A PHASE 4, OPEN-LABEL, SINGLE-ARM TRIAL TO DESCRIBE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF TRUMENBA® WHEN ADMINISTERED TO IMMUNOCOMPROMISED PARTICIPANTS ≥10 YEARS OF AGE

Study Intervention Number:	PF-05212366
Study Intervention Name:	*Neisseria meningitidis* Serogroup B Bivalent Recombinant Lipoprotein 2086 Vaccine (Trumenba)
US IND Number:	13812
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Phase:	4

Short Title: Trial to Describe the Safety, Tolerability, and Immunogenicity of Trumenba When Administered to Immunocompromised Participants ≥10 Years of Age

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
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1. PROTOCOL SUMMARY

1.1. Synopsis

Individuals with anatomic asplenia or some degree of functional asplenia (eg, sickle cell anemia) or complement deficiencies (including but not limited to deficiencies in C5-C9, properdin, factor D, or factor H) are known to be at increased risk of severe infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis*, and Hib.

This study (designed to functionally assess antibody production in asplenic and complement-deficient individuals) is a Phase 4, open-label, single-arm trial evaluating the safety, tolerability, and immunogenicity of 2 doses of Trumenba® on a 0- and 6-month schedule in immunocompromised participants ≥10 years of age. The 2-dose schedule, which is safe and well tolerated and provides protective immunity to a high proportion of healthy individuals, will be evaluated in this population. Historical data from age-matched healthy participants from the Phase 3 MnB Study B1971057, which confirmed the safety and high degree of protective immunity achieved after vaccination with Trumenba on a 2-dose, 0- and 6-month schedule, will be used as a reference for safety and immunogenicity of Trumenba in healthy adolescents and young adults when reporting the results from this study.

Objectives, Estimands, and Endpoints

The objective of this study is to describe the immunogenicity and safety of Trumenba in individuals with asplenia or complement deficiencies with reference to historical data from randomly selected age-matched healthy participants.

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To describe the immune response induced by 2 doses of Trumenba in immunocompromised participants and historical age-matched healthy participants as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein.	In immunocompromised participants or historical age-matched healthy participants separately, who are receiving 2 doses of study intervention and are in compliance with key protocol criteria (evaluable participants): • The proportion of participants with hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for each of the 4 primary MnB test strains 1 month after Vaccination 2.	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
Primary Safety:	**Primary Safety:**	**Primary Safety:**
To evaluate the safety profile of Trumenba in immunocompromised participants and historical age-matched healthy participants.	In immunocompromised participants or historical age-matched healthy participants separately, who are receiving at least 1 dose of study intervention:	• Local reactions (pain at the injection site, redness, and swelling).

Objectives	Estimands	Endpoints

	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each vaccination with Trumenba.
	• The percentage of participants with at least 1 SAE and at least 1 MAE during the following time periods:
	  • 30 Days after each vaccination.
	  • 30 Days after any vaccination.
	  • During the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).
	  • During the follow-up phase (from 1 month after Vaccination 2 through 6 months after Vaccination 2).
	  • From Vaccination 1 through 6 months after Vaccination 2).
	• The percentage of participants with at least 1 AE occurring during the following time periods:
	  • 30 Days after each vaccination.
	  • 30 Days after any vaccination.
	  • During the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).
	• The percentage of participants with at least 1 immediate AE after each vaccination.
	• The percentage of participants with at least 1 NDCMC occurring during the following time periods:
	  • During the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).
	  • During the follow-up phase (from 1 month after Vaccination 2 through 6 months after Vaccination 2).
		• Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain).
		• Use of antipyretic medication.
		• AEs.
		• SAEs.
		• MAEs.
		• Immediate AEs.
		• NDCMCs.
		• Days missing from school or work because of AEs.

Objectives	Estimands	Endpoints
	• From Vaccination 1 through 6 months after Vaccination 2. • Number of days participants missed school or work because of AEs during the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).	

Overall Design

This is a Phase 4, open-label, single-arm, multicenter trial in which up to 50 immunocompromised participants ≥10 years of age with asplenia (anatomic or functional) or complement deficiency will be enrolled and receive Trumenba on a 2-dose, 0- and 6-month schedule. All participants will be naive to any meningococcal serogroup B vaccine prior to enrollment.

Historical data from age-matched healthy participants from a pivotal Phase 3 MnB study (that has previously completed the primary analysis) will be used as a reference for the safety and immunogenicity of Trumenba. Healthy adolescents and young adults (10 to <26 years of age) from Study B1971057 will be randomly selected and details on how these participants will serve as controls are in Section 9.4.1.

For this study, immunocompromised participants are individuals at increased risk for meningococcal disease due to anatomic asplenia or functional asplenia (eg, sickle cell anemia) or complement deficiencies (including but not limited to deficiencies in C5-C9, properdin, factor H, or factor D).

Enrolled participants will be vaccinated with 2 doses of Trumenba at Months 0 and 6 (Visits 1 and 3). Blood samples (approximately 20 mL per visit) for immunogenicity analysis by hSBA (performed with 4 primary MenB test strains as detailed in Section 3) will be collected prior to Vaccination 1 and 1 month after Vaccination 2 (Visits 1 and 4). Given the immunocompromised population enrolled in this study, participants will receive an on-site follow-up visit 1 month after Vaccination 1 (Visit 2). Participants will attend 4 study visits and a telephone contact will be made at Visit 5 (6 months after the last vaccination).

Statistical Methods

This is a descriptive study; therefore, an estimation approach will be utilized to address the immunogenicity objectives. All binary immunogenicity endpoints will be presented with 2-sided exact 95% CIs. Safety endpoints will be descriptively summarized via proportions of participants with any local reactions, systemic events, AEs, MAEs, SAEs, NDCMCs, and immediate AEs and the associated 2-sided exact 95% CIs. Immunogenicity and safety will

be reported descriptively for the immunocompromised participants and historical age-matched healthy control participants.

1.2. Schema

	Vaccination 1	**Safety Follow-up Visit**	**Vaccination 2**	**Post–Vaccination 2 Blood Draw**	**Telephone Contact**
Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Approximate month	0	1	6	7	12
Vaccination	Trumenba		Trumenba		
Blood draw	20 mL			20 mL	

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed info1mation on each procedure and assessment required for compliance with the protocol.

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

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Visit Description	**Vaccination 1**	**Safety Follow-up Visit**	**Vaccination 2**	**Post-Vaccination 2 Blood Draw**	**Telephone Contact**
Approximate Month	0	**1**	**6**	7	**6 Months After Last Study Vaccination**
Visit Window	**Dayl**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days Afte1· Visit 3**	**168 to 196 Days Afte1· Visit 3**
Infonued consent	**X**				
Review eligibility criteria	**X**				
Demography	**X**				
Confinu continued eligibility3		**X**	**X**	**X**	
Medical history and physical examination	**X**				
Record previous pneumococcal and meningococcal sero1Zrouo ACWY vaccinations	**X**				
Record blood transfusions within prior 3 months	**X**				
Urine pregnancy test for all female participants	**X**		**X**		
Obtain prevaccination oral temperature	**X**		**X**		
IVRS/IWRS kit assignment	**X**		**X**		
Obtain blood sample	20mL			20mL	
Study intervention administration and observationb	**X**		**X**		
Record nonstudy vaccinations and any blood transfusions		**X**	**X**	**X**	
Provide the participant with a contact card	**X**				
Provide the participant with a memo,y aid		**X**		**X**	

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Visit Description	**Vaccination 1**	**Safety Follow-up Visit**	**Vaccination 2**	**Post-Vaccination 2 Blood Draw**	**Telephone Contact**
Approximate Month	0	**1**	**6**	7	**6 Months After Last Study Vaccination**
Visit Window	**Dayl**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days Afte1· Visit 3**	**168 to 196 Days Afte1· Visit 3**
Provide the participant with e-diary or ensure dia1y app downloaded	**X**		**X**		
Review and collect e-diary		**X**		**X**	
Provide caliper, measuring tape, and thermometer, if necessary	**X**		**X**		
Assess reactogenicity and record use of antipyretic medication'	Daylto7		Day **1** to 7		
Collect e-diary, if applicable		**X**		**X**	
Complete Study Visit/Telephone Contact AE Checklistd		**X**	**X**	**X**	**X**
Record concomitant medications used to treat AEs	**X**	**X**	**X**	**X**	**X**
(S)AE collection appropriate for the visit•	**X**	**X**	**X**	**X**	**X**

Abbreviations: ACWY = *Neisseria meningitidis* serogroups A, C, W-135, and Y; e ia1y = electronic diary; IVRS = interactive voice response system; IWRS = interactive Web-based response system.

a. Ensure that the participant continues to be eligible for the study, does not meet anytempora1y delay criteria, and continues to comply with contraception requirements, as appropriate.
b. Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions.
c. Between visits, review the e-dia1y data online at frequent intervals. Contact the pa1ticipant/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-dia1y was completed.
d. Checklist includes questions regarding newly diagnosed chronic medical conditions; hospitalizations, visits to other medical facilities, medication use, and missed days of school or work due to AEs; and neuroinflammatoryand autoinununе conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
e. Afollow-up contact with the pa1ticipant must be scheduled at the end of the AE/SAE active collection period as defined in Se-ction 8.3.1.

