the AE reporting schedule (Table 3).

  - Inquire whether the subject had any NDCMCs since the last visit.
  - Record RRIs and nonserious AEs occurring during the 48-hour period after the blood draw.
- Record any nonstudy vaccination received since the previous visit.
- Complete the source documents.
- Complete the CRF.

6.2.4. Study Visit 4 – Serology Follow-up (24 Months [676-764 Days] After the Last Dose of Bivalent rLP2086 in the Primary Study, or After the Last Injection of Investigational Product in the Primary Study if Vaccine Assignment Is Blinded)

The following information will be collected and the following assessments will be made at Visit 4:

- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).
- Ensure the subject continues to be eligible for the study.
- Draw a blood sample of approximately 20 mL as described in the SRM and the schedule of activities (Table 1).
- Record AEs as described in Section 8 and the AE reporting schedule (Table 3).
  - Inquire whether the subject had any NDCMCs since the last visit.
  - Record RRIs and nonserious AEs occurring during the 48-hour period after the blood draw.
- Record any nonstudy vaccination received since the previous visit.
- Complete the source documents.
- Complete the CRF.

6.2.5. Study Visit 5 – Serology Follow-up (36 Months [1036-1124 Days] After the Last Dose of Bivalent rLP2086 in the Primary Study, or After the Last Injection of Investigational Product in the Primary Study if Vaccine Assignment Is Blinded)

The following information will be collected and the following assessments will be made at Visit 5:

- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).

- Ensure the subject continues to be eligible for the study.
- Draw a blood sample of approximately 20 mL as described in the SRM and the schedule of activities (Table 1).
- Record AEs as described in Section 8 and the AE reporting schedule (Table 3).
    - Inquire whether the subject had any NDCMCs since the last visit.
    - Record RRIs and nonserious AEs occurring during the 48-hour period after the blood draw.
- Record any nonstudy vaccination received since the previous visit.
- Complete the source documents.
- Complete the CRF.

6.2.6. Study Visit 6 – Serology Follow-up (48 Months [1396-1484 Days] After the Last Dose of Bivalent rLP2086 in the Primary Study, or After the Last Injection of Investigational Product in the Primary Study if Vaccine Assignment Is Blinded)

The following information will be collected and the following assessments will be made at Visit 6:

- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).
- Ensure the subject continues to be eligible for the study.
- Draw a blood sample of approximately 20 mL as described in the SRM and the schedule of activities (Table 1).
- Record AEs as described in Section 8 and the AE reporting schedule (Table 3).
    - Inquire whether the subject had any NDCMCs since the last visit.
    - Record RRIs and nonserious AEs occurring during the 48-hour period after the blood draw.
- Record any nonstudy vaccination since the previous visit.
- Complete the source documents.
- Complete the CRF.

6.3. Booster Stage

6.3.1. Visit 7, Booster Vaccination of Bivalent rLP2086 (48 Months [1396-1484 Days] After the Last Dose of Bivalent rLP2086 in the Primary Study, and within 42 Days After Visit 6)

Visit 6 procedures must precede Visit 7 procedures, even if conducted on the same day.

For subjects who are not completing Visit 6 on the same day as Visit 7:

- Collection of vital sign measurements and recording of nonstudy vaccinations should be repeated on the day of Visit 7 as indicated below and in the schedule of activities.

- Visit 7 procedures should be conducted within 42 days after Visit 6.

In the case of temporary delay of vaccination, the procedures and assessments will be reperformed or reconfirmed on the day of vaccination.

- Obtain written informed consent, specific for participation in Visits 7 to 10 of the booster stage, before performing the booster stage-specific procedures. The date of informed consent will be recorded in the CRF.

- Complete the study visit/AE checklist to:

    - Inquire whether the subject had any NDCMCs since the last visit.

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

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

- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.

- Perform a physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, 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. A negative pregnancy test result is required before the subject may receive the investigational product.

- On the day of vaccination, collect vital sign measurements, before administration of vaccine, including blood pressure, pulse rate, and temperature (oral).

- On the day of vaccination, record nonstudy vaccinations and allergen immunotherapy as described in Section 5.7.

- Ensure that all of the inclusion criteria for Stage 1 and the booster stage, none of the exclusion criteria for Stage 1 and the booster stage, and none of the temporary delay criteria are met.

