Protocol C4601012

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

Statistical Analysis Plan
(SAP)

Version: 3

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TABLE OF CONTENTS

LIST OF TABLES 3
APPENDICES 4
1. VERSION HISTORY 5
2. INTRODUCTION 6
2.1. Modifications to the Analysis Plan Described in the Protocol 6
2.2. Study Objective, Endpoints, and Estimands 6
2.2.1. Primary Estimands 6
2.2.1.1. Primary Safety Estimands 6
2.2.2. Secondary Estimands 7
2.2.3. Additional Estimands 7
2.3. Study Design 7
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 8
3.1. Primary Endpoints 8
3.1.1. Primary Safety Endpoints 8
3.1.1.1. Local Reactions 9
3.1.1.2. Systemic Events 13
3.1.1.3. Adverse Events and Serious Adverse Events 15
3.2. Secondary Endpoints 16
3.3. Other Endpoints 16
3.4. Baseline Variables 16
3.4.1. E-Diary Completion for Each Dose 16
3.5. Safety Endpoints 17
3.5.1. Adverse Events 17
4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS) 17
5. GENERAL METHODOLOGY AND CONVENTIONS 18
5.1. Hypotheses and Decision Rules 18
5.2. General Methods 19
5.2.1. Analyses for Safety Endpoints 19
5.3. Methods to Manage Missing Data 19

5.3.1. Safety Data....19
5.3.1.1. Reactogenicity Data....19
5.3.2. Analyses for Continuous Data....20
6. ANALYSES AND SUMMARIES....20
6.1. Primary Endpoint....20
6.1.1. Local Reactions and Systemic Events....20
6.1.1.1. Main Analysis....20
6.1.1.2. Supplementary Analysis....21
6.1.1.3. Sensitivity Analysis of Reactogenicity....21
6.1.2. AEs, NDCMCs, and SAEs....21
6.1.2.1. Main Analysis....21
6.1.2.2. Supplementary Analysis....22
6.2. Secondary Endpoints....22
6.3. Subset Analyses....22
6.4. Baseline and Other Summaries and Analyses....22
6.4.1. Baseline Summaries....22
6.4.2. Study Conduct and Participant Disposition....23
6.4.3. Nonstudy Vaccines and Concomitant Medications....23
6.5. Other Summaries and Analyses....23
6.5.1. Adverse Events....23
7. INTERIM ANALYSES....24
8. REFERENCES....24
9. APPENDICES....25

LIST OF TABLES

Table 1. Summary of Changes....5
Table 2. Study Objective, Endpoints, and Estimands....6
Table 3. Derived Variables for *Each Local Reaction*....10
Table 4. Derived Variables for *Any Local Reaction*....10
Table 5. Grading Scale for Local Reactions....11
Table 6. Summary of Analysis Sets....17

APPENDICES

Appendix 1. List of Abbreviations.....25

1. VERSION HISTORY

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 17 Mar 2023	Original 25 Jul 2022	N/A	N/A
2 03 Aug 2023	Original 25 Jul 2022	To update the reactogenicity analysis based on CBER feedback.	Updated to include both related and unrelated AEs within 7 days of each dose for pooling with the reactogenicity data in Section 3.1.1. Added e-diary completion details for each dose to Section 3.4.1 and Section 6.4.2. Specified safety population details for each dose and added e-diary safety population details for each dose to Section 4. Clarified the handling of missing e-diary data in Section 5.3.1.1. In Section 6.1.1 and Section 6.1.2, added sensitivity analyses of the maximum severity of reactogenicity events and AEs.
3 01 Aug 2025	Original 25 Jul 2022	To update the analysis to include reactogenicity events collected in the AE CRF per FDA comments.	Updated Section 3.5.1 to include Tier 1 events. Updated Section 3.1.1 and Section 4 to include as reactogenicity data, all prompted local reactions and systemic events reported in the AE CRF for 7 days following study intervention administration (Day 1 through Day 7). Added “AE CRF” to Section 5.3.1.1 to clarify that it may be considered reactogenicity data. Replaced “e-diary” with “reactogenicity” in Section 6.1.1. Modified the sensitivity analysis information in Section 3.1.1.3, Section 6.1.1.3, and Section 6.1.2.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4601012.