2. INTRODUCTION

Bivalent rLP2086 (Trumenba®) is indicated for active immunization to prevent invasive disease caused by MnB. Trumenba is approved by the US FDA for use in individuals 10 through 25 years of age and by the EMA in individuals 10 years of age and older.

2.1. Study Rationale

Individuals with anatomic asplenia or some degree of functional asplenia (eg, sickle cell anemia) or complement deficiencies (including but not limited to deficiencies in C5-C9, properdin, factor D, or factor H) are known to be at increased risk of severe infections caused by encapsulated bacteria, including *S pneumoniae, N meningitidis*, and Hib.

This study, as described in Section 4, is a Phase 4, open-label, single-arm trial evaluating the safety, tolerability, and immunogenicity of 2 doses of Trumenba on a 0- and 6-month schedule in immunocompromised participants ≥10 years of age. Historical data from age-matched healthy participants from the Phase 3 MnB Study B1971057, which confirmed the safety and high degree of protective immunity achieved after vaccination with Trumenba on a 2-dose, 0- and 6-month schedule, will be used as a reference for the safety and immunogenicity of Trumenba in healthy adolescents and young adults when reporting the results from this study.

2.2. Background

2.2.1. *Neisseria meningitidis* Disease Background and Medical Need

N meningitidis is a leading cause of bacterial meningitis in infants, adolescents, and young adults. Meningococcal disease incidence peaks in infants and children <5 years of age, adolescents and young adults 15 to 24 years of age, and adults ≥65 years of age. Currently, meningococcal serogroups A, B, C, W, and Y cause virtually all IMD globally.[1,2,3] In particular, MnB was the most common cause of meningococcal infections in Europe between 1999 and 2004, with an overall non–serogroup-specific case-fatality rate of 8% in 2004.[4] In Europe during 2015, MnB accounted for approximately 50% of all deaths associated with IMD.[5] In England between 2007 and 2011, among 5115 hospitalized cases of confirmed IMD, MnB accounted for 87% of cases overall and 94% of cases in those younger than 15 years of age. For MnB, the overall case-fatality rate was 4.2% for IMD and the odds of death among adolescents and young adults (OR 2.49; 95% CI 1.60, 3.88; p<0.001) was higher than in infants.[6]

From 2007 to 2018, IMD (including IMD caused by MnB) has been declining in general in Europe and in the United States.[7,8,9,10] In 2017, the estimated incidence of IMD caused by MnB was 0.04 per 100,000 individuals in the US and 0.3 per 100,000 in Europe. Therefore, the overall risk of IMD during periods of stable endemicity in both the US and Europe is extremely low.[11,12] However, during outbreaks at college campuses, incidence rates have been as high as 134 per 100,000 among undergraduates at Princeton University (2013/2014), 21.1 per 100,000 among 17- to 22-year-olds at the University of California Santa Barbara (2013), and 44 per 100,000 among undergraduates at Providence College in Rhode Island

(2015).[13,14,15] However, fluctuations in epidemiology, the unpredictable nature of the disease, and its potentially fatal consequences still pose a serious threat to public health. The need for a comprehensive approach to prevent meningococcal disease relies on vaccination and implementation of health authorities' recommendations for immunization.

Individuals with anatomic asplenia or some degree of functional asplenia (eg, sickle cell anemia) or complement deficiencies (including but not limited to deficiencies in C5-C9, properdin, factor D, or factor H) are known to be at increased risk of severe infections caused by encapsulated bacteria.[16] *S pneumoniae, N meningitidis*, and Hib account for more than half of the severe bacterial infections in asplenic individuals, and the lifetime risk of infection is higher in children than in adults.[17] It is therefore important to protect immunocompromised individuals, particularly those with asplenia or complement deficiencies, against encapsulated bacterial pathogens, such as *N meningitidis,* because of the increased risk of morbidity and mortality.[17,18] In a previously conducted Phase 3, open-label, controlled study to evaluate the safety and immunogenicity of MenACWY-TT given on a 0- and 2-month schedule in anatomically or functionally asplenic individuals (N=43) from 1 to <18 years of age, hSBA response rates in this population for the 4 serogroups ranged from 55.6% to 77.1% 1 month after Vaccination 1 and 73.0% to 100.0% 1 month after Vaccination 2. No safety signals were identified in this population. So far, no clinical study has been conducted in the immunocompromised population in the Trumenba development program. No additional adverse reactions to those already known for MenACWY-TT were identified in this population.

Trumenba is currently licensed for active immunization to prevent IMD caused by MnB and can be administered either according to a 3-dose (0, 1-2, and 6 months) or a 2-dose (0 and 6 months) schedule. Individuals with altered immunocompetence may have reduced immune responses to Trumenba, but that has not been evaluated prior to this proposed study. Because immunological clearance of *N meningitidis* from the bloodstream is complement-mediated and dependent on splenic production of antibodies and antigen processing by splenic macrophages for clearing opsonized encapsulated bacteria, adequate antibody production must be demonstrated in asplenic and complement-deficient individuals to assess the potential for protective immunity following vaccination. This can be assessed using hSBAs with exogenous complement in the same way this assay is utilized in assessing protective immunity in healthy, immunocompetent individuals. However, even if antibody levels are adequate, hSBA results may not be predictive of protection from disease in complement-deficient individuals because the assay employs exogenous complement. This is well reported and is borne out by the occurrence of IMD in complement-deficient individuals who have been vaccinated with 4CMenB.[19]

This study is designed to functionally assess antibody production in asplenic and complement-deficient individuals. The 2-dose schedule, which is safe and well tolerated and provides protective immunity to a high proportion of healthy individuals, will be evaluated in this population. In Phase 3 Study B1971057, conducted in healthy adolescents and young adults, the proportion of participants achieving a 4-fold or higher rise in hSBA titer over

baseline 1 month after the second vaccination ranged from 67.4% to 95.0% for the 4 primary MenB test strains (A22, A56, B24, and B44) with a composite response (proportion of participants with hSBA titers ≥ LLOQ for all 4 MenB test strains) of 74.3%. Proportions of participants achieving hSBA titers ≥ LLOQ for 10 secondary strains (A29, A06, A12, A07, A15, A19, B16, B09, B03, and B15) were also high, ranging from 71.1% to 96.8%. These results are comparable to those obtained using the 3-dose schedule in pivotal Phase 3 clinical trials B1971009 and B1971016 in healthy adolescents and young adults, respectively, and support routine use of the 2-dose schedule over the 3-dose schedule outside of the setting of an outbreak. In the setting of an outbreak, 2 doses over a short period of time is desirable to afford more expeditious protection; those 2 doses during the outbreak should be followed by the third dose at 6 months to complete the series.

There is no reason to expect that asplenic individuals' immune responses, as measured by hSBA, would be significantly different from healthy individuals' responses after MenB vaccination, given observations that 2 doses of 4CMenB were similarly immunogenic in this immunocompromised population compared to healthy children.[20] Although there was a trend toward decreased hSBA responses in individuals taking eculizumab who had terminal complement deficiency, the small sample size necessitates further monitoring for vaccine failures.[20] This study is therefore designed to evaluate the safety and immunogenicity of Trumenba when given on the same 2-dose schedule that proved safe and highly immunogenic in healthy adolescents and young adults who participated in Phase 3 Study B1971057.

2.2.2. Bivalent rLP2086 (Trumenba)

Trumenba (bivalent rLP2086), developed by Pfizer, is targeted to a conserved, surface-exposed lipoprotein, LP2086, a meningococcal virulence factor that binds human factor H, and therefore is designated as fHBP.[21,22] 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.[23] The lipoproteins segregate into 2 antigenically and immunologically distinct subfamilies, A and B.[24,25] 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).