- If a subject is eligible for the booster stage of the study, allocate a vaccine kit to the subject using an IVRS, IWRS, or equivalent system.

- Administer a single 0.5-mL intramuscular injection of bivalent rLP2086 into the upper deltoid muscle. 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 (see Section 7.2).

- Record AEs as described in the Safety section (Section 7.2), the Adverse Event Reporting section (Section 8), and the AE reporting schedule (Table 3). 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 Section 5.7.

- Issue an e-diary to the subject or the subject's parent(s)/legal guardian and provide instruction on its completion.

- Ask the subject to complete the e-diary from Day 1 to Day 7 after vaccination.

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

    - Instruct the subject or subject's 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 7.4.

  - Instruct the subject or subject's parent(s)/legal guardian to contact the investigator immediately if the subject experiences a severe redness or swelling (>20 caliper units) at the injection site, a fever ≥39°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 6.4).

  - If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 7.5.1), the subject or subject's 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.

    - Instruct the subject or subject's 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 ≤21 caliper units.

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

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

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

- Complete the source documents.

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

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

6.3.2. Visit 8 (28 to 42 Days after Visit 7), Postvaccination Blood Draw 1

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 4) and none of the temporary delay of blood draw criteria (Section 4.4).

- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).

- 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 NDCMCs since the last visit as described in Section 8 and the AE reporting schedule (Table 3).
  - Inquire whether the subject had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. 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 Safety section (Section 7.2), the Adverse Event Reporting section (Section 8), and the AE reporting schedule (Table 3).
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.7).
- Record nonstudy vaccinations and allergen immunotherapy as described in the Concomitant Treatment(s) section (Section 5.7).
- Collect a blood sample (approximately 20 mL).
- Provide the subject with a memory aid. Instruct the subject to use the memory aid between Visits 8 and 10 to remind him or her to review with study site personnel any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility. Please refer to the SRM for additional details. Schedule an appointment for the next visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

6.3.3. Visit 9 (168 to 196 Days after Visit 7), Safety Telephone Contact

Telephone contact should occur approximately 6 months after the booster vaccination; this contact should be attempted for all subjects who have received booster vaccination, including subjects who withdraw from the booster stage prior to Visit 9, unless they have withdrawn consent.

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 4) and none of the temporary delay of blood draw criteria (Section 4.4).

- Complete the study visit/telephone contact checklist to:
  - Inquire whether the subject had any NDCMCs since the last visit as described in Section 8 and the AE reporting schedule (Table 3).
  - Inquire about SAEs, NDCMCs, 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 8.7.
- Record AEs as described in the Safety section (Section 7.2) the Adverse Event Reporting section (Section 8), and the AE reporting schedule (Table 3).
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.7).
- Record nonstudy vaccinations and allergen immunotherapy as described in the Concomitant Treatment(s) section (Section 5.7).
- Complete the source documents.
- Complete the CRFs.

6.3.4. Visit 10 (12 Months [330-390 Days] after Visit 7), Postvaccination Blood Draw 2

- Ensure that the subject continues to be eligible for the study (Section 4) and meets none of the temporary delay of blood draw criteria (Section 4.4).
- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).
- Record AEs as described in the Safety section (Section 7.2), the Adverse Event Reporting section (Section 8), and the AE reporting schedule (Table 3).
- Record NDCMCs as described in the Safety section (Section 7.2), the Adverse Event Reporting section (Section 8), and the AE reporting schedule (Table 3).
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.

- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.7).
- Record nonstudy vaccinations and allergen immunotherapy as described in the concomitant treatment section (Section 5.7).
- Collect a blood sample (approximately 20 mL).
- Complete the source documents.
- Complete the CRFs.
- Remind the subject or subject's parent(s)/legal guardian to report any AEs or RRIs within 48 hours following Visit 10.