This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

There are no changes in any analyses from the plan specified in the protocol.

2.2. Study Objective, Endpoints, and Estimands

The estimands corresponding to each primary are described in Table 2. There are no secondary or exploratory objectives in this study.

Table 2. Study Objective, Endpoints, and Estimands

Type	Objective	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.

2.2.1. Primary Estimands

2.2.1.1. Primary Safety Estimands

The primary estimands for the primary safety objective will use the treatment policy strategy and estimate the safety rate regardless of whether an intercurrent event occurs.

Reactogenicity estimands have the following 5 attributes:

- **Treatment condition**: VLA15 or placebo.

  As this is a multidose vaccine safety study, the 2 groups of VLA15 and placebo assignment will be based on the vaccine actually received. Participants will be assigned to the VLA15 group if at least 1 dose of VLA15 was received; participants will be assigned to the placebo group if all of the doses received were only placebo. For participants who erroneously received a combination of VLA15 and placebo (in the VLA15 group), refer to the endpoints in Section 3 for analysis.

- **Population**: Participants as defined by study inclusion/exclusion criteria.

- **Variables**: Each item included in the e-diary from Days 1 through 7 after each dose or any dose with VLA15 or placebo (refer to Section 3.1.1.1 and Section 3.1.1.2).

- **Population-level summary**: The rates of reporting for each prompted reactogenicity item in the VLA15 group or the placebo group, separately for each age group and for the combined age groups.

- **Intercurrent events**: The intercurrent events for this safety study will be participants who did not complete the study. However, all participants will be followed for safety monitoring until 6 months after the last dose. Therefore, the treatment policy strategy will be used to handle the intercurrent event; all data collected after the intercurrent event will be included in the analysis for safety purposes.

AE, NDCMC, and SAE estimands are defined in the same way as the reactogenicity estimands, except for the variables of AEs through 1 month following each dose of VLA15 or placebo. The analysis will include the proportion of participants reporting NDCMCs or SAEs, beginning with the first dose of VLA15 or placebo, throughout the study (refer to Section 3.1.1.1 and Section 3.1.1.2).

2.2.2. Secondary Estimands

No secondary estimands are defined in this study.

2.2.3. Additional Estimands

No additional estimands are defined in this study.

2.3. Study 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 3550 healthy participants will be recruited from sites in the US and randomized to receive VLA15 or placebo (saline). Randomization will be stratified by age at the time of study entry (5 through 11 and 12 through 17 years), with a minimum of 600 participants enrolled in each age group. Within each age group, 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.

Vaccine Safety

AEs will be collected through 1 month following each study intervention administration. NDCMCs 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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

Primary safety endpoints include both reactogenicity data and AEs collected from the e-diary and the AE CRF.

Based on feedback from the FDA on multiple vaccine programs, reactogenicity data will utilize both e-diary data (prompted local reactions and systemic events) and reactogenicity events reported in the AE CRF during the e-diary collection period.

Since the AE CRF does not designate a specific page to collect reactogenicity data for an untransmitted e-diary, Pfizer has adopted a process of providing a listing of AEs reported within 7 days after vaccination for the clinical team to review and determine ("flag") which PTs should be considered reactogenicity events before the database lock. AEs reported on the same day of vaccination that are missing a start time are defaulted to AEs reported after vaccination. Following these review steps, those AEs reported within 7 days after vaccination that match flagged PTs will be considered reactogenicity data. If the same reactogenicity event is reported on the same day from both the e-diary and the AE CRF, the highest grade from the 2 data sources will be used for that specific day for analysis.