Trumenba has been approved in the United States (October 2014) for active immunization to prevent invasive disease caused by MnB, for use in individuals 10 through 25 years of age. The US CDC's ACIP gives a shared clinical decision-making recommendation for administration of a 2-dose series of Trumenba for adolescents and young adults 16 to 23 years of age, with particular focus on the 16- to 18-year age group. ACIP also provides a stronger recommendation for vaccination of individuals ≥10 years of age at risk because of persistent complement component deficiencies, anatomic or functional asplenia, routine exposure as a microbiologist, or in the setting of a serogroup B meningococcal disease outbreak.[26] Trumenba has also been approved by the EMA (May 2017) for use in individuals 10 years of age and older in the EU and has now received regulatory approval in 47 countries and is currently marketed in 26 countries. 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 has not been previously evaluated in individuals with altered immunocompetence.

2.2.3. Functional Antibody Assay as a Surrogate of Efficacy

MnB clearance from the bloodstream is primarily by complement-dependent bacteriolysis. The in vivo complement-dependent bacteriolysis of MnB is mimicked by the in vitro hSBA, a functional serological assay shown to be the correlate of protection against IMD and recognized as the surrogate marker of vaccine efficacy.[27,28,29,30]

Four primary MnB test strains for hSBA representative of LP2086 subfamily A and B variants were selected from the clinically relevant strain pool of 1263 MnB isolates,[31] taking into account the population distribution of LP2086 surface expression. It was known from earlier studies that in vitro surface expression of LP2086 is an important predictor for susceptibility in hSBA. Thus, only MnB strains with LP2086 surface-expression levels above that threshold (majority of isolates) were candidates for random selection of primary MnB test strains to be used in hSBAs supporting late-phase clinical studies. This approach, coupled with identification of epidemiologically prevalent (circulating) strains in the United States and Europe, was used to select the 4 Phase 3 primary MnB test strains: 2 each from subfamilies A and B. Two MnB test strains (ie, 1 from subfamily A [PMB2001 (A56)] and 1 from subfamily B [PMB2707 (B44)]) were selected in an unbiased fashion, while the other 2 test strains (ie, 1 from subfamily A [PMB80 (A22)] and 1 from subfamily B [PMB2948 (B24)]) were selected based on epidemiological prevalence. These 4 test strains will be used in the hSBA for determination of the immunogenicity endpoints.

2.2.4. Clinical Overview

Approval of Trumenba by the FDA was initially based on Phase 2 studies demonstrating its safety and ability to induce serum bactericidal activity against 4 MnB strains as analyzed by hSBA, which meets criteria for a serological correlate of protection against MnB IMD.[27,28,29,30] Subsequently, as a requirement of US licensure, Phase 3 studies were conducted to confirm the safety and immune responses associated with the 3-dose schedule. Robust serum bactericidal activities were demonstrated not only by the 4 primary MnB strains (A22, A56, B24, and B44), but also by an additional 10 MnB strains (A29, A06, A12, A07, A15, A19, B16, B09, B03, and B15), all expressing heterologous LP2086 variants, suggesting broad coverage conferred by Trumenba against MnB. As of 28 October 2019, it is estimated that >23,500 participants have been vaccinated in the Trumenba clinical development program.

Clinical studies also demonstrated that Trumenba may be coadministered with MCV4, Tdap, HPV4, and dTaP-IPV without meaningfully impacting the immunogenicity or safety of the vaccines, which may facilitate introduction of Trumenba into national immunization programs.

The safety data from the completed clinical studies in participants 10 years of age and older support an acceptable safety profile for Trumenba in the population age group proposed for this study. Overall, the rates of local reactions and systemic events are higher following administration of Trumenba than for saline control (but similar to the active control groups). AEs other than reactogenicity that have been considered related to Trumenba by investigators are infrequent, and SAEs are infrequent and mostly considered not related to Trumenba by investigators. The percentage of participants who withdraw from studies because of AEs is low.

2.3. Benefit/Risk Assessment

Common AEs noted after vaccination with Trumenba (licensed in the US, EU, and other countries) are primarily related to reactogenicity, including local reactions (pain, swelling, and redness around the injection site) and systemic events (headache, fatigue, myalgias, arthralgias, nausea/vomiting, diarrhea, chills, and fever).

As with any vaccine, an allergic reaction may occur. Symptoms of an allergic reaction can include swelling of the lips, mouth, and throat, which may cause difficulty in swallowing or breathing; skin rash; swelling of the hands, feet, and ankles; dizziness; and fainting. A severe allergic shock (anaphylactic shock) may occur. There may also be additional risks related to the vaccines administered in the study that are unknown at this time.

Risks that may be associated with study procedures include risk from blood sampling, such as feeling faint, dizziness, fainting, pain, swelling, bruising, and infection in the vicinity of the vein from where blood is taken.

Safety assessments described in this protocol and ongoing safety data reviews by the investigator, and the sponsor's global medical monitor, the internal safety data review subcommittee, the internal risk management committee, and the DMC, will serve to monitor and mitigate these risks.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Trumenba may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention - Trumenba		
Risks associated with Trumenba in adolescents and adults 10 years of age and older based on clinical trial experience with bivalent rLP2086 are headache, nausea, diarrhea, vomiting, myalgia, arthralgia, injection site pain, fatigue, chills, injection site swelling, injection site redness, and fever. Risks associated with Trumenba based on postmarketing experience are allergic reactions and syncope.	The potential risks are based on the known safety profile of Trumenba as presented in the Trumenba IB (based on the bivalent rLP2086 CDS).	Eligibility criteria have been selected to ensure that only appropriate healthy participants are included in the study (see Section 5). E-diary and AE data will be monitored at frequent intervals by the investigator (or designee) after each vaccination (Section 8.2). Individuals with significant reactions after the first vaccination or AEs considered by the investigator to present increased risk to the participant if rechallenged with the second vaccination or who develop exclusionary conditions during the conduct of the study will be excluded from further vaccinations.
Study Procedures - Venipuncture		
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site, as well as dizziness related to the procedure.	Only qualified nurses, physicians, nurse practitioners, physician's assistants, phlebotomists, or medical assistants certified or otherwise authorized to draw blood per the standards and procedures of the investigative site as allowed by institutional, local, and country guidance will be allowed to draw blood, to minimize local complications.

2.3.2. Benefit Assessment

Based on the known degree of protective immunogenicity afforded by the licensed vaccine Trumenba, the potential benefits of participation in this study and receipt of all vaccination doses include potential protection against IMD caused by MenB.

Other benefits to the individual participant may include physical examination by a medical provider at the start of the study, a thorough review of the participant's vaccination status, and evaluation and management of some illnesses (AEs) that occur during participation in the study as part of protocol-specified scheduled and unscheduled assessments.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with Trumenba primarily include well-established local and systemic vaccination reactions, which are mostly mild to moderate in severity and transient in nature, or minor complications expected from needlesticks (vaccination or venipuncture) and are justified by the anticipated benefits (protective immunity against IMD caused by MenB) that may be afforded to immunocompromised participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

The objective of this study is to describe the immunogenicity and safety of Trumenba in individuals with asplenia or complement deficiencies with reference to historical data from randomly selected age-matched healthy participants.

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
To describe the immune response induced by 2 doses of Trumenba in immunocompromised participants and historical age-matched healthy participants as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein.	In immunocompromised participants or historical age-matched healthy participants separately, who are receiving 2 doses of study intervention and are in compliance with key protocol criteria (evaluable participants): • The proportion of participants with hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for each of the 4 primary MnB test strains 1 month after Vaccination 2.	• hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
Primary Safety:	**Primary Safety:**	**Primary Safety:**

To evaluate the safety profile of Trumenba in immunocompromised participants and historical age-matched healthy participants.	In immunocompromised participants or historical age-matched healthy participants separately, who are receiving at least 1 dose of study intervention:
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each vaccination with Trumenba.
	• The percentage of participants with at least 1 SAE and at least 1 MAE during the following time periods:
	  • 30 Days after each vaccination.
	  • 30 Days after any vaccination.
	  • During the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).
	  • During the follow-up phase (from 1 month after Vaccination 2 through 6 months after Vaccination 2).
	  • From Vaccination 1 through 6 months after Vaccination 2.
		• Local reactions (pain at the injection site, redness, and swelling).
		• Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain).
		• Use of antipyretic medication.
		• AEs.
		• SAEs.

