A PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED, OBSERVER-BLINDED TRIAL TO EVALUATE THE SAFETY OF A 6-VALENT OspA-BASED LYME DISEASE VACCINE (VLA15) IN HEALTHY CHILDREN 5 THROUGH 17 YEARS OF AGE

Study Intervention Number:	PF-07307405
Study Intervention Name:	6-Valent OspA-Based Lyme Disease Vaccine (VLA15)
US IND Number:	17199
EudraCT/CTIS Number:	N/A
ClinicalTrials.gov ID:	TBD
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4601012
Phase:	3

Brief Title: Safety Study of a Lyme Disease Vaccine in Healthy Children

Document History

Document	Version Date
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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Placebo-Controlled, Observer-Blinded Trial to Evaluate the Safety of a 6-Valent OspA-Based Lyme Disease Vaccine (VLA15) in Healthy Children 5 Through 17 Years of Age

Brief Title: Safety Study of a Lyme Disease Vaccine in Healthy Children

Regulatory Agency Identification Number(s):

US IND Number:	17199
EudraCT/CTIS Number:	N/A
ClinicalTrials.gov ID:	TBD
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4601012
Phase:	3

Rationale:

The overall goal of this study is to help ensure a robust safety database for VLA15 in children 5 through 17 years of age, for which LD incidence exceeds that of some older adult age cohorts and there exists an unmet medical need for LD prevention. This study in the pediatric population helps fulfill the regulatory requirement for the safety profile of VLA15 in children.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary Safety		
• To describe the safety profile of VLA15 as measured by the percentage of participants reporting local reactions, systemic events, AEs, NDCMCs, and SAEs.	• Prompted local reactions (pain at the injection site, redness, and swelling). • Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain). • AEs. • NDCMCs. • SAEs.	In participants receiving at least 1 dose of study intervention: • The proportion of participants reporting prompted local reactions within 7 days following each study intervention administration • The proportion of participants reporting prompted systemic events within 7 days following each study intervention administration • The proportion of participants reporting AEs through 1 month following each study intervention administration. • The proportion of participants reporting NDCMCs throughout the study. • The proportion of participants reporting SAEs throughout the study.

Overall Design:

This is a Phase 3, randomized, placebo-controlled, observer-blinded trial to evaluate the safety of a 6-valent OspA-based LD vaccine, VLA15, in healthy children 5 through 17 years of age.

Approximately 3000 healthy participants will be recruited from sites in the US and randomized to receive VLA15 or placebo (saline) in a ratio of 3:1. Randomization will be stratified by age groups (5 through 11 years and 12 through 17 years of age), with a minimum of 600 participants enrolled in each age stratum. Within each age stratum, site-based randomization will be used to assign individuals to groups. Randomization will occur after informed consent and eligibility review.

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

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

Number of Participants:

Approximately 3000 participants will be enrolled in the study.

Study Population:

Key inclusion and exclusion criteria are listed below; see Sections 5.1 and 5.2 for the full listing of eligibility criteria.

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Male or female participants 5 through 17 years of age at enrollment (signing of ICD or assent to participate).

2. Healthy children who are determined by medical history and clinical judgment of the investigator at enrollment to be eligible for inclusion in the study. Participants with stable preexisting chronic medical conditions may be included.

3. Participants and/or participants' parent(s)/legal guardian, as age appropriate, who are willing and able to comply with all scheduled visits, investigational plan, lifestyle considerations, and other study procedures; are expected to be available for the duration of the study; and can be contacted by telephone during study participation.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Any diagnosis of LD within the past 3 months, or history of Lyme arthritis, carditis, neuroborreliosis, or other disseminated LD, regardless of when diagnosed.

2. Congenital or acquired immunodeficiency (known or suspected) or other conditions or treatments associated with immunosuppression that could inhibit the ability to mount an immune response to a vaccine.

3. Receipt of a previous vaccination for LD.

Study Groups and Duration:

Participants will receive VLA15 or placebo in a 3:1 ratio. The primary series dosing schedule will be a 3-dose series given at Months 0, 2, and 6. A booster dose will be given approximately 12 months after primary series completion, at Month 18.

Study Interventions		
Intervention Name	**PF-07307405 (VLA15)**	**Normal Saline (Placebo)**
Unit Dose Strength(s)	0.5 mL	0.5 mL
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP

The approximate duration of the study for each participant is 24 months.

Statistical Methods:

The primary safety objective will be evaluated with descriptive summary statistics for local reactions, systemic events, AEs, NDCMCs, and SAEs. A 3-tier approach will be used to summarize AEs.

Ethical Considerations:

The results of ongoing studies of VLA15 support the investigation of VLA15 for healthy children 5 through 17 years of age, and there is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to participants, the potential risks associated with VLA15 are justified by the anticipated benefits that may be afforded to healthy participants 5 through 17 years of age.

- Participants may benefit from clinical assessment by a medical provider at the start of the study that would not otherwise occur in standard pediatric care.
- This Phase 3 study utilizes a saline placebo for comparison to evaluate safety related to VLA15 and its components. Based on the experience with VLA15 and previously studied Lyme vaccines, the potential risks for VLA15 include well-established local reactions and systemic events common to many vaccines that are mostly mild to moderate in severity and transient in nature, or minor complications expected from vaccine administration. Participants may experience some discomfort while undergoing study assessments. All participants must avoid vaccination with live attenuated vaccines for 28 days preceding and following each study dose. In addition, participants of childbearing potential must agree to use appropriate contraception methods.
- LD demonstrates a bimodal incidence by age, with children 5 to 15 years of age representing one of the highest-risk age groups. Participants in the study group receiving VLA15 may potentially have protection from LD.

1.2. Schema

Not applicable.

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 information 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 participant.

Visit Number	1	2	3	4	5	6	7	8
Visit Identifier[a]	Month 0 Dose 1 (Start of Primary Series)	Month 2 Dose 2	Month 6 Dose 3 (End of Primary Series)	Month 7	Month 12 Telephone Call	Month 18 Booster Dose	Month 19	Month 24 Telephone Call
Visit Window[b]	Day 1	50-70 Days After Visit 1	172-192 Days After Visit 1	28-42 Days After Visit 3	355-375 Days After Visit 1	535-555 Days After Visit 1	28-42 Days After Visit 6	172-192 Days After Visit 6
Obtain informed consent (and assent, as appropriate)	X							
Assign participant number	X							
Obtain demography and medical history	X							
Perform clinical assessment[c]	X							
Measure prevaccination temperature	X	X	X			X		
Perform urine pregnancy test (females ≥10 years of age)	X	X	X			X		
Confirm use of contraceptives (if appropriate)	X	X	X	X		X	X	
Record nonstudy vaccine information	X	X	X	X	X	X	X	X
Record medication information	X	X	X	X	X	X	X	X
Review inclusion and exclusion criteria	X							
Confirm continued eligibility[d]		X	X	X	X	X	X	