It should be noted that the data collection in the AE CRF is different from that of the e-diary:

- For redness, swelling, and fever, the measured size of redness and swelling at the injection site and temperature are recorded in the e-diary but not in the AE CRF. As the missing e-diary entries are monitored in an ongoing review of the prompted reactions reported in the AE CRF, any measurement recorded in the query response will be considered for the primary analysis, using the data handling memo for analysis purposes. For the 7 days, only the maximum grading from both sources will be used for the aggregated severity analysis.

- For pain at the injection site and all other systemic events, the severity grading algorithm for the e-diary data and the AE CRF may not be the same. Pfizer will choose the highest severity grade.

Any AEs recorded on the AE CRF for 7 days following study intervention administration (Day 1 through Day 7) that are considered local reactions or systemic events will be consolidated with the e-diary data and included in the reactogenicity report.

The subsections below describe how to derive each safety endpoint.

3.1.1.1. Local Reactions

The local reactions reported in the e-diary are redness, swelling, and pain at the injection site from Day 1 through Day 7 after each vaccination dose, where Day 1 is the day of each dose of VLA15 or placebo. Any reactogenicity events reported in the AE CRF during the e-diary collection period are included in the derivation discussed below.

This section describes derivations with details for the assessment of local reactions, ie, presence, maximum severity, duration, and onset day of local reactions.

3.1.1.1.1. Presence of Local Reactions Within 7 Days After Vaccination

For the summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 after vaccination, where Day 1 is the day of each vaccination dose, the following 6 variables are derived for each participant in the e-diary safety population:

- Presence (yes or no) of each local reaction on any day (Day 1 through Day 7) for each dose of VLA15 or placebo

- Presence (yes or no) of each local reaction on any day (Day 1 through Day 7) for any dose of VLA15 or placebo

The derivation is described in Table 3.

Table 3. Derived Variables for *Each Local Reaction*

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Days 1-7) for *each dose*	Participant reports *the reaction* as "yes" on any day (Days 1-7) for each dose of VLA15 or placebo.	Participant reports *the reaction* as "no" on all 7 days or as a combination of "no" and "missing" on all 7 days for the dose.	Participant reports *the reaction* as missing on all 7 days for the dose.
Any day (Days 1-7) for *any of the 4 doses*	Participant reports *the reaction* as "yes" on any day (Days 1-7) for any dose of VLA15 or placebo.	Participant reports *the reaction* as "no" on all 7 days or as a combination of "no" and "missing" on all 7 days on any dose of the primary series and booster dose.	Participant reports *the reaction* as "missing" on all 7 days on any dose of the primary series and booster dose.

a. The variable will be defined for each of the 3 local reactions. For participants who received mixed vaccines across doses (eg, VLA/placebo/VLA, or placebo/VLA15/placebo), only the reactogenicity after VLA15 will be included, and the dose number will be based on the actual dose of VLA15. Reactions reported after placebo was given erroneously will not be counted in the VLA15 group.

- Presence (yes or no) of any local reaction on any day (Day 1 through Day 7) for each dose of VLA15 or placebo
- Presence (yes or no) of any local reaction on any day (Day 1 through Day 7) for any dose of VLA15 or placebo

For any local reaction on any day, a similar definition can be applied as given in Table 4.

Table 4. Derived Variables for *Any Local Reaction*

Variable	Yes (1)	No (0)	Missing (.)
Any day (Days 1-7) for *each dose*	Participant reports *any local reaction* as "yes" on any day (Days 1-7) for the dose.	Participant reports *all reactions* as "no" on all 7 days or as a combination of "no" and "missing" on all 7 days for all 3 local reactions for the dose.	Participant reports *all local reactions* as "missing" on all 7 days for the dose.
Any day (Days 1-7) for *any of the 4 doses*	Participant reports *any local reaction* as "yes" on any day (Days 1-7) for any dose of the primary series and booster dose.	Participant reports *all reactions* as "no" on all 7 days or as a combination of "no" and "missing" on all 7 days for all 3 local reactions for any dose of the primary series and booster dose.	Participant reports *all local reactions* as "missing" on all 7 days for any dose of the primary series and booster dose.