Objectives	Estimands	Endpoints

	• The percentages of participants with at least 1 AE occurring during the following time periods:
	  • 30 Days after each vaccination.
	  • 30 Days after any vaccination.
	  • During the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).
	• The percentage of participants with at least 1 immediate AE after each vaccination.
	• The percentage of participants with at least 1 NDCMC occurring during the following time periods:
	  • During the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).
	  • During the follow-up phase (from 1 month after Vaccination 2 through 6 months after Vaccination 2).
	  • From Vaccination 1 through 6 months after Vaccination 2.
	• Number of days participants missed school or work because of AEs during the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2).
		• MAEs.
		• Immediate AEs.
		• NDCMCs.
		• Days missing from school or work because of AEs.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 4, open-label, single-arm, multicenter trial in which up to 50 immunocompromised participants ≥10 years of age with asplenia (anatomic or functional) or complement deficiency will be enrolled and receive Trumenba on a 2-dose, 0- and 6-month schedule. All participants will be naive to any meningococcal serogroup B vaccine prior to enrollment.

Historical data from age-matched healthy participants from 1 previously completed pivotal Phase 3 MnB study will be used as a reference for the safety and immunogenicity of Trumenba in the general population. Healthy adolescents and young adults (10 to <26 years of age) from Study B1971057 will be randomly selected. Details on how these participants will serve as controls are in Section 9.4.1.

For this study, immunocompromised participants are individuals at increased risk for meningococcal disease due to anatomic asplenia or functional asplenia (eg, sickle cell anemia) or complement deficiencies (including but not limited to deficiencies in C5-C9, properdin, factor H, or factor D).

Enrolled participants will be vaccinated with 2 doses of Trumenba at Months 0 and 6 (Visits 1 and 3). Blood samples (approximately 20 mL per visit) for immunogenicity analysis by hSBA will be collected prior to Vaccination 1 and 1 month after Vaccination 2 (Visits 1 and 4). Given the immunocompromised population enrolled in this study, participants will receive an on-site follow-up visit 1 month after Vaccination 1 (Visit 2). Participants will attend 4 study visits and a telephone contact will be made at Visit 5 (6 months after the last vaccination).

4.1.1. Approximate Duration of Participation for Each Participant

The duration of study participation for each participant will be approximately 12 months, including a telephone contact 6 months after the last vaccination.

The study duration will be approximately 3 years. The sponsor may decide to close recruitment if enrollment of 50 participants becomes challenging after 2 years of active enrollment.

4.1.2. Approximate Number of Participants

Up to 50 immunocompromised participants will be enrolled in the study.

4.2. Scientific Rationale for Study Design

This Phase 4 study will describe the immunogenicity, tolerability, and safety of Trumenba in individuals with asplenia or complement deficiencies with reference to historical data from randomly selected age-matched healthy participants.

Trumenba will be given in an open-label manner and on a 0- and 6-month schedule to immunocompromised participants ≥10 years of age.

Refer to Section 2.1 for further detail about the rationale of the study design.

Trumenba is approved for active immunization against IMD caused by serogroup B without any contraceptive precautions. There is no suspicion of human genotoxicity or teratogenicity based on the intended pharmacology and World Health Organization guidance.[32] See Appendix 3 for contraceptive requirements.

4.3. Justification for Dose

Trumenba (120 µg, meningococcal group B vaccine) is indicated for active immunization to prevent invasive disease caused by MnB. Trumenba, supplied as a 0.5-mL dose PFS, is approved for use in Europe in individuals 10 years of age and older and in the US in individuals 10 through 25 years of age.

The safety, tolerability, and immunogenicity of Trumenba is well established in adolescents and young adults. With the exception of recommendations for use of the 3-dose (0, 1-2, and 6 months) schedule to allow for more rapid increase in protective antibody responses after the second dose given at Month 2 in persons at increased risk for meningococcal disease during serogroup B meningococcal disease outbreaks (higher-intensity risk over shorter time period), the 2-dose, 0- and 6-month schedule is anticipated to provide similar hSBA responses among individuals with anatomic or functional asplenia and complement deficiencies as healthy individuals during lower-risk periods of low endemicity.

4.4. End of Study Definition

End of the trial in all participating countries is defined as the date of the last participant's last visit for all scheduled procedures shown in the SoA.

5. STUDY POPULATION

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

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants ≥10 years of age at the time of consent.

    - Refer to Appendix 3 for reproductive criteria for male (Section 10.3.1) and female (Section 10.3.2) participants.

Type of Participant and Disease Characteristics:

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

3. Participants with an increased risk for meningococcal disease due to anatomic asplenia or functional asplenia (eg, sickle cell anemia) or complement deficiencies (including but not limited to C5-C9, properdin, factor H, or factor D).

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

5. Female participants of childbearing potential must agree to use a highly effective method of contraception through at least 28 days after the last study vaccination. A participant is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active. This criterion is not applicable to male participants.

6. Negative urine pregnancy test for all female participants; pregnancy test is not applicable to male participants.

Informed Consent:

7. Participants who are, or whose parent(s)/legal guardian(s) are, capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

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

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

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

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

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

6. Any confirmed or suspected human immunodeficiency virus infection, based on medical history and physical examination (no laboratory testing required).

7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

8. Previous vaccination with any meningococcal serogroup B vaccine.

9. Participants who are receiving any allergen immunotherapy with a nonlicensed product or receiving allergen immunotherapy with a licensed product and are not on stable maintenance doses.

10. Receipt of immunoglobulin infusion or injection during the 42 days preceding enrollment.

11. Current chronic use of systemic antibiotics.

12. Previous receipt or current use of complement inhibitors (eg, eculizumab, ravulizumab).

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

Not applicable.

Other Exclusions:

14. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

15. Pregnant female participants; breastfeeding female participants; female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception (see Appendix 3).

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual female participant and her partner(s) from the permitted list of contraception methods (see Appendix 3) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

5.5.1. Criteria for Temporarily Delaying Vaccine Administration

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

- Current febrile illness (temperature ≥38.0°C [100.4°F]) or other acute illness within 48 hours before study intervention administration.
- Participant has received a nonlive vaccine (or intramuscular/sublingual allergen immunotherapy) within 14 days, or live vaccine within 28 days, before study intervention administration.
- Participant has received systemic antibiotic therapy within 5 days before study intervention administration.

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

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

5.5.2. Criteria for Temporarily Delaying Immunogenicity Blood Draw

The following condition is temporary and blood may be drawn once the condition has resolved and the participant is eligible for blood collection:

- Participant has received systemic antibiotic therapy within the last 5 days.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

For this study, the study intervention to be provided is Trumenba (bivalent rLP2086 and meningococcal serogroup B vaccine [Trumenba] may be used interchangeably).

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

The study intervention will be provided by the sponsor to each study site. The study vaccine will be labeled as study intervention with a unique DU number in accordance with the current guidelines and applicable local and legal regulatory requirements. This study will be open-label.

Immunocompromised participants will receive study intervention at each of the vaccination visits (Visits 1 and 3) according to Section 1.2.

Intervention Name	Trumenba
Dose Formulation	0.5 mL in a PFS
Unit Dose Strength(s)	60 µg each of a purified subfamily A and a purified subfamily B rLP2086 protein
Dosage Level(s)	0.5-mL dose at Visits 1 and 3
Route of Administration	Intramuscular
IMP or NIMP	IMP
Sourcing	Pfizer
Packaging and Labeling	Study intervention will be provided in a single-dose PFS. Each syringe will be labeled as required per country requirement.

6.1.1. Administration

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

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

Study intervention administration details will be recorded on the CRF.

Trumenba should be administered intramuscularly by injecting 0.5 mL into the upper deltoid muscle of the left or right arm.

In the event of a product quality complaint, please refer to Section 10.5.4.

6.1.2. Medical Devices

1. In this study, the medical device being used will be a PFS for Trumenba.

2. Instructions for medical device use are provided in the IP manual.

3. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Study intervention will be shipped to the study site after required regulatory and legal documents have been received by the sponsor. These will be shipped at +2°C to +8°C. Upon receipt at the study site, the study intervention should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum

temperatures since previously documented for all site storage locations upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

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

7. Study interventions should be stored in their original containers.

8. See the IP manual for storage conditions of the study intervention once reconstituted.

9. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. Used needles and syringes should be disposed of according to local practice. Empty outer study intervention containers must be retained until reviewed by the sponsor's representative and then may be destroyed after the sponsor's representative has performed accountability. Study intervention returned for destruction must be documented on the accountability log.

10. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

Additional detals about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

The study intervention will be dispensed using an IRT drug management system at each vaccination visit (Visits 1 and 3). A qualified staff member will dispense the study intervention via the unique DU number provided. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.3. Measures to Minimize Bias: Randomization and Blinding

This will be an open-label, single-arm study – participants will not be randomized to vaccine assignment.