Visit Number	1	2	3	4	5	6	7	8
Visit Identifier[a]	Month 0 Dose 1 (Start of Primary Series)	Month 2 Dose 2	Month 6 Dose 3 (End of Primary Series)	Month 7	Month 12 Telephone Call	Month 18 Booster Dose	Month 19	Month 24 Telephone Call
Visit Window[b]	Day 1	50-70 Days After Visit 1	172-192 Days After Visit 1	28-42 Days After Visit 3	355-375 Days After Visit 1	535-555 Days After Visit 1	28-42 Days After Visit 6	172-192 Days After Visit 6
Review temporary delay criteria	X	X	X			X		
Obtain randomization number	X							
Obtain study intervention allocation	X	X	X			X		
Administer study intervention	X	X	X			X		
Postvaccination observation (30 min) and assessment of immediate AEs	X	X	X			X		
Provide participant contact card	X							
Explain e-diary completion requirements[e]	X	X	X			X		
Assist with downloading e-diary app, or issue provisioned device[e]	X	X	X			X		
Provide/ensure participant's parent(s)/legal guardian has the provided thermometer and caliper/tape measure[e]	X	X	X			X		
Review e-diary data (daily review is optimal during the active diary period)[e]	X	X	X			X		
Review ongoing e-diary symptoms and obtain stop dates[e]		X	X	X			X	

Visit Number	1	2	3	4	5	6	7	8
Visit Identifier[a]	Month 0 Dose 1 (Start of Primary Series)	Month 2 Dose 2	Month 6 Dose 3 (End of Primary Series)	Month 7	Month 12 Telephone Call	Month 18 Booster Dose	Month 19	Month 24 Telephone Call
Visit Window[b]	Day 1	50-70 Days After Visit 1	172-192 Days After Visit 1	28-42 Days After Visit 3	355-375 Days After Visit 1	535-555 Days After Visit 1	28-42 Days After Visit 6	172-192 Days After Visit 6
Collect AEs, NDCMCs, and SAEs as appropriate[f]	X	X	X	X	X	X	X	X
Collect e-diary (or assist with deletion of app at final site visit)[e]				X			X	

a. If approved by the sponsor, visits may take place at the investigator's site or an alternate site location approved by the investigator.
b. Day relative to the start of study intervention (Day 1).
c. Including, if indicated, a PE.
d. If a participant is withdrawn, the investigator should request that the participant return for 1 final visit to perform the safety-related procedures as indicated for the next scheduled study visit. A final telephone contact visit ~6 months after the last vaccination preceding withdrawal should be performed. See Section 7.2 for details.
e. Provide instructions on e-diary completion and ask the participant's parent(s)/legal guardian to complete the e-diary each day from Day 1 through Day 7, with Day 1 being the day of vaccination. E-diaries will be returned in person at Visits 4 and 7 (ie, after Dose 3 and after the booster dose, respectively).
f. AEs (nonserious) and SAEs will be collected from the time informed consent is obtained through and including a minimum of 1 month after each vaccination. NDCMCs and SAEs will be collected throughout the study.

2. INTRODUCTION

A 6-valent OspA-based LD vaccine (VLA15) is being investigated for active immunization for the prevention of LD caused by *Borrelia* species in individuals ≥5 years of age. A vaccine would fulfill an unmet medical need regarding prevention of LD, as personal protective measures against tick bites are often incomplete and antimicrobial treatment may not be fully effective.

2.1. Study Rationale

While the pivotal efficacy trial (C4601003) will include children 5 through 17 years of age, pediatric enrollment in that study may be insufficient to satisfy regulatory requirements for the size of the pediatric safety database. This additional trial, which involves only pediatric participants, will help ensure that sufficient numbers of children are included in the Phase 3 clinical development of VLA15 to meet regulatory requirements on the size of the pediatric database and to support an initial indication for use of the vaccine in children.

2.2. Background

LD is caused by *Borrelia burgdorferi* s.l. spirochetes. OspA is a major outer surface protein expressed while the *Borrelia* spirochetes are inside the tick and is both a well-established protective antigen and a means of serotyping *B burgdorferi* s.l.[1,2]

LD is the most prevalent vector-borne disease in humans across much of the northern hemisphere.[3] Its clinical manifestations range from early syndromes, including a characteristic rash accompanied by fever and generalized arthralgia or myalgia, to disseminated illness that may result in arthritis, carditis, meningitis, or other acute neurologic deficits. More severe LD syndromes can be prevented by early diagnosis and appropriate treatment, but early LD frequently goes unrecognized.

LD is a nationally notifiable disease in the US, with the most recent CDC data indicating 30,000 to 40,000 cases (confirmed and probable) reported through passive surveillance each year; given the passive nature of the surveillance system, LD is likely underreported.[3,4] Based on administrative medical claims data, the CDC has estimated an annual incidence of approximately 476,000 laboratory and clinically identified cases from 2010 to 2018.[4] In both the surveillance data and medical claims analysis, LD incidence peaks among persons 5 through 15 years of age and >50 years of age.[3,5]

OspA is expressed by *B burgdorferi* s.l. when present in the tick vector and downregulated following migration to an animal host. The mechanism of action for OspA-based vaccines is antibody-based and occurs within the tick. Vaccine-induced circulating antibody directed against OspA is taken up along with the blood meal taken by the tick after a bite. This OspA antibody then acts on OspA-expressing spirochetes within the tick gut, thereby blocking migration of the spirochetes to the salivary glands and preventing transmission of the *Borrelia* spirochetes to the animal host.[2] Two OspA (serotype 1 [ST1] only)–based vaccines have been shown to be efficacious in preventing LD in humans. LYMErix (SmithKline Beecham) and ImuLyme (Pasteur Mérieux Connaught; never marketed) demonstrated VEs of 49% and 68%, respectively, after the primary series (0 months and 1 month) during the first

year's LD season. After a single booster dose administered 12 months after the initial dose of the primary series and prior to the subsequent year's LD season, VEs for the 2 vaccines were 76% and 92%, respectively.[6,7]

Although LYMErix was licensed in the US in 1998 for people 15 through 70 years of age, it was voluntarily withdrawn from the market in 2002, primarily because of unsubstantiated public concerns around vaccine safety and weak ACIP recommendations that led to poor uptake.[8] Since its withdrawal, no LD vaccine has been available, despite an increasing unmet medical need for LD prevention in all ages.

Pfizer and Valneva are developing a 6-valent vaccine for the prevention of LD caused by *Borrelia* strains expressing OspA ST1 through ST6. While LD in the US is nearly universally caused by *B burgdorferi* ST1, the inclusion of 6 serotypes will allow for its use outside the US, where the causative genospecies and serotypes of LD are more diverse.

2.2.1. Clinical Overview

Data from 3 Phase 2 studies supported the decision to administer the vaccine at the 180-µg dose level (VLA15-201 and VLA15-202) and as a 3-dose extended-schedule primary series over 6 months (VLA15-202 and VLA15-221) for further studies because the higher dose and wider-interval vaccination schedule resulted in higher levels of circulating antibodies. The VLA15-221 study also includes participants as young as 5 years of age; data collected to date shows VLA15 is well tolerated with no unexpected safety findings.