3.1.1.1.2. Maximum Severity of Local Reactions Within 7 Days After Vaccination

The grading of local reactions is listed below in Table 5. Age at each vaccination dose will be used to determine the grading scale for local reactions.

Table 5. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Participants ≥5 to <12 Years Old				
Redness	0.5 cm to 2.0 cm (1 to 4 caliper units from the e-diary) or mild from the AE CRF	>2.0 cm to 7.0 cm (5 to 14 caliper units from the e-diary) or moderate from the AE CRF	>7 cm (>14 caliper units from the e-diary or severe from the AE CRF	Necrosis or exfoliative dermatitis
Swelling	0.5 cm to 2.0 cm (1 to 4 caliper units from the e-diary) or mild from the AE CRF	>2.0 cm to 7.0 cm (5 to 14 caliper units from the e-diary) or moderate from the AE CRF	>7 cm (>14 caliper units from the e-diary or severe from the AE CRF	Necrosis
Pain (at the injection site)	Does not interfere with activity (mild from the e-diary or the AE CRF)	Interferes with activity (moderate from the e-diary or the AE CRF)	Prevents daily activity (severe from the e-diary or the AE CRF)	Emergency room visit or hospitalization for severe pain at the injection site
Participants ≥12 Years Old				
Redness	>2.0 cm to 5.0 cm (5 to 10 caliper units from the e-diary) or mild from the AE CRF	>5.0 cm to 10.0 cm (11 to 20 caliper units from the e-diary) or moderate from the AE CRF	>10 cm (>20 caliper units from the e-diary) or severe from the AE CRF	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 caliper units from the e-diary) or mild from the AE CRF	>5.0 cm to 10.0 cm (11 to 20 caliper units from the e-diary) or moderate from the AE CRF	>10 cm (>20 caliper units from the e-diary) or severe from the AE CRF	Necrosis
Pain (at the injection site)	Does not interfere with activity (mild from the e-diary or the AE CRF)	Interferes with activity (moderate from the e-diary or the AE CRF)	Prevents daily activity (severe from the e-diary or the AE CRF)	Emergency room visit or hospitalization for severe pain at the injection site

a. Grade 4 assessment should be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the AE CRF.

The following variables are derived for each participant:

- Maximum severity of each local reaction on any day (Day 1 through Day 7) for each dose

  The maximum severity (highest grading) of each local reaction within 7 days after each vaccination dose will be derived. It should be noted that for participants in the VLA15 group, if a participant erroneously received placebo, the data after the placebo dose will not be derived. The maximum severity will be derived as follows:

  - "Missing," if values are missing for all days (Day 1 through Day 7)
  - 0, if the participant reports all reactions as "no" or a combination of "missing" and "no" for all days (Day 1 through Day 7)
  - *Highest grade* (maximum severity) within 7 days after vaccination (either from the e-diary data or from the AE CRF) if the answer is not "no" for at least 1 day

- Maximum severity of each local reaction on any day (Day 1 through Day 7) for any dose

  The maximum severity (highest grading) of each local reaction within 7 days after any vaccination dose will be derived after any VLA15 dose for the VLA15 group, and after any placebo dose for the placebo group, and will be based on the variable of the maximum severity of each local reaction for each dose. Reactions reported after placebo was given erroneously will not be counted in the VLA15 group.

- Maximum severity of any local reaction on any day (Day 1 through Day 7) for each dose

  The maximum severity for any local reaction on any day for each dose will be derived in the bullet list below. Again, the data after administration of placebo for participants in the VLA15 group will not be used for derivation:

  - "Missing," if values are missing for all days (Day 1 through Day 7) across all 3 local reactions
  - 0, if the participant reports all reactions as "no" or a combination of "missing" and "no" for all days (Day 1 through Day 7) for all individual local reactions
  - *Highest grade* (maximum severity) within 7 days after vaccination if the answer is not "no" for at least 1 day, for at least 1 local reaction

- Maximum severity of any local reaction on any day (Day 1 through Day 7) for any dose

  The maximum severity for any local reaction on any day will be derived after any VLA15 dose for the VLA15 group, and after any placebo dose for the placebo group, based on the variable of the maximum severity for any local reaction for each dose. Reactions reported after placebo was given erroneously will not be counted in the VLA15 group.