6.3.1. Allocation of Study Intervention

This is an open-label study; however, allocation of vaccine to participants will proceed through the use of an IRT system that is accessible 24 hours a day, 365 days a year. Having logged in, the site personnel (study coordinator or specified designee) will be required to enter or select certain information, including, but not limited to, the user's ID and password, protocol number, participant number, and date of birth of the participant. The site personnel will then be provided with a participant "randomization number" (used as a participant identifier in this study) and DU or container number. The randomization number and the date on which the randomization number was assigned will be recorded on the CRF. Once participant numbers, DU numbers, and randomization numbers have been assigned, they cannot be reassigned. The IRT system will provide a confirmation report containing the participant randomization number and DU or container number assigned. The confirmation report must be stored in the site's files.

The investigator's knowledge of the vaccine assignment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

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

6.4. Study Intervention Compliance

Both doses of study intervention will be administered by the appropriately designated study staff at the investigator site.

6.5. Concomitant Therapy

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD up to Visit 4 will be recorded on the CRF.

The name, start and stop dates, and route of administration for concomitant medications (prescription and nonprescription) used to treat an AE (excluding events recorded only in the e-diary) from the signing of the ICD to Visit 5 will be recorded in the CRF.

The date and type of any blood transfusion (eg, whole blood, packed cells) received within the 3 months before enrollment through Visit 4 will be recorded on the CRF.

6.5.1. Prohibited During the Study

1. Nonlive vaccines are not permitted within 14 days before and through 14 days after any study vaccination; live nonstudy vaccines are not permitted within 28 days before and through 28 days after any study vaccination.

2. Intramuscular/sublingual allergen immunotherapy is not permitted within 14 days before and through 14 days after any study vaccination.

3. Systemic (oral, intravenous, or intramuscular) corticosteroid therapy is not permitted within 28 days before through 28 days after any study vaccination.

6.5.2. Permitted During the Study

1. All treatments that reflect standard of care for immunocompromised participants are permitted.

2. Blood transfusions are permitted during the study.

3. Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed. In such situations, effort should be made to appropriately plan the administration of study intervention around dosing of the pandemic vaccine.

4. Nonstudy vaccines that are part of recommended immunization schedules are allowed at any time during the study but should not be administered within 14 days (for nonlive vaccines) and 28 days (for live vaccines) of study intervention administration.

5. Antipyretics and other pain medications to treat symptoms associated with study intervention are permitted.

6. Local anesthetic may be applied before blood draw.

7. Topical antibiotics are permitted.

8. Topical and inhaled corticosteroids are permitted.

6.5.3. Prior Treatment

1. If the participant is known to have ever received prior vaccination with any of the following vaccines, the name of the vaccine and date of administration will be recorded

on the CRF. It is acceptable to obtain this information from a history obtained verbally from the participant, or via written vaccination record.

- Pneumococcal vaccine
- Meningococcal vaccines containing 1 or more ACWY serogroups

2. The start date and type of blood transfusion (eg, whole blood, packed cells) that immunocompromised participants receive within the 3 months before enrollment in the study will be recorded on the CRF.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participant at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: AEs; parent(s)/legal guardian or participant request; protocol violation.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for the collection of safety information. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, postvaccination study follow-up, and/or future collection of additional information.

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study intervention safety problems, or at the discretion of Pfizer. If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating participants 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.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Parent(s)/legal guardian or participant request;
- Protocol violation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant or the participant's parent(s)/legal guardian. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The participant or the participant's parent(s)/legal guardian should be questioned regarding reason for withdrawal. The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

The participant or the participant's parent(s)/legal guardian should be requested to return for a final visit, if applicable, and the investigator will perform the procedures indicated for the next visit. Any AEs or SAEs that are continuing at the time of withdrawal from the study should be followed until resolution or, in case of permanent impairment, until the condition stabilizes.

A final telephone contact 6 months after the last vaccination (Section 8.11.5) for the collection of safety information should be completed for all participants who withdraw or have been withdrawn after administration of study intervention, unless consent for further contact has been withdrawn, or the participant is lost to follow-up. Participant withdrawal should be explained in the source documents, and should include whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or postvaccination study follow-up.

If the participant withdraws from the study and his/her parent(s)/legal guardian also withdraws consent (see Section 7.2.1) 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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and the participant (or the participant's parent[s]/legal guardian[s]) is unable to be contacted by the study site.

The following actions must be taken if a participant fails to respond to a safety telephone call or return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

The total blood sampling volume for individual participants in this study is approximately 40 mL.

8.1. Efficacy and/or Immunogenicity Assessments

To facilitate immunogenicity analyses, participants will have approximately 20 mL of blood collected at Visits 1 and 4 during the study as described in Section 8.11 and the SoA. Sample collection, storage, and shipping information can be found in the ISF.

Sera obtained at these study visits will be used in immunogenicity assays as described below.

8.1.1. Serum Bactericidal Assays

For assessment of the immune response, functional antibodies will be analyzed in hSBAs with MnB test strains. The hSBA measures antibodies in human sera that result in complement-dependent killing of the target MnB strain.

Sera obtained from participants at all time points as shown in Section 1.2 will be used in these assays. Validated MnB hSBAs will be performed using the 4 primary MnB test strains.

Validated hSBA LODs and LLOQs for the 4 primary MnB strains are shown in Table 1.

Table 1. Validated hSBA LODs and LLOQs for the 4 Primary MnB Strains

Strain LP2086 Variant	LOD	LLOQ
A22	1:4	1:16
A56	1:4	1:8
B24	1:4	1:8
B44	1:4	1:8

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD = limit of detection; LP2086 = lipoprotein 2086; MnB = *Neisseria meningitidis* serogroup B.

8.1.2. 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 participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed.

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

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

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Any participant who receives at least 1 dose of study intervention will be included in the evaluation for safety. The following safety parameters will be assessed as described in Section 8.11 and in the SoA:

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

A medical history will be obtained and a physical examination will be performed on all participants at Visit 1 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 on the CRF.

The safety parameters include reactogenicity, ie, both local reactions and systemic events that occur in the 7 days (Days 1 through 7, where Day 1 is the day of vaccination) after study intervention administration. These prompted e-diary events are:

- Local reactions at the site of study intervention 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 will be collected using an e-diary. For events that resolve after Day 7, the end date will be collected in the CRF. If a participant does not complete the e-diary for 7 days, end dates of local reactions, systemic events, or antipyretic medication use that was ongoing on the last day the e-diary was completed by the participant will be collected on the CRF.

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

MAEs and NDCMCs will also be assessed throughout the study and documented on the appropriate AE CRF. An MAE 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 SoA and reported as defined in Section 8.3. AE-related hospitalizations, visits to other medical facilities, medication use, and days of school or work missed will be collected and recorded in the CRF.

Hospitalizations and visits to medical facilities not associated with an AE, such as elective hospitalizations, healthcare visits for preventive care, or routine physical examinations, will not be collected. Non–AE-related concomitant medications and days of school or work missed not associated with an AE will not be collected.

A Study Visit/Telephone Contact AE Checklist will be used as a guide, will be completed at each scheduled study visit/telephone contact (except at Visit 1), and will be included in the source documentation. Please refer to the ISF for details.

The participant or participant's parent(s)/legal guardian will be given a memory aid at Visits 2 and 4. The memory aid will be used to remind participants to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. Participants may use the memory aid as needed between Visits 2 and 3, or during the telephone contact at Visit 5, to prompt recall of events. These may be used to assist in reporting and discussion of events with study staff, but these memory aids will not be considered source documents and will not be collected at study visits. Only information collected by study staff as part of a study visit (Visit 1 through Visit 4) or telephone contact (Visit 5) will be included in the source documents and entered into the CRF.

In addition, AEs and SAEs will be collected as defined in Section 8.3.

8.2.1. Electronic Diary

The participant or parent(s)/legal guardian will be required to use an e-diary, installed on a provisioned device or an app on a personal device, and will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following vaccination (Days 1 through 7, where Day 1 is the day of vaccination). The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time.

For local reactions, systemic events, and use of antipyretic medication that resolve after Day 7, the end date will be collected on the CRF. The investigator or designee should contact the parent(s)/legal guardian or participant in order to obtain stop dates for any solicited reactions or other solicited data ongoing on the last day that the e-diary was completed; these stop dates will be collected in the CRF.

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

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

8.2.1.1. Local Reactions

Local reactions (redness, swelling, and pain) at the site of study intervention administration will be recorded daily for 7 days (Days 1 through 7, where Day 1 is the day of vaccination) after each vaccination. Only local reactions at the injection site of study intervention administration will be recorded.

8.2.1.2. Redness and Swelling

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

In the event the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units), the parent(s)/legal guardian or participant will also measure the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided and report this immediately to the investigator.