2.3. Benefit/Risk Assessment

OspA ST1–based vaccines have been shown to be protective against LD in humans in 2 previous independent efficacy studies, thus validating the OspA target and mechanism of action. VLA15 has been protective in animal models and induced immune responses in the majority of study participants in Phase 1 and 2 studies. As VLA15 is a new multivalent construct that has not yet been tested for clinical efficacy, study participants who receive it might not directly benefit from vaccination with VLA15. The available safety data has been reviewed by an internal RMC, which concluded that the potential benefits of VLA15 outweigh its known risks, ie, the benefit/risk profile is favorable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of VLA15 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(s): VLA15		
Potential for local reactions and systemic events following vaccination.	To date, based on study intervention information obtained from Phase 1 and Phase 2 studies, common AEs noted after vaccination with the study intervention VLA15 are primarily related to reactogenicity, including local reactions (pain, tenderness, swelling, induration/hardening, itching, and erythema/redness around the injection site) and systemic events (headache, fatigue, myalgias, arthralgias, chills, fever, rash, and flu-like symptoms). These are common adverse reactions seen with other vaccines, as noted in the FDA CBER guidelines on toxicity grading scales for healthy volunteers enrolled in preventive vaccine clinical trials.[9] These studies and observed AEs are further described in the IB.	Eligibility criteria have been selected to help ensure that only appropriate participants are included in the study. 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. Safety assessments described in this protocol and ongoing safety data reviews by the investigator, the sponsor's global medical monitor, the internal RMC, and the external DMC.

Additional Risks:

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.

2.3.2. Benefit Assessment

Benefits to individual participants include:

- Clinical assessment by a medical provider at the start of the study.
- Receipt of a vaccine that may potentially prevent LD.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with VLA15 primarily include well-established local reactions and systemic events common to many vaccines and that are mostly mild to moderate in severity and transient in nature, or minor complications expected from vaccine administration, and are justified by the anticipated benefits that may be afforded to healthy pediatric participants, ie, the benefit/risk profile is favorable.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary Safety		
• To describe the safety profile of VLA15 as measured by the percentage of participants reporting local reactions, systemic events, AEs, NDCMCs, and SAEs.	• Prompted local reactions (pain at the injection site, redness, and swelling). • Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain). • AEs. • NDCMCs. • SAEs.	In participants receiving at least 1 dose of study intervention: • The proportion of participants reporting prompted local reactions within 7 days following study each intervention administration. • The proportion of participants reporting prompted systemic events within 7 days following study each intervention administration. • The proportion of participants reporting AEs through 1 month following each study intervention administration. • The proportion of participants reporting NDCMCs throughout the study. • The proportion of participants reporting SAEs throughout the study.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, placebo-controlled, observer-blinded trial to evaluate the safety of a 6-valent OspA-based LD vaccine, VLA15, in healthy children 5 through 17 years of age.

Approximately 3000 healthy participants will be recruited from sites in the US and randomized to receive VLA15 or placebo (saline). Randomization will be stratified by age group (5 to 11 years and 12 to 17 years), with a minimum of 600 participants enrolled in each age stratum. Within each age stratum, site-based randomization will be used to assign individuals to groups. Randomization will occur after informed consent and eligibility review. Participants will be randomized in a 3:1 ratio to receive VLA15 or placebo.

The primary series dosing schedule will be a 3-dose series given at Months 0, 2, and 6. A booster dose will be given approximately 12 months after primary series completion at Month 18.

AEs will be collected through 1 month following each study intervention administration. NDCMCs (see Section 10.3.2) and SAEs will be collected throughout the study. E-diaries will be used to collect prompted local reaction and systemic event data for 7 days after each vaccination (Days 1 through 7, where Day 1 is the day of vaccination) for all participants. Reported Grade 3 reactogenicity will be assessed by the study site to determine if an unscheduled visit is required.

The approximate duration of the study for each participant is 24 months. Participants who withdraw after randomization will not be replaced.

4.2. Scientific Rationale for Study Design

The overall scientific rationale for the study design is presented in Sections 2.1 and 2.2 of the protocol.

4.2.1. Age of Participants

The age range of participants is based on the epidemiology of LD. Although individuals of all ages can be affected by LD, in the US, there is a bimodal distribution of the incidence of LD with a peak in children 5 to 15 years of age, after which rates decline until a second peak in adults older than 50 years of age.[3,5] While children age 5 years and older are included in the pivotal efficacy trial, additional safety data beyond that study in this population are required.

4.3. Justification for Dose

The 180-µg VLA15 dose (60 µg of each of the 3 heterodimers) has been evaluated in 2 completed studies (VLA15-201 and VLA15-202) and 1 ongoing study (VLA-221). The results have shown that the vaccine candidate is safe, is well tolerated, and induces higher

GMTs against all 6 OspA serotypes than lower doses, including results from the VLA-221 study with participants 5 through 17 years of age.

4.3.1. Dose Schedule

The extended-interval primary series schedule is justified based on results from Study VLA15-202 in which immunogenicity was better with the Months 0, 2, and 6 schedule than the Months 0, 1, and 2 schedule seen in Study VLA15-201. The decision to use a 3-dose primary series rather than a 2-dose primary series is based on preliminary findings from Study VLA-221, which showed a superior immunogenicity profile with the 3-dose primary series given at Months 0, 2, and 6 vs the 2-dose primary series given at Months 0 and 6. Administration of the booster dose approximately 12 months after completion of the primary series is supported by previous results from Phase 3 clinical trials for LYMErix and ImuLyme in which VE increased after a booster dose, as well as from the Phase 2 Study VLA15-202 in which a robust anamnestic immune response was observed following the booster dose when administered 12 months after completing the primary series.

4.3.2. Placebo Control

This study will use an inactive placebo control (normal saline). The rationale for use of a saline control for all participants in the study is outlined below:

- Enhances the understanding of the safety profile of VLA15 by reducing potential confounding variables.
- Decreases study complexity and risk of error, thereby safeguarding participants.
- No single active control vaccine is available that would be appropriate to administer in all participants or at all study vaccination visits.

In addition, the FDA has recommended the use of a normal-saline control for all US VLA15 trials in all age groups.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

Study completion for each participant is defined as a participant who has completed all periods of the study, including the last visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. 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 5 through 17 years of age at enrollment (signing of ICD or assent to participate).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Disease Characteristics:

Not applicable.

Other Inclusion Criteria:

2. Healthy children who are determined by medical history and clinical judgment of the investigator at enrollment to be eligible for inclusion in the study. Participants with stable preexisting chronic medical conditions may be included.

3. Participants and/or participants' parent(s)/legal guardian, as age appropriate, who are willing and able to comply with all scheduled visits, investigational plan, lifestyle considerations, and other study procedures; are expected to be available for the duration of the study; and can be contacted by telephone during study participation.

5.2. Exclusion Criteria

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

1. Pregnant female participants; breastfeeding female participants; positive urine pregnancy test for female participants at Visit 1 (prior to vaccination); WOCBP who are, in the opinion of the investigator, sexually active and at risk for pregnancy; and fertile men and WOCBP who are unwilling or unable to use effective methods of contraception as outlined in this protocol from the signing of the informed consent through 28 days after completion of the primary vaccination series and from the booster dose through 28 days after the booster vaccination.

Medical Conditions:

2. Any contraindication to vaccination or vaccine components, including previous anaphylactic reaction to any vaccine or vaccine-related components.

3. Any diagnosis of LD within the past 3 months.

4. Any history of Lyme arthritis, carditis, neuroborreliosis, or other disseminated LD, regardless of when diagnosed.

5. Known tick bite within the past 4 weeks.

6. Congenital or acquired immunodeficiency (known or suspected) or other conditions or treatments associated with immunosuppression that could inhibit the ability to mount an immune response to a vaccine, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, HIV infection, leukemia, lymphoma, or organ or bone marrow transplant.

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. Receipt of a previous vaccination for LD.

   Note: This criterion includes Lyme vaccine clinical trials where study intervention was received or is unknown.

9. Treatment for LD in the 3 months prior to study intervention administration.

10. Receipt of blood/plasma products or immunoglobulins within 6 months before study intervention administration through conclusion of the study.