3.1.1.1.3. Duration of Each Local Reaction After Each Dose and Any Dose

The duration of each local reaction will be calculated in days as (resolution date of reaction - start date of reaction + 1) after each dose. Resolution of the event is the last day on which the event is recorded in the e-diary (or the AE CRF), or the date the event ends if it is unresolved during the participant's e-diary recording period (the end date collected on the CRF) or AE stop date, whichever is longer, unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to "missing." Participants with no reported reaction have no duration.

As this study includes multiple vaccination doses, the date that the reaction ended for one dose should not be after the date of the subsequent dose. Therefore, if a reaction was ongoing at the time of a subsequent dose, the end date for the reaction after the previous vaccination would be the day before the subsequent dose date, which will be used for the duration computation.

The duration for each local reaction after any dose will be derived after any VLA15 dose for the VLA15 group, and after any placebo dose for the placebo group, based on the total duration across all doses for each local reaction.

For the participants of the VLA15 group who received placebo in error, reactogenicity data after placebo administration will not be included in the derivation.

3.1.1.1.4. Onset Day of Each Local Reaction After Each Dose and Any Dose

The onset day of each local reaction will be derived after each dose. Onset day is defined as the first day of reporting any reaction of any severity.

The onset day for each local reaction after any dose will be derived after any VLA15 dose for the VLA15 group, and after any placebo dose for the placebo group, based on the variable of the first (earliest) onset day for each local reaction across all doses.

For participants in the VLA15 group with placebo administration in error, reactogenicity data after placebo administration will not be included in the derivation.

3.1.1.2. Systemic Events

Systemic events, including fever, fatigue, headache, muscle pain, and joint pain, are reported via the e-diary from Day 1 through Day 7 after vaccination, where Day 1 is the day of each dose of VLA15 or placebo. The derivations listed below for systemic events will be handled similarly to the way local reactions are handled for the presence for each participant, severity level, duration, and onset day:

- Presence (yes or no) of <u>each</u> systemic event on any day (Day 1 through Day 7) for <u>each dose</u>

- Presence (yes or no) of each systemic event on any day (Day 1 through Day 7) for any dose
- Presence (yes or no) of any systemic event on any day (Day 1 through Day 7) for each dose
- Presence (yes or no) of any systemic event on any day (Day 1 through Day 7) for any dose
- Maximum severity of each systemic event on any day (Day 1 through Day 7) for each dose
- Maximum severity of each systemic event on any day (Day 1 through Day 7) for any dose
- Maximum severity of any systemic event on any day (Day 1 through Day 7) for each dose
- Maximum severity of any systemic event on any day (Day 1 through Day 7) for any dose
- Duration of each systemic event after each dose and any dose
- Onset day of each systemic event after each dose and any dose

The grading scale for systemic events is provided in the protocol. However, the derivation of severity of each systemic event on each day should be based on the maximum severity reported in the e-diary or the AE CRF, if data are reported from both sources, or the e-diary alone if not reported in the AE CRF.

Fever is defined as a temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. For reporting purposes, fever will be analyzed using the following temperature ranges:

- Mild (≥38.0°C to 38.4°C from the e-diary or mild grade from the AE CRF)
- Moderate (>38.4°C to 38.9°C from the e-diary or moderate grade from the AE CRF)
- Severe (>38.9°C to 40.0°C from the e-diary or severe grade from the AE CRF)
- Grade 4 (>40.0°C from the e-diary or severe grade from the AE CRF plus documented >40.0°C in the CRF query or other sources)

If any temperature is confirmed as incorrect, the correct temperature will be used for the analysis. Those for which the correct temperature is unknown will not be included in the analysis.