The parent(s)/legal guardian or participant 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 2. Grading of Redness and Swelling

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

8.2.1.2.1. Injection Site Pain

If the participant experiences injection site pain, the pain will be graded using the scale in Table 3. The assessment will then be recorded in the e-diary.

Table 3. Grading of Pain

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

8.2.1.3. Systemic Events

8.2.1.3.1. Temperature

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

Temperature will be measured and recorded to 1 decimal place and then categorized according to the severity scale in Table 4.

Table 4. Severity Scale for Fever

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

8.2.1.3.2. Other Systemic Events

The e-diary will be used to record the presence of other systemic events, including vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain, daily for 7 days (Day 1 through Day 7, where Day 1 is the day of vaccination) after each vaccination, using the scales in Table 5.

Table 5. 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.

8.2.1.3.3. 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 through Day 7, where Day 1 is the day of vaccination) for each vaccination.

8.2.2. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in all female participants at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention.

In the case of a positive confirmed pregnancy at Visit 1, the participant will not be eligible for participation.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 2.

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 5. Device deficiencies are covered in Section 8.3.9.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study (see Section 7.1).

Each participant/parent/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

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

At Month 12 (Visit 5, telephone contact), the parent(s)/legal guardian or participant will be contacted by telephone to inquire about SAEs, NDCMCs, or AEs that resulted in evaluation at a medical facility since Visit 4.

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

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of administration of study intervention will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of administration of study intervention are recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until the pregnancy is completed (or terminated) for pregnancies that initiate within 6 months after administration of study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including 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 study intervention.

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

the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

Per exclusion criterion 15, breastfeeding and pregnancy are exclusionary, and pregnant participants will be withdrawn from the study prior to breastfeeding.

An exposure during breastfeeding occurs if:

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Reporting Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study for the purpose of administering study intervention. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 5.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1 through 8.3.4 and Appendix 2 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 5.

8.3.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP manual.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

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

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

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose. In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Visit 1 (Day 1): Vaccination 1

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

- Obtain written informed consent, and assent if appropriate, before performing study-specific procedures. The date of informed consent will be recorded on the CRF.
- Record the participant's demographic information, including sex, race, ethnicity, and the complete date of birth (birth day, month, and year will be collected to critically evaluate the immune response and safety profile by age).
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.
- Record previous pneumococcal and meningococcal serogroup ACWY (containing 1 or more ACWY serogroups) vaccinations as described in the Prior Treatment section (Section 6.5.3).
- Record blood transfusions received within 3 months prior to enrollment as described in the Prior Treatment section (Section 6.5.3).
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and 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 for all female participants. A negative pregnancy test result is required before the participant may receive the study intervention.

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

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

- If a participant is eligible for the study, randomize the participant using an IVRS, an IWRS, or an IRT equivalent system.

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

- Administer a single 0.5-mL intramuscular injection of Trumenba into the upper deltoid muscle of the left or right arm. The time of administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.3).

- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA. Time of onset will be recorded for any AEs that occur on the same day as study intervention administration.

- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).

- Assist the participant or participant's parent(s)/legal guardian in downloading the e-diary app onto the participant/parent/legal guardian's own device or issue a provisioned device if required (see Section 8.2).

- Provide instruction regarding e-diary completion. Ask the parent(s)/legal guardian or participant to complete the e-diary from Days 1 through 7 after vaccination. Day 1 is the day of vaccination. Instructions on daily transfer of data and charging the battery should also be provided.

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

- Measurement of any redness or swelling at the injection site must be collected by the parent(s)/legal guardian for minor participants. All data must be recorded in the e-diary by the parent(s)/legal guardian for minor participants.

- Ask the parent(s)/legal guardian or the participant 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 8.2.1.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if the participant experiences a severe redness or swelling (>20 caliper units) at the injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.12).

  - If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 8.2.1.2), the parent(s)/legal guardian or the participant should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

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

- Provide the participant with a contact card (Section 10.1.10).

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

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

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

- Complete the source documents.

- Complete the CRF and update the study intervention accountability records.

Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the participant 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 participant.

8.11.2. Visit 2 (28 to 42 Days After Visit 1): Safety Follow-up Visit

- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements as detailed in Section 5.3.1.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7.2.
- If previously provided to the participant's parent(s)/legal guardian, collect the provisioned e-diary device.
- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant 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 ISF for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.
- Report any SAEs to the sponsor as defined in Section 8.3.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).
- Record any blood transfusion (eg, whole blood, packed cells) received by the participant as described in the Concomitant Therapy section (Section 6.5).
- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).
- Provide the parent(s)/legal guardian or the participant with a memory aid. Instruct the participant to use the memory aid between Visits 2 and 3 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with

study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF and Section 8.2 for additional details.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

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

- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 5.3.1.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7.2 and none of the temporary delay of vaccination criteria as described in Section 5.5.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant 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 ISF for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the ISF for additional details.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA. Time of onset will be recorded for any AEs that occur on the same day as study intervention administration.
- Report any SAEs to the sponsor as defined in Section 8.3.
- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still continuing.
- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).

- Record any blood transfusion (eg, whole blood, packed cells) received by the participant as described in the Concomitant Therapy section (Section 6.5).

- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).

- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the study intervention.

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

- Allocate a vaccine kit to the participant using an IVRS, IWRS, or equivalent IRT system.

- Administer a single 0.5-mL intramuscular injection of Trumenba into the upper deltoid muscle of the left or right arm. The time of administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the study intervention administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.3).

- Issue an e-diary to the participant or the participant's parent(s)/legal guardian (or ensure that the diary app is downloaded) and provide instruction on its completion. Ask the parent(s)/legal guardian or participant to complete the e-diary from Day 1 through Day 7 after vaccination. Day 1 is the day of vaccination. Instructions on daily transfer of data and charging the battery should also be provided.

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

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

- Ask the parent(s)/legal guardian or the participant 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 8.2.1.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if the participant experiences a severe redness or swelling (>20 caliper units) at the injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.12).

- If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 8.2.1.2), the parent(s)/legal guardian or the participant should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

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

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

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

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

- Complete the source documents.

- Complete the CRF and update the study intervention accountability records.

- Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the participant 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 participant.

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

- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements as detailed in Section 5.3.1.

- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7.2 and none of the temporary delay of blood draw criteria as described in Section 5.5.

- If previously provided to the participant's parent(s)/legal guardian, collect the provisioned e-diary device.

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

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

- Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant 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 ISF for additional details.

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

- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.

- Report any SAEs to the sponsor as defined in Section 8.3.

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

- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).

- Record any blood transfusion (eg, whole blood, packed cells) received by the participant as described in the Concomitant Therapy section (Section 6.5).

- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).

- Provide the parent(s)/legal guardian or the participant with a memory aid. Instruct the participant to use the memory aid between Visits 4 and 5 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF and Section 8.2 for additional details.

- Collect a blood sample (approximately 20 mL).

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

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

- Complete the source documents.

- Complete the CRFs.

8.11.5. Visit 5 (168 to 196 Days After Last Vaccination): Telephone Contact

- This telephone contact should occur approximately 6 months after the last vaccination (Visit 3); this contact should be attempted for all participants who have received at least 1 study vaccination, unless they have withdrawn consent.
- Contact the parent(s)/legal guardian or the participant by telephone.
- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire about SAEs, NDCMCs, or AEs that resulted in evaluation at a medical facility since the last visit. Please refer to the ISF for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. A checklist will be provided as a guide. Please refer to the ISF for additional details.
- Report any SAEs to the sponsor as defined in Section 8.3.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.
- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Complete the source documents.
- Complete the CRFs.

8.12. Unscheduled Visits

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

If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 8.2.1.2), ensure the parent(s)/legal guardian or participant has also measured the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided.

Ask the parent(s)/legal guardian or participant to report the maximum diameter of the redness and/or swelling at the injection site daily until the reaction becomes ≤20 caliper units. Record these measurements in the CRF.

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

If the unscheduled visit does not take place following participant 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.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

No specific hypotheses will be tested in this study.

9.1.1. Estimands

The estimand(s) corresponding to each primary objective are described in the table in Section 3. The estimand to evaluate the immunogenicity objective is based on the evaluable population (see Section 9.3 for definition). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed.

In the primary safety objective evaluations, missing AE dates will be imputed according to Pfizer safety rules.

9.2. Sample Size Determination

The study sample size is not based on any hypothesis-testing criteria. The study aims to enroll up to 50 participants to allow for sufficient numbers when describing findings with regard to this particular population.