6.3.5. Visit 11 (26 Months [750-810 Days] after Visit 7), Postvaccination Blood Draw 3

- Obtain written informed consent specific for participation in Visit 11 of the booster stage before performing any Visit 11 procedures. The informed consent specific to Visit 11 may be obtained at Visit 11 or any earlier visit. The date of informed consent will be recorded in the CRF.
- Ensure that subjects participating in Visit 11 have met Visit 11 eligibility criteria (Section 4) and meet none of the temporary delay of blood draw criteria (Section 4.4).
- Collect vital sign measurements, including blood pressure, pulse rate, and temperature (oral).
- Record AEs as described in the Safety section (Section 7.2), the Adverse Event Reporting section (Section 8), and the AE reporting schedule (Table 3).
- Record NDCMCs as described in the Safety section (Section 7.2), the Adverse Event Reporting section (Section 8), and the AE reporting schedule (Table 3).
- 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 8.7.
- Complete the study visit/telephone contact checklist.
- Record concomitant medications used to treat AEs as described in the Concomitant Treatment(s) section (Section 5.7).
- Record nonstudy vaccinations and allergen immunotherapy as described in the Concomitant Treatment(s) section (Section 5.7).

- Collect a blood sample (approximately 20 mL).
- Complete the source documents.
- Complete the CRFs.
- Remind the subject or subject's parent(s)/legal guardian to report any AEs or RRIs within 48 hours following Visit 11.

6.4. Unscheduled Visits

If the subject or parent(s)/legal guardian reports a severe redness or swelling at the injection site (>20 caliper units), a temperature ≥39°C (102.1°F), or a severe headache in the 7 days after vaccination, a study site visit should be arranged as soon as possible to assess the extent of the event. The subject contact will be documented in the CRF.

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

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

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

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

6.5. Subject Withdrawal

The investigator and/or sponsor may withdraw a subject from the study if deemed appropriate at any time. Eligibility criteria as listed under Inclusion Criteria (refer to Section 4.1) and Exclusion Criteria (refer to Section 4.2) should be taken into consideration when determining if a subject must be withdrawn from the study.

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

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

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

When a subject discontinues or is withdrawn from the study, the investigator will notify the sponsor. When possible, the investigator will perform the procedures indicated for the next visit. If the subject has received the booster vaccination, but withdraws prior to Visit 9, provide the subject with a memory aid and complete the activities detailed for Visit 9.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety 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 for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

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

7. ASSESSMENTS

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

7.1. Immunogenicity

To facilitate immunogenicity analyses, subjects will have approximately 20 mL of blood collected at Visits 1 through 6, 8, 10, and 11. Sample collection, storage, and shipping information can be found in the SRM.

All serum samples should be frozen 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°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.

7.1.1. Bivalent rLP2086 Serum Bactericidal Assay - Primary Test Strains

For assessment of the immune response to bivalent rLP2086, functional antibodies will be analyzed in hSBAs with MnB strains. The hSBA measures antibodies in human sera that initiate 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 sera obtained from all subjects at all study visits. The MnB hSBAs are validated before any testing is performed.

Sera obtained 1 month following the last vaccination with bivalent rLP2086 in the primary study will be reassayed concurrently with sera obtained during B1971033 study visits.

Sera in subjects who did not receive bivalent rLP2086 in study B1971015 (Group 2) will also be assayed in amendment 3.

Pfizer plans to complete all MnB hSBA testing at its Pearl River Laboratories.

7.1.2. Bivalent rLP2086 Serum Bactericidal Assay - Secondary Test Strains

Ten (10) secondary test strains may be used to perform hSBA testing in sera obtained from subjects.

Sera obtained from subjects 1 month following the last vaccination with bivalent rLP2086 in the primary study and prior to booster vaccination with bivalent rLP2086 (Visit 6), as well as 1 month, 12 months, and 26 months after the booster vaccination (Visits 8, 10, and 11), may be used for hSBA testing on the 10 secondary test strains.

hSBA tests are qualified for the 10 secondary test strains.

7.2. Safety

Any subject who receives 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 (Table 1 and Table 2):

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

A medical history will be obtained and a review of NDCMCs as well as a physical examination will be performed on all subjects at Visit 7 to establish a baseline. When taking the medical history and performing the physical examination, particular care must be taken to note any neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Significant medical history and observations from the physical examination will be documented in the CRF. In addition, a urine pregnancy test will be performed on all female subjects.

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

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

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

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.