3.1.1.3. Adverse Events and Serious Adverse Events

Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer vaccine data standard rules. Completely missing AE start dates will not be imputed.

The following derivations (yes/no) will be included for each participant:

- Any AE reported within 30 days (Day 1 through Day 31) after each dose and after any dose
- Any related AE reported within 30 days (Day 1 through Day 31) after each dose and after any dose
- Any immediate AE (AE start time is within 30 minutes after vaccination) reported after each dose and after any dose
- Any severe AE reported within 30 days (Day 1 through Day 31) after any dose
- Any AE leading to study withdrawal after the first dose
- Any AE leading to death after the first dose

AE reports will exclude any reactogenicity events (but not exclude reactogenicity SAEs) reported in the AE CRF during the e-diary collection period.

- Any AESI reported during the study after the first dose

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 AESI PTs will be included in the data handling memo before the database lock.

- NDCMCs reported during the study after the first dose
- SAEs reported during the study after the first dose (including reactogenicity events reported in the AE CRF during the e-diary collection period)
- Related SAEs reported during the study after the first dose (including reactogenicity events reported in the AE CRF during the e-diary collection period)

3.2. Secondary Endpoints

No secondary endpoints are defined in this study.

3.3. Other Endpoints

No other endpoints are defined in this study.

3.4. Baseline Variables

Day 1 is defined as the day of the first vaccination dose for the overall study assessment.

Demographic variables to be collected include sex, race, ethnicity, and date of birth. Age at Dose 1 (in years) will be derived based on birthday. Two age groups will be derived: 5 through 11 and 12 through 17 years.

Medical history of clinical significance will be collected and categorized according to the current version (at the time of reporting) of MedDRA.

3.4.1. E-Diary Completion for Each Dose

An e-diary will be considered transmitted if any data for the local reactions and systemic events are present for any day. If all data are missing from all items (local reactions and systemic events) in the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted. An e-diary will be considered transmitted for a given day if any data are present for that day. The following variables will be derived:

- e-diary data transmitted on each day (Day 1 through Day 7)
- e-diary data transmitted on any day (Day 1 through Day 7)
- e-diary data transmitted on both Day 1 and Day 2
- e-diary data transmitted from Day 1 through Day 3
- e-diary data transmitted from Day 1 through Day 4
- e-diary data transmitted from Day 1 through Day 5
- e-diary data transmitted from Day 1 through Day 6
- e-diary data transmitted for all 7 days

3.5. Safety Endpoints

3.5.1. Adverse Events

A 3-tier approach will be used to summarize AEs, PTs, and SOCs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers:

- Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's safety surveillance review plan.
- Tier 2 events: These are events that are not Tier 1 but are "relatively common." A MedDRA PT is defined as a Tier 2 event if it is reported by at least 1% of participants in any vaccine group.
- Tier 3 events: These are AEs that are neither Tier 1 nor Tier 2 events.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per standard operating procedures.

For purposes of analysis, the following analysis sets are defined in Table 6.

Table 6. Summary of Analysis Sets

Participant Analysis Set	Description
Enrolled/entered	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 received at least 1 dose of the study intervention. The safety population will be defined below for each dose: • Safety population for Dose 1: The participants who received the first dose of the study intervention (VLA15 or placebo). • Safety population for Dose 2: The participants who received 2 doses of the study intervention. • Safety population for Dose 3: The participants who received 3 doses of the study intervention. • Safety population for Dose 4: The participants who received 4 doses of the study intervention.