The probability of observing at least 1 occurrence of any AE for true event percentages between 1.0% and 5.0%, when Trumenba is administered to 50 participants, is displayed in Table 6.

Table 6. Probability of Observing at Least 1 Event by Assumed True Event Rates

Assumed True Event Percentage	Probability (N=50)
1.0%	0.39
1.5%	0.53
2.0%	0.64
3.2%	0.80
5.0%	0.92

In order to share the expected precision for the primary immunogenicity endpoint (proportion of participants achieving hSBA titer ≥ LLOQ at 1 month after the second vaccination), the width of the exact 95% CIs is calculated for 50 participants when the proportion ranges from 0.5 to 0.9 (see Table 7).

Table 7. Width of 95% Exact Confidence Interval by Response Rate

Assumed Proportion	Width of Exact 95% Confidence Interval (N=50)
0.5	0.289
0.6	0.284
0.7	0.267
0.8	0.237
0.9	0.185

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	All participants who sign the ICD, or whose parent(s)/legal guardian(s) sign the ICD.
Study intervention allocated	All participants who are assigned a randomization (participant identification) number in the IRT system.
Evaluable	All participants who were eligible, received all doses of the study intervention according to the vaccine schedule, had blood drawn for assay testing within the required time frames, had valid and determinate assay results for the proposed analysis, and had no major protocol deviations.

Participant Analysis Set	Description
	A major protocol deviation is one that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. Prior to the immunogenicity analysis, major protocol deviations will be identified, documented, and evaluated, using predefined protocol deviation categories and subcategories. Detailed analyses for each immunogenicity endpoint will be addressed in the SAP.
mITT	All participants who have at least 1 valid and determinate MnB assay result available at any time point from Day 1 through 1 month after the second vaccination (Visit 4 for this study).
Safety	All enrolled participants who receive at least 1 dose of the study intervention and have safety data reported after vaccination.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary objectives.

9.4.1. Historical Age-Matched Healthy Controls

Historical data from age-matched healthy participants from Study B1971057, a pivotal Phase 3 MnB study that has previously completed the primary analysis, will be used as a reference for safety and immunogenicity of Trumenba. Healthy adolescents and young adults (10 to <26 years of age) from B1971057 will be randomly selected and a historical age-matched healthy control group will be used to provide context and assist with the interpretation of the immunogenicity and safety data for the immunocompromised participants. The safety and immunogenicity data will be reported separately for the immunocompromised and healthy control participants. The selection of the participants for the historical age-matched controls is based on 1 previously completed Phase 3 MnB study, B1971057 (Stage 1). Study B1971057 followed the same 0- and 6-month dosing schedule and used the same methodology for assessment of immunogenicity and safety as in this study. Healthy adolescents and young adults (10 to <26 years of age) were enrolled in B1971057 and the immunopersistence stage of the study (Stage 2) is ongoing. The same age distribution will be ensured for both the healthy controls and the immunocompromised participants by randomly selecting age-matched healthy participants from Study B1971057

who were randomized to Trumenba. For immunocompromised participants 10 to <26 years of age in this study, age-matched control participants will be randomly selected from Study B1971057. For immunocompromised participants older than 25 years of age in this study, the controls will be randomly selected from participants 25 years of age from Study B1971057. No participants will be randomly selected as control more than once. For Study B1971057, only participants randomized to Group 2 or Group 4 (Trumenba groups) will be eligible to be selected as healthy controls. Further details will be available in the SAP.

9.4.2. Immunogenicity Analyses

The immunogenicity data for the immunocompromised participants will be reported separately from historical data of the age-matched healthy participants. The immunogenicity will be reported in the historical age-matched controls for the time points corresponding to those for the immunocompromised participants.

Primary	For each of the 4 primary MenB test strains, the percentage of participants with an hSBA titer ≥ LLOQ at baseline and at 1 month after the second dose will be calculated. The primary analysis for the primary MenB strains is based on the evaluable population. Exact 2-sided 95% CIs for the percentages will be provided using the Clopper-Pearson method. A supportive analysis will be performed based on the mITT population. Missing serology data will not be imputed. The immunogenicity analysis will be based on observed, valid, and determinate assay results. Descriptive summaries will show the reasons for missing hSBA data for each primary strain and the percentages for each reason.

9.4.3. Safety Analyses

All safety analyses will be performed on the safety population. Separate safety populations will be defined for each vaccination visit and follow-up phase and will be detailed in the SAP. The safety data for the immunocompromised participants will be reported separately from the historical data of the age-matched healthy participants. The safety will be reported in the historical age-matched controls for corresponding analysis intervals to those for the immunocompromised participants.

Endpoint	**Statistical Analysis Methods**
Primary	The proportion of participants reporting local reactions at the study intervention administration site and systemic events within the 7-day period after each vaccination will be descriptively summarized.

Endpoint	Statistical Analysis Methods
	Two- sided 95% CIs based on the Clopper Pearson method will be presented with the proportions. Severities of local reactions and systemic events reported after each vaccination will also be descriptively summarized. The proportion of participants reporting the use of antipyretic medication for Days 1 through 7 will be summarized after each vaccination. The percentage of participants reporting at least 1 SAE, the percentage of participants reporting at least 1 MAE, and the percentage of participants reporting at least 1 NDCMC will be descriptively summarized (percentages and associated Clopper-Pearson 95% CIs) for each time period defined in Section 3. All AEs and SAEs will be categorized according to the latest version of MedDRA. An MAE 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, SAEs, MAEs, and NDCMCs will be summarized. Missing AE dates will be handled according to the Pfizer safety rules. Detailed analyses for each safety endpoint will be addressed in the SAP.

9.4.4. Demographic and Baseline Characteristics

The following demographic characteristics will be descriptively summarized for the immunocompromised participants: sex, race, ethnicity, and age at first vaccination. Medical history and baseline physical examination data will also be descriptively summarized. The same demographic and baseline characteristics will be reported separately for participants in the historical age-matched control group.

9.5. Interim Analyses

No interim analysis is planned for the study. Only 1 analysis will be performed at the completion of the study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

Safety data will be reviewed by the DMC throughout the study. No alpha adjustments will be made to the immunogenicity summaries (CIs) for these periodic safety assessments.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or parent(s)/legal guardian and answer all questions regarding the study. The participant or parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or parent/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or parent/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or parent(s)/legal guardian.

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

Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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 results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The

investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Study Reference Manual.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. 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 ISF.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occunence in a patient or clinical study paiiicipant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abno1mal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abno1mal laborato1y test results (hematology, clinical chemistiy, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnonnal laborato1y test results that meet any of the conditions below must be recorded as an AE: • Is associated with accompanying symptoms. • Requires additional diagnostic testing or medicaVsurgical inte1vention. • Leads to a change **in** study dosing (outside of any protocol-specified dose adjustinents) or discontinuation from the study, significant additional concomitant diug ti·eatment, or other therapy. • Exacerbation of a chronic or intennittent preexisting condition including either an increase **in** frequency and/or intensity of the condition. • New conditions detected or diagnosed after study inte1vention adininisti·ation even though it may have been present before the staii of the study. • Signs, symptoms, or the clinical sequelae of a suspected diug-diug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study inte1vention or a concomitant medication. Overdose per se will not be repo1ied as an AE/SAE unless it is an intentional overdose taken with possible

suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, "lack of efficacy" or "failure of expected phannacological action" constitutes an AE or SAE.

Events Meeting the AE Definition

- Any clinically significant abno1mal laborato1y findings or other abno1mal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiiicipant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the paiiicipant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untowai·d medical occunence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the staii of the study that do not worsen.

10.2.2. Definition of an NDCMC

An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or is othe1wise long-lasting in its effects.

10.2.3. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The te1m "life-threatening" in the definition of "serious" refers to an event in which the paiticipant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the pa1ticipant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occmTed or was necessa1y, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The tenn disability means a substantial disrnption of a person's ability to conduct n01mal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, dialThea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent eve1yday life functions but do not constitute a substantial disrnption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the paiticipant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, 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 chug dependency or chug abuse.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laborato1y findings indicating an infection in a patient exposed to a Pfizer product. The te1ms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pha1macovigilance personnel. Such cases are also considered for repo1iing as product defects, if appropriate.