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

AEs (serious and nonserious), NDCMCs, and visits to other medical facilities will be assessed at study visits as specified in the AE reporting schedule (Table 3) and reported as defined in Section 8. AE-related hospitalizations, visits to other medical facilities, medication use, and days of school or work missed will be collected and recorded in the AE CRF. Hospitalizations and visits to medical facilities not associated with an AE, such as elective hospitalizations, healthcare visits for preventive care, or routine physical examinations, will not be collected. Non–AE-related concomitant medications and days of school or work missed not associated with an AE will not be collected. A study visit/telephone contact AE checklist will be used as a guide, completed at each scheduled study visit/telephone contact, and included in the source documentation. Please refer to the SRM for details.

Subjects will be given a memory aid at Visit 8. The memory aid will be used to remind subjects to review with study site personnel any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility. Subjects may use the memory aid as needed during the safety telephone call at Visit 9 to prompt recall of events. This 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 visit or telephone call will be included in the source documents and entered into the CRF.

In addition, AEs and SAEs will be collected as defined in AE reporting schedule (Table 3). For the purposes of this study, these are referred to as unsolicited AEs and will be recorded and reported as described in Section 8.

7.3. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of the booster dose. A negative pregnancy test result is required before the subject may receive investigational product.

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. Electronic Diary

The subject or 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 of antipyretic medication for 7 days after 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 Enrolled in Preventive Vaccine Clinical Trials.[25] 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. End dates of local reactions, systemic events, and use of antipyretic medication (associated with vaccine administration) that were ongoing on the last day the e-diary was completed 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) 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.

7.5. Local Reactions

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

7.5.1. Injection Site Redness and Swelling

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

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

Table 6. Grading of Redness and Swelling

None	0 to 2.0 cm (0 to 4 caliper units)
Mild	2.5 to 5.0 cm (5 to 10 caliper units)
Moderate	5.5 to 10.0 cm (11 to 20 caliper units)
Severe	>10.0 cm (>20 caliper units)

7.5.2. Injection Site Pain

The subject or, where relevant, 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 7. 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.

7.6. Systemic Events

7.6.1. Temperature

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

Temperature will be measured and recorded to 1 decimal place and presented for the following ranges:

Table 8. Temperature Categories

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

7.6.2. Use of Antipyretic Medication

The use of antipyretic medication will be recorded in the e-diary daily during the active safety observation period (Day 1 to Day 7) immediately following the booster vaccination of bivalent rLP2086. The use of antipyretics to prevent fever or pain is not encouraged.

7.6.3. Other Systemic Events

The e-diary will be used to record the presence of other systemic events, including vomiting, diarrhea, chills, 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 9. Grading of Other Systemic Events

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

Abbreviation: IV=intravenous.

7.7. Risks and Benefits

Potential risks associated with participation in Stage 1 of this study are limited to those associated with drawing blood (bruising, mild bleeding, momentary discomfort, fainting, and, rarely, infection), as well as any potential long-term side effects (later-emerging events) that may be related to bivalent rLP2086, administered previously in the primary studies. Refer to the most recent version of the bivalent rLP2086 IB for a summary of the known risks and potential benefits of the vaccine to human subjects after primary and booster vaccinations.

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.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent for the booster stage, which is obtained prior to the subject's participation in the booster stage of the study, ie, prior to undergoing any booster stage study-related procedure and/or receiving investigational product, through and including Visit 9, which is to occur 6 months after 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 the study vaccine are to be reported to the sponsor.

NDCMCs identified from the time of the 6-month telephone call in the primary study through Visit 11 must be recorded in the CRF.

Particular care should be taken at all visits during the booster stage to note and report any neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. The investigator is required to assess whether the AE may be related to the subject's participation in the study.

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 subject or, where relevant, parent(s)/legal guardian on the need to report AEs and SAEs during this time period.

SAEs with an onset during Stage 1 (ie, prior to the booster stage) will be reported under the primary study protocol (ie, the protocol the subject was enrolled in PRIOR to being enrolled in B1971033). SAEs with an onset during the booster stage will be reported under Study B1971033.

8.2.1. Stage 1

In addition to items noted in Section 8.2, in Stage 1, investigators are reminded of the obligation to report SAEs occurring during Stage 1 of B1971033 that an investigator may become aware of by reporting the event back to the primary study by following the SAE reporting procedures as specified in the protocol for the primary study. At a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study vaccine are to be reported to the sponsor. AEs, including SAEs and suspected unexpected serious adverse reactions (SUSARs), reported to the primary study from which the subjects proceeded into this follow-on study (B971033, Stage 1) will be reported to regulatory authorities in accordance with applicable local regulations.