11. Receipt of systemic corticosteroids for ≥14 days within 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical corticosteroids are permitted.

12. Receipt of chronic systemic treatment with other known immunosuppressant medications, or radiotherapy, within 6 months before study intervention administration.

13. Current use of any prohibited concomitant medication(s) or participants unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9.

Prior/Concurrent Clinical Study Experience:

14. Participation in other studies involving investigational drug(s), investigational vaccine(s), or investigational device(s) within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusion Criteria:

15. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) 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 acceptable 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, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number if they later meet eligibility criteria.

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

The following conditions may allow a participant to be randomized once the conditions have resolved and the participant is otherwise eligible. These criteria apply for each vaccination. Participants meeting these criteria at Visit 1 will be considered screen failures if enrollment has closed prior to resolution of the condition(s).

- Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration.
- Receipt of any nonlive vaccine (including licensed or emergency use authorized COVID-19 vaccines) within 14 days or any live vaccine within 28 days before study intervention administration.
- Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical corticosteroids are permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to VLA15 and placebo.

6.1. Study Intervention(s) Administered

Intervention Name	PF-07307405 (VLA15)	Normal Saline (Placebo)
Type	Vaccine	Placebo
Dose Formulation	120 µg/mL Lip-D1B2B, 120 µg/mL Lip-D4Bva3B, 120 µg/mL Lip-D5B6B, 10 mM sodium phosphate (pH 6.7), 150 mM sodium chloride, 10 mM L-methionine, 5% sucrose, 0.05% polysorbate 20, 1.0 mg/mL aluminum (as aluminum hydroxide)	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	0.5 mL	0.5 mL
Route of Administration	Intramuscular injection	Intramuscular injection
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP

Intervention Name	PF-07307405 (VLA15)	Normal Saline (Placebo)
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in PFSs. Each PFS will be labeled as required per country requirement.	Study intervention will be provided in PFSs. Each PFS will be labeled as required per country requirement.

6.1.1. Administration

Participants will receive 1 dose of VLA15 or placebo at each vaccination visit (Visits 1, 2, 3, and 6) in accordance with the study's SoA.

VLA15 or placebo should be administered intramuscularly by injecting 0.5 mL into the deltoid muscle, preferably of the nondominant arm.

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 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.

6.1.2. Medical Devices

VLA15 and placebo will be provided in PFSs, which should be considered medical devices.

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 8.4.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. 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 upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, 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 excursion definition and information to report for each excursion will be provided to the site in the IPM.

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff 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.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. 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 IPM.

6.2.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced unblinded 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. A second unblinded staff member will verify the preparation and dispensing.

The study intervention will be administered in such a way as to ensure that the participants, parent(s)/legal guardian, and blinded site personnel remain blinded.

6.3. Assignment to Study Intervention

Allocation (randomization) of participants to study intervention groups will proceed through the use of an IRT system. The site personnel (blinded study coordinator or specified blinded designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The blinded site personnel will then be provided with a randomization number corresponding to the assigned study intervention group, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be dispensed and administered by the unblinded, qualified dispenser/administrator at the study visits summarized in the SoA.

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

6.4. Blinding

This is an observer-blinded (third party–blinded) study.

6.4.1. Blinding of Participants

Participants and their caregivers will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

In this observer-blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. Since the carton label is blinded, blinded personnel may receive and store the study intervention in the event that unblinded staff is not available. Kits remain blinded until the tamper-evident seal is broken. All other study and site personnel, including the investigator, investigator staff, participants, and parent(s)/legal guardian, will be blinded to study intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because VLA15 and the placebo are different in physical appearance, the study intervention will be administered in a manner that prevents the study participants and parent(s)/legal guardian from identifying the study intervention group based on the study intervention's appearance.

The PI will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study participant. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers/administrators and study participants should be kept to a minimum, ie, limited to administering the injection. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the study

intervention assigned to any study participant and must not be allowed to see the study intervention container contents.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4.3. Blinding of the Sponsor

The majority of sponsor staff will be blinded to study intervention allocation. The following sponsor staff will be unblinded:

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded vendor supporting interactions with the DMC on safety (see Section 10.1.5). This supporting team will include a statistician. The unblinded safety analysis for the DMC will be performed by Pfizer/vendor programmers who are separate from the study team.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, he/she should make every effort to contact the study medical monitor prior to unblinding a participant's study intervention assignment unless this could delay further management of the participant. If a participant's study intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

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

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention from appropriately authorized site personnel. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6. Dose Modification

Not applicable.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation.

6.8. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose 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 study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

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

6.9. Prior and Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- Any vaccinations received from 28 days prior to study enrollment through conclusion of the study.
- Prohibited medications listed in Section 6.9.1.
- Medications to treat AEs.

6.9.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7). Medications should not be withheld if required for a participant's medical care.

- Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 6 months before study intervention administration through conclusion of study participation.

- Receipt of systemic corticosteroids for ≥14 days is prohibited from 28 days before study intervention administration through 28 days after the end of the primary series and from 28 days before the booster dose through 28 days after the booster dose.

- Receipt of blood/plasma products or immunoglobulins within 6 months before study intervention administration through conclusion of study participation.

- Receipt of nonstudy investigational vaccines, drugs, or medical devices through conclusion of study participation.

- Prophylactic antipyretics and other pain medications taken to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.9.2. Permitted During the Study

- Receipt of any nonlive vaccine (including licensed or emergency use authorized COVID-19 vaccines) is permitted >14 days before or after study intervention administration. Receipt of any live vaccine is permitted >28 days before or after study intervention administration.

- The use of antipyretics and other pain medication is permitted except for prophylactic use prior to study intervention administration.

- Medication other than that described as prohibited in Section 6.9.1 is permitted.

- Inhaled/nebulized, intra-articular, intrabursal, or topical corticosteroids are permitted.

- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: AEs; parent(s)/legal guardian or participant request; investigator request; pregnancy; and protocol deviation (including no longer meeting all inclusion criteria or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety. All participants for whom study intervention was discontinued after the last dose of the primary series or the booster dose will be followed for safety and immunogenicity, as applicable. 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.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following: refused further study procedures; lost to follow-up; death; study terminated by sponsor; AEs; pregnancy; parent(s)/legal guardian or participant request; medication error without an associated AE; no longer meets eligibility criteria; protocol deviation; other.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant or participant's parent(s)/legal guardian. All attempts to contact the participant or participant's parent(s)/legal guardian 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 investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant is withdrawn, the investigator should request that the participant return for 1 final visit to perform the safety-related procedures indicated for the next study scheduled 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 unplanned telephone contact visit ~6 months after the last vaccination preceding withdrawal for the collection of safety information, unless consent for further contact has been withdrawn or the participant is lost to follow-up, should be performed.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request (or whose parent(s)/legal guardian 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 or participant's parent(s)/legal guardian specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants or participants' parent(s)/legal guardian 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 postvaccination 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 the participant repeatedly fails to return for scheduled visits and he or she, or the participant's parent(s)/legal guardian, is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant or the participant's parent(s)/legal guardian and reschedule the missed visit as soon as possible. Counsel the participant or the participant's parent(s)/legal guardian on the importance of maintaining the assigned visit schedule, and ascertain whether 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 or the participant's parent(s)/legal guardian (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 or the participant's parent(s)/legal guardian continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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 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 they have 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.