Table 6. Summary of Analysis Sets

Participant Analysis Set	Description
E-diary safety population	All participants who received the study intervention (VLA15 or placebo) and had at least 1 day of reactogenicity data reported through the e-diary or AE CRF. Note: If all participants had at least 1 day of e-diary transmitted, this will be the same as the safety population. The e-diary safety population will be defined below for each dose: • E-diary safety population for Dose 1: The participants who received the first dose of the study intervention (VLA15 or placebo) and had at least 1 day of reactogenicity data reported through the e-diary or AE CRF during the Dose 1 e-diary collection period. • E-diary safety population for Dose 2: The participants who received 2 doses of the study intervention (VLA15 or placebo) and had at least 1 day of reactogenicity data reported through the e-diary or AE CRF during the Dose 2 e-diary collection period. • E-diary safety population for Dose 3: The participants who received 3 doses of the study intervention (VLA15 or placebo) and had at least 1 day of reactogenicity data reported through the e-diary or AE CRF during the Dose 3 e-diary collection period. • E-diary safety population for Dose 4: The participants who received 4 doses of the study intervention (VLA15 or placebo) and had at least 1 day of reactogenicity data reported through the e-diary or AE CRF during the Dose 4 e-diary collection period.

If a participant received a vaccine dose not as randomized, the safety analysis set will be based on the vaccine actually received. Participants are assigned to the VLA15 group if they received at least 1 dose of VLA15; participants are assigned to the placebo group if they received only placebo throughout the study.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis as this is a descriptive safety study. The estimands corresponding to the primary safety objective are described in Section 2.2.

5.2. General Methods

Unless otherwise stated, "vaccine group" in this section refers to the study intervention (ie, VLA15, placebo) group; "CI" refers to the 2-sided (1 - alpha) × 100% CI in this document.

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 difference in percentages, may also be presented, where appropriate.

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

The subsections below describe the analyses for different endpoints.

5.2.1. Analyses for Safety Endpoints

In general, safety endpoints are binary variables. 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 difference in percentages, may also be presented, where appropriate:

- The 95% CI for the proportion (within study intervention group) will be constructed by the Clopper-Pearson method described by Newcombe.[1] The 95% CI will be presented in terms of percentage.

- The 95% CI for the difference in the proportions (between study intervention groups) will be computed using the Miettinen and Nurminen method.[2] The 95% CI will be presented in terms of percentage.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in the safety rulebook summary.

Missing data handling rules on the safety data are described in detail in the corresponding endpoint sections.

5.3.1.1. Reactogenicity Data

For the derived variables based on reactogenicity e-diary data, if any day of the 7-day e-diary is available, the "any day (Day 1 through Day 7)" data will be considered as nonmissing.

The reactogenicity data are collected in the e-diary, which does not allow participants to skip any questions. Therefore, for a specific day, if the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are nonmissing.

In general, any participant with all 7 days of reactogenicity data missing from the e-diary and AE CRF will not be included in the analysis (ie, assuming MCAR). If only Days 1 through 6 of the 7 days of e-diary data are transferred, it is expected that these reactogenicity events would be queried by the investigator for the missing e-diary days and entered in the AE CRF if any reactogenicity was not reported in the e-diary due to missed days; therefore, the primary analysis will use the reactogenicity recorded in the AE CRF to impute the partially missing e-diary data to estimate the reactogenicity rate during the e-diary collection period. The AE CRF is designed as a log, which means only events that were observed by the participant will be recorded, and events that were not observed will not be recorded. Therefore, after applying the AE CRF data, imputing the remaining e-diary missing days as "no" for the primary analysis is reasonable. However, data for the missing day(s) will not be imputed in the analysis of each specific day.

A sensitivity analysis will be planned for completers. Only participants with all 7 days of e-diary data transferred will be included in this sensitivity analysis.

5.3.2. Analyses for Continuous Data

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

The CI for the mean of the continuous variables will be constructed by the standard method based on the Student t distribution.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Local Reactions and Systemic Events

Analyses of reactogenicity endpoints are based on the set of participants with any reactogenicity data reported after vaccination. As the participants will receive multiple doses of vaccine, the safety analysis will be summarized by vaccine group (as received) after each dose and after any dose. Participants will be summarized by vaccine group according to the study interventions they actually received within each age group (5 through 11 and 12 through 17 years).