At Visits 1-6 (Stage 1), the site will inquire about any RRIs (Section 8.6) and nonserious AEs occurring during the 48-hour period after blood draw. These events must be recorded in the CRF and the events must be followed.

8.2.2. Booster Stage

In addition to the reporting requirements noted in Section 8.2, in the booster stage, all nonserious AEs occurring from the time the subject provides informed consent for the booster stage to Visit 8, and then from Visit 8 until 48 hours after the Visit 8 blood draw and from Visit 10 and Visit 11 until 48 hours after each blood draw, will be reported and recorded.

SAEs and nonserious AEs resulting in evaluation at a medical facility (medically attended events) are reportable from Visits 7 through 9.

Any RRIs within 48 hours following Visits 10 and 11 will also be reported.

8.3. Definition of an Adverse Event

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

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;

- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

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

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

8.4. 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, but not limited to:

- 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;
- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;

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

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

8.5. Abnormal Test Findings

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

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

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

8.6. Research-Related Injury

Should a subject in the first 48 hours following blood draw, in the investigator's opinion, suffer a medically important RRI caused by his or her participation in the study, 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.

8.7. 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 on Serious Adverse Event Reporting Requirements).

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 ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

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

Concurrent with:

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

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

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

8.8. Hospitalization

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

Table 10. Severity Assessment Grade

GRADE	If required on the AE 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:	
1	MILD	Does not interfere with subject's usual function.
2	MODERATE	Interferes to some extent with subject's usual function.

Table 10. Severity Assessment Grade

3	SEVERE	Interferes significantly with subject's usual function.

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

8.10. 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 SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.11. Exposure during Pregnancy

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

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

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

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

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

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

Additional information regarding the EDP 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 the drug safety unit within 24 hours of the investigator's awareness, using the SAE Report Form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE Report Form is maintained in the investigator site file.

8.13. Withdrawal Due to Adverse Events (See also the Section on 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/parent/legally acceptable representative. In addition, each study subject/parent/legally acceptable representative 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 EDP, exposure via breastfeeding, and occupational exposure cases.

For subjects enrolled in the booster stage, 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 or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

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.

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 in Section 8. 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.

8.15.4. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including SUSARs, 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

Study sample size is not based on statistical considerations. In recognition of the variability introduced with the inclusion of subject populations from various studies (such as population age, number of doses received, and concomitant vaccine usage), the study aims to enroll up to 800 subjects to allow for sufficient numbers when describing findings with regard to particular variables.

9.2. Immunogenicity Analysis

This is a descriptive study; no hypothesis testing will be performed. Therefore, an estimation approach will be utilized for immunogenicity.

The immunogenicity descriptive summaries will be presented for the overall population as well as by subgroup (eg, dose schedule, age group, administration of concomitant vaccine, region). A mixed model with repeated measures adjusted with covariates (dose schedule, age group, region, etc) will also be used to estimate the GMTs at different time points (including time points from the primary studies).

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

hSBA assays using the 4 primary test strains will be conducted using sera obtained at Visits 1 to 6 from all subjects entered into stage 1, including subjects who did not receive bivalent rLP2086 in the primary study (B1971015 Group 2). Serum samples collected at Visits 8, 10, and 11 during the booster stage will also be analyzed by hSBA against the 4 primary test strains.

9.2.1. Analysis of Primary Endpoint

The proportion of subjects in each group achieving hSBA titer ≥ LLOQ at each blood sampling time point will be computed for each of the 4 primary test strains along with 2-sided exact 95% confidence intervals (CIs).[26]

CCI

CCI

[redacted]

[redacted]

[redacted]

9.3. Immunogenicity Analysis Populations

Only subjects who were compliant with primary study eligibility criteria while enrolled in the primary study will be included in this study. Therefore, the modified intent-to-treat (mITT) population will be used for Stage 1 immunogenicity analyses. The Stage 1 mITT population will include subjects who have at least 1 valid and determinate assay result in Stage 1 of Study B1971033.