8.1.1. Mobile Visits

Mobile visits may take place as approved by the sponsor.

In the event that an in-person visit is not feasible at the site, the following may be performed by a licensed healthcare professional at an alternate site approved by the investigator (see the SoA):

- All study activities.

8.2. Efficacy and/or Immunogenicity Assessments

This study does not include immunogenicity or efficacy assessments.

8.3. Safety Assessments

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

A clinical assessment, including medical history, will be performed on all participants at their first visit to establish a baseline. Significant medical history will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.4.

Acute reactions within the first 30 minutes after administration of the study intervention will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions, systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.3.3.1.

8.3.1. Clinical Assessments and Physical Examinations

A clinical assessment, including medical history, will be performed on all participants prior to the first vaccination to determine participant eligibility and to establish a clinical baseline. Significant medical history and significant findings from any PE (if needed to comprehensively evaluate the participant) will be recorded as medical history in the CRF.

PE findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward PE findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

Prevaccination temperature will be measured as per usual clinical practice.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Electronic Diary

All participants will report prompted local and systemic events in an e-diary to assess reactogenicity. The participant's parent(s)/legal guardian will be asked to monitor and record local reactions, systemic events, including fever, and antipyretic/pain medication used to treat symptoms, each evening for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination) on a system that uses a PDA or other technology. This system, hereafter referred to as the participant's 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. Data on local reactions, systemic events, and antipyretic/pain medication used to treat symptoms reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting. These data do not need to be reported by the investigator in the CRF. However, if a participant withdraws because of prompted reactogenicity events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

Investigators (or an appropriately qualified designee) are required to review the e-diary data online to evaluate participant compliance and as part of the ongoing safety review.

The investigator or designee must contact the participant's parent(s)/legal guardian in order to obtain stop dates for any reactions 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 in the CRF.

8.3.3.1. Grading Scales

The grading scales used in this study to assess AEs as described below are based on concepts outlined in the FDA CBER guidelines on toxicity grading scales for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials, with adaptations for applicability to healthy younger children.[9]

8.3.3.2. Local Reactions

From Day 1 through Day 7, where Day 1 is the day of vaccination, participants' parent(s)/legal guardian(s) will be asked to assess redness, swelling, and pain at the participant's injection site and to record the findings in the e-diary in the evening. For participants <12 years of age, redness and swelling will be measured and recorded in caliper units (range: 1 to 14) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 1. For participants ≥12 years of age, redness and swelling will be measured and recorded in caliper units (range: 1 to 21) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 2. Caliper units can be converted to centimeters according to the following scale: 1 caliper unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant's parent(s)/legal guardian as mild, moderate, or severe according to the grading scale in Table 1 or Table 2. The parent(s)/legal guardian of a participant with severe (Grade 3 or above) redness or swelling will be prompted to contact the investigator to perform an unscheduled visit and assess the reaction.

Only an investigator is able to classify a participant's local reaction as Grade 4, after PE of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, telephone contact with the participant's parent(s)/legal guardian. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the participant's parent(s)/legal guardian regarding signs and symptoms that would prompt site contact. The procedure for notification of the sponsor is provided in the study documentation.

If a local reaction persists beyond the end of the e-diary period following vaccination, the participant's parent(s)/legal guardian will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Table 1. Local Reaction Grading Scale – Participants ≥5 to <12 Years of Age

	Grade 1 Mild	Grade 2 Moderate	Grade 3[a] Severe	Grade 4[b]
Redness	0.5 cm to 2.0 cm (1 to 4 caliper units)	>2.0 cm to 7.0 cm (5 to 14 caliper units)	>7 cm (>14 caliper units)	Necrosis or exfoliative dermatitis
Swelling	0.5 cm to 2.0 cm (1 to 4 caliper units)	>2.0 cm to 7.0 cm (5 to 14 caliper units)	>7 cm (>14 caliper units)	Necrosis
Pain at injection site (tenderness)	Does not interfere with activity	Interferes with activity	Prevents daily activity[c]	Emergency room visit or hospitalization for severe pain (tenderness) at the injection site

a. Participants experiencing ≥ Grade 3 local reactions may be seen by the study site. Refer to the Unscheduled Visits section (Section 8.11) for further guidance.
b. Grade 4 assessment should be made by an investigator; Grade 4 will not be collected in the diary but will be collected in the case report form.
c. Prevents daily activity, ie, results in missed days of school or is otherwise incapacitating, or includes use of narcotics for analgesia.

Table 2. Local Reaction Grading Scale – Participants ≥12 Years of Age

	Grade 1 Mild	Grade 2 Moderate	Grade 3[a] Severe	Grade 4[b]
Redness	>2.0 cm to 5.0 cm (5 to 10 caliper units)	>5.0 to 10 cm (11 to 20 caliper units)	>10 cm (>20 caliper units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 caliper units)	>5.0 cm to 10.0 cm (11 to 20 caliper units)	>10 cm (>20 caliper units)	Necrosis
Pain at injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity[c]	Emergency room visit or hospitalization for severe pain at the injection site

a. Participants experiencing ≥ Grade 3 local reactions may be seen by the study site. Refer to the Unscheduled Visits section (Section 8.11) for further guidance.
b. Grade 4 assessment should be made by an investigator; Grade 4 will not be collected in the diary but will be collected in the case report form.
c. Prevents daily activity, ie, results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

8.3.3.3. Systemic Events

From Day 1 through Day 7, where Day 1 is the day of vaccination, participants' parent(s)/legal guardian will be asked to assess headache, fatigue, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the participant's parent(s)/legal guardian as mild, moderate, or severe according to the grading scale in Table 3. The parent(s)/legal guardian of a participant with a severe headache or severe joint pain will be prompted to contact the investigator to perform an unscheduled visit and assess the reaction. Participants' parent(s)/legal guardian will also be instructed to contact site staff if the participant experiences any possible Grade 4 prompted systemic event

(ie, emergency room visit or hospitalization for headache, fatigue, muscle pain, or joint pain) within 7 days after vaccination. Study staff may also contact the participant's parent(s)/legal guardian to obtain additional information on Grade 3 events entered into the e-diary.

Only an investigator is able to classify a participant's systemic event as Grade 4, after PE of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant or participant's parent(s)/legal guardian. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. The procedure for notification of the sponsor is provided in the study documentation.

If a systemic event persists beyond the end of the e-diary period following vaccination, the participant's parent(s)/legal guardian will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Table 3. Systemic Event Grading Scale

	Grade 1 Mild	Grade 2 Moderate	Grade 3[a] Severe	Grade 4[b]
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily activity[c]	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily activity[c]	Emergency room visit or hospitalization for severe headache
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily activity[c]	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily activity[c]	Emergency room visit or hospitalization for severe joint pain

a. Participants experiencing ≥ Grade 3 systemic events may be seen by the study site. Refer to the Unscheduled Visits section (Section 8.11) for further guidance.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the diary but will be collected in the case report form.
c. Prevents daily routine activity, ie, results in missed days of work or school or is otherwise incapacitating, or includes use of narcotics for analgesia.