10.2.4. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for repo1iing serious adverse events on the Vaccine SAE Reporting F01m to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Repo1iing Fo1m for repo1iing of SAE info1mation is not the same as the AE page of the CRF. When the same data are collected, the fo1ms must be completed in a consistent manner. AEs should be recorded using concise medical te1minology and the same AE te1m should be used on both the CRF and the Vaccine SAE Repo1iing Fo1m for repo1iing of SAE info1mation.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None

Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental fonn for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laborat01y reports, and diagnostic repo1is) related to the event.
- The investigator will then record all relevant AE/SAE infonnation in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the paiiicipant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Repo1iing Fonn/AE/SAE CRF page.
- There may be instances when copies of medical records for ce1iain cases ai·e requested by Pfizer Safety. In this case, all paiiicipant identifiers, with the exception of the paiticipant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical infonnation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE repo1ted during the study and assign it to 1 of the following categories:

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

	3	SEVERE	Interferes significantly with pa1ticipant's usual function.	

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occmTence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be rnled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product infonnation, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occmTed and the investigator has minimal infonnation to include in the initial repo1t to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up infonnation and send an SAE follow-up repo1t with the updated causality assessment.
- The causality assessment is one of the criteria used when detennining regulato1y repo1ting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for repo1ting pmposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedmes, the investigator must record this causal relationship in the somce documents and CRF, and repo1t such

an assessment in the dedicated section of the Vaccine SAE Repo1iing Fo1m and in accordance with the SAE repo1iing requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perfo1m or anange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laborato1y tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during paiiicipation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmo1iem findings including histopathology.
- New or updated info1mation will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the info1mation.

10.2.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The prima1y mechanism for repo1iing an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to repo1i the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entiy of new data or changes to existing data.
- If a site receives a repo1i of a new SAE from a study participant or receives updated data on a previously reported SAE after the electi·onic data collection tool has been taken off-line, then the site can repo1i this infonnation on a paper SAE fo1m (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

- Facsimile transmission of the Vaccine SAE Repo1iing Fonn is the prefe1Ted method to transmit this info1mation to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Fo1m sent by overnight mail or cou ne r serv ce.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Repo1iing Fonn pages within the designated repo1iing time frames.

10.3. Appendix 3: Contraceptive Guidance

10.3.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as there is no reasonable expectation of genotoxicity and teratogenicity/fetotoxicity was not observed in animal studies with Trumenba. Please refer to the Trumenba IB for further details.

10.3.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.3.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.3.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

- high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

- Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
10. Male or female condom with or without spermicide.
11. Cervical cap, diaphragm, or sponge with spermicide.
12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.4. Appendix 4 : Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

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

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

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

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

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

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

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

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

10.5. Appendix 5: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device repo1iing requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.5.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occunence, unintended disease or injmy, or untoward clinical signs (including abnonnal laborato1y finding) in study paiiicipants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or compai·ator for study paiiicipants, users, and other persons. This definition also includes events considered related to procedures for study paiiicipants only. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instmctions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use enor or from intentional Inisuse of the investigational medical device.

10.5.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injmy. The te1m "life-threatening" in the definition of serious refers to an event in which the paiiicipant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe. • A pe1manent impaiiment of a body stmcture or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure requii·ed by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injmy or pennanent impai1ment to a body stmcture or a body function.
c. Led to fetal distress, fetal death, or a congenital abno1mality or bi1ih defect.
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences chai·acteristic of a serious adverse event.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the cmTent version of the risk analysis management file.

10.5.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or perfonnance. Device deficiencies include malfunctions, use enors, and inadequate labeling.

10.5.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE and SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laborato1y reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency infonnation in the paiiicipant's medical records, in accordance with the investigator's nonnal clinical practice and on the appropriate fo1m of the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the repo1iing process described in the IP Manual and completing the Medical Device Complaint CRF.
- There may be instances when copies of medical records for certain cases ai·e requested by Pfizer Safety. In this case, all paiiicipant identifiers, with the exception of the paiiicipant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical infonnation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is ve1y impo1iant that the investigator describes any conective or remedial actions taken to prevent recmTence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessaiy to prevent recunence of a device deficiency. This includes any ainendment to the device design to prevent recmTence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency repo1ied during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the paiiicipant, causing minimal discomfo1i and not interfering with eve1yday activities.
- Moderate: An event that causes sufficient discomfort and interferes with n01mal eve1yday activities.
- Severe: An event that prevents nonnal eve1yday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a catego1y utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occmTence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be mled out.
- The investigator will use clinical judgment to detennine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product infonnation, for marketed products, in his/her assessment.
- For each AE/SAE/device deficiency, the investigator must document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occmTed and the investigator has minimal infonnation to include in the initial repo1i to the sponsor. However, it is ve1y impo1iant that the investigator always make an assessment of causality for eve1y event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up infonnation and send an SAE follow-up repo1i with the updated causality assessment.
- The causality assessment is one of the criteria used when detennining regulato1y repo1iing requirements.

Follow-up of AE/SAE/Device Deficiency

- The investigator is obligated to perfo1m or aITange for the conduct of supplemental measmements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laborato1y tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a paiiicipant dies during paiiicipation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated infonnation will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the info1mation.

10.5.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primaiy mechanism for repo1iing an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to repo1i the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entiy of new data or changes to existing data.
- If a site receives a repo1i of a new SAE from a study paiiicipant or receives updated data on a previously repo1ied SAE after the electronic data collection tool has been taken off-line, then the site can repo1i this info1mation on a paper SAE fo1m (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

- Facsimile ti·ansinission of the Vaccine SAE Repo1iing Fo1m is the prefened method to ti·ansinit this infonnation to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is accepta ble with a copy of the Vaccine SAE Repo1iing Fo1m sent by overnight mail

  or conner serv ce.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Repo1iing Fo1m pages within the designated reporting time fraines.

10.5.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
NOTE: There are additional repo1iing obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulato1y authorities and other entities about ce1iain safety infonnation relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be repo1ied to the sponsor within 24 homs after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and detennine and doclllllent in writing whether they could have led to an SAE. These shall be reported to the regulato1y authorities and IRBs/ECs as required by national regulations.

10.6. Appendix 6: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

10.6.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications used to treat an AE since the last contact. Refer to Section 6.5.
- Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 3.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.6.2. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the SoA. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements as detailed in Section 5.3.1.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 7.2.
- If previously provided to the participant's parent(s)/legal guardian, collect the provisioned e-diary device.

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

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

  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant 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 ISF for additional details.

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

- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.

- Report any SAEs to the sponsor as defined in Section 8.3.

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

- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).

- Record any blood transfusion (eg, whole blood, packed cells) received by the participant as described in the Concomitant Therapy section (Section 6.5).

- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).

- Provide the parent(s)/legal guardian or the participant with a memory aid. Instruct the participant to use the memory aid between visits (Visits 2 and 3, or Visits 4 and 5, as applicable) to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the ISF and Section 8.2 for additional details.

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

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

- Complete the source documents.

- Complete the CRFs.

10.6.3. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Study intervention should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
4CMenB	4-component meningococcal serogroup B vaccine
ACIP	Advisory Committee on Immunization Practices
ACWY	*Neisseria meningitidis* serogroups A, C, W-135, and Y
ADE	adverse device effect
AE	adverse event
$AlPO_4$	aluminum phosphate
ALT	alanine aminotransferase
app	application
AST	aspartate aminotransferase
bivalent rLP2086	*Neisseria meningitidis* serogroup B bivalent recombinant lipoprotein 2086 vaccine (bivalent rLP2086; subfamily A and B; *Escherichia coli*)
CDC	Centers for Disease Control and Prevention
CDS	core data sheet
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
COVID-19	coronavirus disease 19
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DILI	drug-induced liver injury
DMC	data monitoring committee
dTaP-IPV	diphtheria, tetanus, acellular pertussis, and inactivated poliomyelitis virus vaccine
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
fHBP	factor H binding protein
FSH	follicle-stimulating hormone

Abbreviation	Term
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hib	*Haemophilus influenzae* type b
HIPAA	Health Insurance Portability and Accountability Act
HPV4	quadrivalent human papillomavirus vaccine
HRT	hormone replacement therapy
hSBA	serum bactericidal assay using human complement
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
ISO	International Organization for Standardization
IVRS	interactive voice response system
IWRS	interactive Web-based response system
LFT	liver function test
LLOQ	lower limit of quantitation
LOD	limit of detection
LP2086	lipoprotein 2086
MAE	medically attended adverse event
MCV4	quadrivalent meningococcal polysaccharide conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY-TT	meningococcal polysaccharide groups A, C, W, and Y tetanus toxoid conjugate vaccine
mITT	modified intent-to-treat
MnB	*Neisseria meningitidis* serogroup B
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
OR	odds ratio
PFS	prefilled syringe
PT	prothrombin time
SADE	serious adverse device effect

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
Tdap	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
WOCBP	woman of childbearing potential

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