In general, the evaluable population will include all subjects who were eligible, received all investigational products, 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. A major protocol deviation is one that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. For booster stage time points (Visits 7, 8, 10, and 11), the primary immunogenicity analysis will be based on the evaluable population (for summaries including Visit 11 for the subset of subjects of the evaluable population who participated in Visit 11). Booster stage immunogenicity analyses will also be performed for the booster stage mITT population (for summaries including Visit 11 for the subset of subjects of the booster stage mITT population who participated in Visit 11), which will include subjects who received the booster vaccination and who have at least 1 valid and determinate assay result.

9.4. Analysis of Other Endpoints

The following demographic characteristics will be summarized descriptively: sex, race, ethnicity, and age at first vaccination in the primary study. The study characteristics (eg, dose schedule, age group, administration of concomitant vaccine) based on the primary study will also be summarized.

For each of the primary studies, there will be a descriptive comparison between the subjects enrolled in Study B1971033 and the remaining subjects, to assess representativeness. This comparison will include demographic characteristics as well as immune responses 1 month after the final dose of bivalent rLP2086 or injected saline, such as the percentage of subjects with titers ≥ LLOQ and GMTs to the 4 primary strains.

9.5. Safety Analysis

The safety population will be used for all safety analyses. For Stage 1 time points, the safety population will include all subjects who have at least 1 blood draw in the study. For the booster stage, the safety population will include all subjects who have received the booster vaccination and for whom safety information is available. Missing safety data will not be replaced or imputed. For summaries that include Visit 11 or after Visit 10, the subset of subjects of the safety booster population who participated in Visit 11 will be used.

The proportion of subjects reporting local reactions at the investigational product administration site and systemic events and use of antipyretic medication within the 7-day period after the booster vaccination will be descriptively summarized. Severities of local reactions and systemic events reported after vaccination will also be descriptively summarized. Two (2)-sided exact 95% CIs will be presented with the proportions.

All of the AEs and RRIs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized. A medically attended event is defined as a nonserious AE that results in an evaluation at a medical facility. An NDCMC is defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects. All summaries will show the number and percentage of subjects experiencing at least 1 event and the number of events. Two (2)-sided exact 95% CIs will also be presented for the percentages.

9.6. Analysis Timing

Because of the timing of enrollment into the primary studies, subjects will reach the booster stage of Study B1971033 over an extended period. An interim analysis will be conducted after Visit 8 (1 month after the booster vaccination) immunogenicity data for all subjects who participated in the B1971012 primary study are available. There may also be an interim analysis when the B1971012 subjects have Visit 10 (12 months after the booster vaccination) immunogenicity data available.

The information will be used for internal decision making on further development of the vaccine, and will not modify the current study. Since the study is descriptive, there will be no type I error impact for these interim analyses.

The final analysis will be conducted once Visit 11 (26 months after the booster vaccination) immunogenicity data for all enrolled subjects are available.

9.7. Data Monitoring Committee

This study will use an external data monitoring committee (EDMC). The independent statistical center (ISC) will provide the safety reports to the EDMC. 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. 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 may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the 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. BIOLOGICAL SAMPLES

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity.

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 or, where relevant, the subject's parent(s)/legal guardian may request that his or her 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.

12. DATA HANDLING AND RECORD KEEPING

12.1. Case Report Forms/Electronic Data Record

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

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

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

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

In some cases, the CRF, or part of the CRF, may also serve as 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.

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

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

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

13. ETHICS

13.1. Institutional Review Board (IRB)/Ethics Committee (EC)

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

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

13.2. 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 [CIOMS] 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.

13.3. Subject Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. 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 informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process 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 subjects, as required by local regulations, who have not yet reached the legal age of majority. 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 or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must be reconsented as adults to remain in the study. If the enrollment of "emancipated minors" is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

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

13.4. Subject Recruitment

Subject recruitment efforts are not required for this study because, as of protocol amendment 3, all subjects have been enrolled.

13.5. 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 that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

14. DEFINITION OF END OF TRIAL

14.1. End of Trial in a Member State

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

14.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as the end of the clinical phase of the study, which will be 48 hours after the last study visit (Visit 11) for the last subject (LSLV). At this time, sites will be closed out, the IRB/EC will be informed, and no further CIOMS reports will be sent.

15. 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.

16. PUBLICATION OF STUDY RESULTS

16.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

16.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational vaccine. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

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

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

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

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