8.3.3.4. Fever

In order to record information on fever, a digital thermometer will be given to the participant's parent(s)/legal guardian with instructions on how to measure the participant's oral temperature at home. Temperature will be collected in the evening daily for 7 days following vaccination (Days 1 through 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until the fever has resolved

(1 day of temperature less than 100.4°F [38.0°C] in order to collect a stop date in the CRF). The parent(s)/legal guardian of a participant with a fever >104.0°F (>40.0°C) will be prompted to contact the investigator to assess the fever and perform an unscheduled visit as appropriate. Study staff must also contact the participant's parent(s)/legal guardian to obtain additional information if a temperature of ≥102.1°F (≥39.0°C) is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 4.

Table 4. Ranges for Fever

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

8.3.3.5. Use of Antipyretic/Pain Medication

From Day 1 through Day 7, where Day 1 is the day of vaccination, the participant's parent(s)/legal guardian will be asked to record the participant's use of antipyretic and/or pain medication used to treat symptoms reported in the e-diary in the evening.

8.3.4. Pregnancy Testing

Following screening, pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. This study will use urine tests for pregnancy screening. Pregnancy tests will be performed in all female participants ≥10 years of age 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 but may remain in the study.

8.3.5. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Section 10.6. Device deficiencies are covered in Section 8.4.9.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent[s]/legal guardian), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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 intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant/participant's parent(s)/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.

8.4.1. 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 a minimum of 1 month after each vaccination. NDCMCs and SAEs will be collected throughout the study.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues 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 or his or her parent(s)/legal guardian 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 permanently 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 information on 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 they consider 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.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 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 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be 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.

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

8.4.2. 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 3.

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.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Appendix 3.

8.4.4. 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 toward 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.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. 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 inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by injection, inhalation or skin contact.

- A male family member or healthcare provider who has been exposed to the study intervention by injection, inhalation or skin contact then inseminates 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/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 participant's last visit in the study.

- 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 investigator site file.

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), 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 should be reported as an SAE;

- 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.

For a female participant who becomes pregnant, this information will be shared with the study participant's parent(s)/legal guardian if the participant's age is in accordance with local/country regulations.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

The investigator must report EDB 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 EDB 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 investigator site file.

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

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the Vaccine SAE Reporting Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

For this study, there are no AESIs related to known pharmacology, toxicology, class effects, published literature, or previously identified signals in the product development program safety database. However, because this study does not include active surveillance for LD, diagnosis terms under the ICD-10 code for LD (A69.2) that represent clinical diagnoses of acute LD (early, early disseminated, or late manifestations) made by a qualified healthcare provider will be considered AESIs for this study. The purpose of specifying these conditions as AESIs is to help ensure thorough accounting of incident LD occurring throughout the study.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Vaccine SAE Reporting Form.

8.4.8.1. Lack of Efficacy

Not applicable.

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the unblinded site staff 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 Section 10.6.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.4.1 through 8.4.4 and Appendix 3 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

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

The method of documenting medical device deficiencies is provided in Section 10.6.

8.4.9.2. Follow-Up of Medical Device Deficiencies

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

The unblinded site staff 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 unblinded site staff.

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The unblinded site staff notifies the sponsor by contact method as detailed in the IPM within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint form.

3. If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.4.1.1). All relevant details related to the role of the device in the event must be included in the Vaccine SAE Reporting Form as outlined in Sections 8.4.1.1 and 8.4.1.2.

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

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

The unblinded site staff 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 unblinded site staff, 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.

8.4.10. Vaccination Errors

Vaccination 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.

Vaccination errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the vaccination error	Only if associated with an SAE

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;
- Potential vaccination errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- 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 vaccination 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.

Whether or not the vaccination error is accompanied by an AE, as determined by the investigator, the vaccination 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.

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

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

8.5. Pharmacokinetics

Not applicable.

8.6. Genetics

Not applicable.

8.7. Biomarkers

Not applicable.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics

Not applicable.

8.10. Study Procedures

8.10.1. Visit 1 – Month 0, Dose 1 (Start of Primary Series: Day 1)

Voluntary, written, study-specific informed consent (from the participant's parent(s)/legal guardian), and assent (from the participant, where appropriate), will be obtained before enrollment and before any study-related procedures are performed. Each signature on the ICD and assent (where appropriate) must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD and assent (where appropriate). A copy of the signed and dated ICD and assent (where appropriate) must be given to the participant's parent(s)/legal guardian. The source data must reflect that the informed consent and assent (where appropriate) were obtained before participation in the study.

Once the ICD/assent is obtained, the procedures below should be conducted in a stepwise manner.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the safety profile by age.
- Obtain the participant's clinically significant medical history (if any).
- Perform a clinical assessment. If the clinical assessment indicates that a PE is necessary to comprehensively evaluate the participant, perform a PE and record any findings in the source documents and, if clinically significant, record on the medical history CRF.

- Measure temperature as per usual clinical practice.
- Perform urine pregnancy test on females ≥10 years of age as described in Section 8.3.4.
- If appropriate, discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations and medications as described in Section 6.9.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5
- Obtain the participant's randomization number and study intervention allocation using the IRT system.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IPM for further instructions on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Provide the participant's parent(s)/legal guardian with a contact card.
- Explain the e-diary technologies available for this study and assist the participant's parent(s)/legal guardian in downloading the study app onto the participant's parent(s)/legal guardian's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant's parent(s)/legal guardian to complete the e-diary each day from Day 1 through Day 7, with Day 1 being the day of vaccination.
- Issue a caliper/tape measure to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled visit is required:
    - Fever >104.0°F (>40.0°C).

  - Redness or swelling at the injection site measuring >7 cm (>14 caliper units) for participants 5 through 11 years of age and >10 cm (>20 caliper units) for participants ≥12 years of age.
  - Severe headache or severe joint pain.

- Record AEs/NDCMCs/SAEs as described in Section 8.4. AEs that occur prior to dosing should be noted on the medical history CRF.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.10.2. Visit 2 – Month 2, Dose 2 (50-70 Days After Visit 1)

- Record AEs/NDCMCs/SAEs as described in Section 8.4.
- Measure temperature as per usual clinical practice.
- Perform urine pregnancy test on females ≥10 years of age as described in Section 8.3.4.
- If appropriate, discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations and medications as described in Section 6.9.
- Review the participant's e-diary data from the previous visit. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Ensure and document that the participant is still eligible to continue in the study. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's study intervention allocation using the IRT system.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IPM for further instructions on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure that the participant's parent(s)/legal guardian has a caliper/tape measure to measure local reactions at the injection site and a thermometer for recording daily temperatures, and if not, issue a caliper/tape measure and/or a thermometer (as required) and provide instructions on their use.

- Ensure that the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant's parent(s)/legal guardian to complete the e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled visit is required:

  - Fever >104.0°F (>40.0°C).

  - Redness or swelling at the injection site measuring >7 cm (>14 caliper units) for participants 5 through 11 years of age and >10 cm (>20 caliper units) for participants ≥12 years of age.

  - Severe headache or severe joint pain.

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

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.10.3. Visit 3 – Month 6, Dose 3 (End of Primary Series: 172-192 Days After Visit 1)

- Record AEs/NDCMCs/SAEs as described in Section 8.4.
- Measure temperature as per usual clinical practice.
- Perform urine pregnancy test on females ≥10 years of age as described in Section 8.3.4.
- If appropriate, discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations and medications as described in Section 6.9.
- Review the participant's e-diary data from the previous visit. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Ensure and document that the participant is still eligible to continue in the study. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's study intervention allocation using the IRT system.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IPM for further instructions on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure that the participant's parent(s)/legal guardian has a caliper/tape measure to measure local reactions at the injection site and a thermometer for recording daily temperatures, and if not, issue a caliper/tape measure and/or a thermometer (as required) and provide instructions on their use.
- Ensure that the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant's parent(s)/legal guardian to complete the e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled visit is required:
  - Fever >104.0°F (>40.0°C).
  - Redness or swelling at the injection site measuring >7 cm (>14 caliper units) for participants 5 through 11 years of age and >10 cm (>20 caliper units) for participants ≥12 years of age.
  - Severe headache or severe joint pain.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant's parent(s)/legal guardian to bring the e-diary to the next visit for collection, if applicable.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.10.4. Visit 4 – Month 7 (28-42 Days After Visit 3)

- Record AEs/NDCMCs/SAEs as described in Section 8.4.
- If appropriate, discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations and medications as described in Section 6.9.
- Review the participant's e-diary data from the previous visit. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF. Collect provisioned device, as applicable.
- Ensure and document that the participant is still eligible to continue in the study. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety (see Section 7.1).

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.5. Visit 5 – Month 12 Telephone Call (355-375 Days After Visit 1)

- Ensure and document that the participant is still eligible and willing to continue in the study.
- Record AEs/NDCMCs/SAEs as described in Section 8.4.
- Record nonstudy vaccinations and medications as described in Section 6.9.
- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the participant for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.6. Visit 6 – Month 18, Booster Dose (535-555 Days After Visit 1)

- Record AEs/NDCMCs/SAEs as described in Section 8.4.
- Measure temperature as per usual clinical practice.
- Perform urine pregnancy test on females ≥10 years of age as described in Section 8.3.4.
- If appropriate, discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations and medications as described in Section 6.9.
- Ensure and document that the participant is still eligible to continue in the study. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety (see Section 7.1).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Obtain the participant's study intervention allocation using the IRT system.

- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the (preferably) nondominant arm. Please refer to the IPM for further instructions on this process.

- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.

- Ensure that the participant's parent(s)/legal guardian has a caliper/tape measure to measure local reactions at the injection site and a thermometer for recording daily temperatures, and if not, issue a caliper/tape measure and/or a thermometer (as required) and provide instructions on their use.

- Ensure that the participant's parent(s)/legal guardian remains comfortable with the chosen e-diary platform, supply a provisioned device to them (as applicable), confirm instructions on e-diary completion, and ask the participant's parent(s)/legal guardian to complete the e-diary from Day 1 through Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled visit is required:

  - Fever >104.0°F (>40.0°C).

  - Redness or swelling at the injection site measuring >7 cm (>14 caliper units) for participants 5 through 11 years of age and >10 cm (>20 caliper units) for participants ≥12 years of age.

  - Severe headache or severe joint pain.

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

- Schedule an appointment for the participant to return for the next study visit.

- Remind the participant's parent(s)/legal guardian to bring the e-diary to the next visit for collection, if applicable.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.10.7. Visit 7 – Month 19 (28-42 Days After Visit 6)

- Record AEs/NDCMCs/SAEs as described in Section 8.4.
- If appropriate, discuss contraceptive use as described in Section 10.4.
- Record nonstudy vaccinations and medications as described in Section 6.9.
- Review the participant's e-diary data from the previous visit. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF. Collect the provisioned device or assist the participant's parent(s)/legal guardian with deleting the e-diary application.
- Ensure and document that the participant is still eligible to continue in the study.
- Ask the participant or participant's parent(s)/legal guardian to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the final study telephone call.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.10.8. Visit 8 – Month 24 Telephone Call (172-192 Days After Visit 6)

- Record AEs/NDCMCs/SAEs as described in Section 8.4.
- Record nonstudy vaccinations and medications as described in Section 6.9.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Inform the participant or participant's parent(s)/legal guardian that the participant's study participation has ended.

8.11. Unscheduled Visit for Fever or a Grade 3 or Suspected Grade 4 Reaction

If redness or swelling >14 caliper units for participants 5 through 11 years of age or >20 caliper units for participants ≥12 years of age (Section 8.3.3.2), severe headache, severe joint pain (Section 8.3.3.3), or fever (≥102.1°F [≥39.0°C]) (Section 8.3.3.4) is reported by the participant's parent(s)/legal guardian in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated.

If a suspected Grade 4 local reaction (Section 8.3.3.2), Grade 4 systemic event (Section 8.3.3.3), or fever (>104.0°F [>40.0°C]) (Section 8.3.3.4) is reported by the participant's parent(s)/legal guardian in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm the fever and determine whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant's parent(s)/legal guardian recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions/events should be assessed by the investigator or a medically qualified member of the study staff, such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.3.3.2.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.3.3.
- Assess for other findings associated with the reaction/event and record on the AE page of the CRF, if appropriate.
- The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

9. STATISTICAL CONSIDERATIONS

The methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in the 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. Statistical Hypothesis

There is no statistical hypothesis as this is a descriptive safety study.

The estimand corresponding to the primary safety objective is described in Section 3.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled population	All participants who have a signed ICD.
Randomized population	All participants who are assigned a randomization number in the IRT system.
Safety population	All enrolled participants who receive at least 1 dose of the study intervention.

9.3. 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 and secondary endpoints.

9.3.1. General Considerations

Unless stated otherwise, "vaccine group" in this section refers to participants receiving VLA15 or placebo. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Missing AE dates will be imputed according to Pfizer safety rules. Completely missing e-diary data (ie, all 7 days of e-diary collection were missing) will not be imputed. For partially complete e-diary data (ie, 1-6 days of reactogenicity data are available), it is assumed that no reactions or events were experienced on missing days based on the e-diary data source.

9.3.1.1. Analyses for Binary Data

Descriptive statistics for binary variables are the proportion (%), and the numerator (n) and the denominator (N) used in the proportion calculation. The 95% CI for percentage, and for the difference in percentages, will also be presented, where appropriate.

1. The 95% CI for the proportion will be constructed by the Clopper-Pearson method described by Newcombe. The 95% CI will be presented in terms of percentage.

2. The 95% CI for the difference in the proportions will be computed using the Miettinen and Nurminen method. The 95% CI will be presented in terms of percentage.

9.3.1.2. Analyses for Continuous Data

Unless otherwise specified, descriptive statistics for continuous variables are n, mean, median, SD, minimum, and maximum.

If applicable, CI for the mean of the continuous variable will be constructed by the standard method based on Student's t distribution.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Endpoint	Statistical Analysis Methods
Safety	Any reactogenicity reported within 7 days after vaccination will be summarized. Descriptive statistics will be provided for each reactogenicity endpoint in each vaccine group. All of the safety summary data will be presented for each age group (5 through <12 years and ≥12 to 17 years). Safety data may also be presented for the combined age groups, if appropriate. Local reactions (pain at the injection site, redness, swelling) and systemic events (fever, headache, fatigue, muscle pain, and joint pain) from Day 1 through Day 7 after each dose will be presented by maximum severity and any severity. Descriptive summary statistics will include counts and percentages of participants reporting each event included in the e-diary and the associated Clopper-Pearson 95% CIs (Section 9.3.1.1). AEs, SAEs, and NDCMCs will be categorized according to MedDRA terms. A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan. There are no Tier 1 events identified for VLA15 at this stage. (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in the pooled VLA15 group or placebo group reporting the event. (3) Tier 3 events are those that

Endpoint	Statistical Analysis Methods
	are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in the percentage of participants reporting the events between the pooled VLA15 group and the placebo group will be calculated using the test statistic proposed by Miettinen and Nurminen; in addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

9.4. Interim Analyses

No interim analysis is planned. Data will be summarized after LSLV.

9.5. Sample Size Determination

The overall study sample size is based on the development program of VLA15. In order to ensure sufficient safety data are collected on participants from 5 through 17 years of age who received at least 1 dose of VLA15 across Phase 3 studies, ~3000 pediatric/adolescents are planned for enrollment in this study so that ~2250 are exposed to the vaccine. Table 5 below summarizes the probability of observing at least 1 rare event in a population of this size (approximate number of vaccine recipients in this study). If the true rare event rate is 0.1%, there is an 89.5% probability of observing at least 1 event among participants who received VLA15 in this study.

Table 5. Probability of Observing at Least 1 AE with Different Assumed Rates

Sample Size	Assumed AE Rates		
	0.1%	0.2%	0.3%
N=2250	89.5%	98.9%	99.9%

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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, 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 the ICH GCP guidelines 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/Assent Process

The investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their 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.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/EC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent who reaches the age of consent, parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of the participant's parent(s)/legal guardian.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. The participant's 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's parent(s)/legal guardian and the study participant as applicable are 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's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian is fully informed about their right to access and correct their child's personal data and to withdraw consent for the processing of their child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent, and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

If participants are rescreened, the participants or, where appropriate, the participants' parent(s)/legal guardian are required to sign a new ICD/assent (as applicable).

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 their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

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

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

10.1.6. 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/CTIS, and/or www.pfizer.com, and other public registries and websites 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/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-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 data from these trials available 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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.

10.1.8. 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 and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor.

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

The sponsor or designee will perform monitoring 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 guidelines, and all applicable regulatory requirements.

10.1.9. 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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 the ICH 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.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

A pregnancy test will be performed at the times defined in the SoA section of this protocol.

- Pregnancy test (β-hCG): Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC for female participants ≥10 years of age.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, 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 abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, 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 abnormal laboratory 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 medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant'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 participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence 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 start of the study that do not worsen.

10.3.2. 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 otherwise long-lasting in its effects.

For each AE, please consider if the event should be reported as an NDCMC and report the event on either the AE or NDCMC CRF as appropriate. Please do not report the event on both the AE and NDCMC CRFs.

NDCMCs include conditions that are **undiagnosed prior to study entry** (diagnosed while in the study and confirmed not to be a preexisting condition) and that are **not considered temporary** conditions based upon the expected natural history of the condition. NDCMCs do not include prolonged or recurrent acute events not expected to be chronic in nature.

Consideration of a condition as chronic in a clinical setting is often defined for specific conditions, eg, chronic diarrhea that requires diarrhea to last for a minimum of 4 weeks before being considered chronic. For the purpose of vaccine clinical trials, chronicity of newly diagnosed medical conditions is determined based on characteristics of a condition that render it to be **lifelong** and **incurable** without any expectation of a full recovery, although it may be controlled. The investigator should make the determination as to whether an AE will be reported as an NDCMC. Some examples are provided below; however, if the investigator has any doubts about whether an AE should or should not be categorized as an NDCMC, please discuss further with the Pfizer study clinician.

Examples of NDCMCs (not complete list):

- Rheumatoid arthritis
- Ulcerative colitis
- Diabetes mellitus type 1
- Crohn's disease
- Diabetes mellitus type 2
- HIV infection
- Graves' disease
- Juvenile rheumatoid arthritis
- Psoriasis
- Multiple sclerosis

Examples not considered NDCMCs:

- Mood disorders*
- Recurrent cystitis
- Obesity**
- Tuberculosis
- Nutrient-deficient anemia
- Acne
- Unspecified allergies***

*Mood disorders (depression, anxiety) should not be classified as NDCMCs, given the understanding that the persistence of these conditions is uncertain when diagnosed after an initial episode.

**Obesity should not be classified as an NDCMC, given the understanding that this condition is uncertain when diagnosed in childhood. Additionally, obesity should only be considered an emergent event while the participant is enrolled in the study if the participant was considered to have been of normal weight (documented normal BMI) at study entry.

***Newly diagnosed allergy events in the absence of a specific allergen confirmed by allergy testing or documented exposure should not be classified as NDCMCs. Therefore, diagnoses such as allergic rhinitis, hay fever, unspecified pollen allergies, and seasonal allergies should not be classified as NDCMCs.

10.3.3. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 participant has been admitted (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" occurred or was necessary, 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 or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant 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 drug dependency or drug abuse.

10.3.4. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious 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 Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

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	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**

Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.
** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant 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 information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported 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, and SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.

2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.

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 occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- 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 ruled out.
- 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 information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting 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 reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange 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 laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation 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 information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after completion of the primary vaccination series and from the booster dose through 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom when having sexual intercourse with a WOCBP who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of inclusion criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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 10.4.3).

  OR

- Is a WOCBP and agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 28 days after completion of the primary vaccination series and from the booster dose through 28 days after the booster vaccination). 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.

10.4.3. Woman of Childbearing Potential

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 a 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.
     - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. 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.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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 WOCBP 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.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.

Sexual Abstinence

8. 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.

Other Effective Methods

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).

10.5. Appendix 5: 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 "adaptors" 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 T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, 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, or 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, 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 T bili 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.

10.6. Appendix 6: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

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).

10.6.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.3).
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition
• A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.6.3. 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 performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.6.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the unblinded site staff to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The unblinded site staff will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the unblinded site staff to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. • If the unblinded site staff determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.4).

- For device deficiencies, it is very important that the unblinded site staff describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- 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 ruled out.
- 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 in their assessment.
- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency
• The investigator is obligated to perform or arrange 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 device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.6.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.5).

10.6.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must 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. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.7. Appendix 7: 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 globally and will become effective for other public emergencies only upon written notification from Pfizer.

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

10.7.1. 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 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 (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Review and record any new nonstudy vaccines.

Study participants or their parent(s)/legal guardian must be reminded to promptly notify site staff about any change in the participants' health status.

10.7.2. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits. 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 (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.

- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

- All procedures listed for planned visits with the exception of vaccination and vaccination-related procedures.

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

10.7.3. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Study vaccination 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.

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTIS	Clinical Trial Information System
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCRF	electronic case report form
EDB	exposure during breastfeeding
e-diary	electronic diary
EDP	exposure during pregnancy
eSAE	electronic serious adverse event report
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone

Abbreviation	Term
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
H_0	null hypothesis
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD-10	International Classification of Diseases, 10th Revision
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISO	International Organization for Standardization
LD	Lyme disease
LFT	liver function test
LLOQ	lower limit of quantitation
LSLV	last subject last visit
MCAR	missing completely at random
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MQI	medically qualified individual
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
OspA	outer surface protein A
PDA	personal digital assistant
PE	physical examination
PFS	prefilled syringe
PI	principal investigator
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time

Abbreviation	Term
QTL	quality tolerance limit
RCDC	reverse cumulative distribution curve
RMC	risk management committee
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
s.l.	sensu lato
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
ST	serotype
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
T bili	total bilirubin
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
VLA15	6-valent OspA-based Lyme disease vaccine
WOCBP	woman/women of childbearing potential

11. REFERENCES

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Signed By:	Date(GMT)	Signing Capacity
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