6.1.1.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.1).
- Analysis set: E-diary safety population (Section 4).
- Intercurrent events and missing data: All data collected are included. Partially missing e-diary data are imputed from the AE CRF as "no" (Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.

- Analysis methodology: Calculation of the 95% CI of the proportion of participants reporting each event using the Clopper-Pearson method (Section 5.2.1).
- Analysis timing: At the end of the study.
- Descriptive statistics including the proportion (%) and the numerator (n) and the denominator (N) used in the proportion calculation, and 95% CI for percentage using the Clopper-Pearson method, will be presented after each dose and after any dose for each vaccine group, for each age group and for the combined age groups. Data reported from Day 1 through Day 7 after each and any vaccination will be presented by maximum severity and any severity.
- Bar charts with the proportions of participants for each and any local reactions and each and any systemic events, within 7 days after any dose, will be plotted for each vaccine group by age group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Supplementary Analysis

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.1.1 and Section 3.1.1.2, will be summarized as supplementary analyses with the same analysis population:

- Duration (days) of each local reaction and each systemic event after each dose and any dose.
- Onset day of each local reaction and each systemic event after each dose and any dose.

6.1.1.3. Sensitivity Analysis of Reactogenicity

- Maximum severity of reactogenicity is assessed for participants with all 7 days of e-diary data transmitted.

6.1.2. AEs, NDCMCs, and SAEs

Participants will be summarized by vaccine group according to the study interventions they actually received. As the participants will have received multiple doses, the safety analysis will be summarized by vaccine group after each dose, and after any dose. All AEs after informed consent and prior to the first vaccination will not be included in the analyses but will be listed.

6.1.2.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1.1).
- Analysis set: Safety population (Section 4).

- Intercurrent events and missing data: All data collected are included.
- Analysis methodology: Calculation of the 95% CI of the proportion of participants reporting those events will use the Clopper-Pearson method (Section 5.2.1).
- Descriptive statistics including the proportion (%) and the numerator (n) and the denominator (N) used in the proportion calculation, and 95% CI for percentage using the Clopper-Pearson method, will be presented for each vaccine group. Data will be summarized by age group separately (5 through 11 and 12 through 17 years), as well as for the overall study population.
- The main analysis will be based on AEs and will exclude the reactogenicity events that were reported in the AE CRF (except for SAEs) (Section 3.1.1.3).

6.1.2.2. Supplementary Analysis

To support the assessment of AEs, the endpoints below, as specified in Section 3.1.1.3, will be summarized with the same analysis population using the same presentation as specified in the main analysis.

6.2. Secondary Endpoints

No secondary endpoint is defined in this study.

6.3. Subset Analyses

All safety data will be summarized by age group (5 through 11 and 12 through 17 years) and overall.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

For each vaccine group, descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, and ethnicity) will be generated, as well as for all participants, based on the safety population.

Summary data may also be presented for additional analysis populations.

Participant demography and baseline characteristics data will also be listed.

For medical history, all data reported across all participant IDs will be included in the analysis.

6.4.2. Study Conduct and Participant Disposition

The number and proportion of participants enrolled, randomized, and vaccinated at each dose will be included in the participant disposition summary. In addition, participants who received each dose, completed the study, and who were withdrawn after each dose and any dose, along with the reasons for withdrawal, will be tabulated by vaccine group and for all participants included in the randomized population. The reasons for withdrawal will be those specified in the database.

The e-diary completion rate will be summarized for the safety population by vaccine group, as well as summarized for the categorized days specified in Section 3.4.1.

Standard listings will be generated, including, but not limited to, participants who withdraw during the study, participants who are excluded from the analysis populations, participants with major protocol violations, and participants who do not receive the vaccine as randomized.

6.4.3. Nonstudy Vaccines and Concomitant Medications

Nonstudy vaccines recorded after signing the informed consent through the end of the study will be categorized according to the WHODrug Dictionary, and may be summarized by vaccine group and for all participants included in the safety population.

Concomitant medications for treatment of AEs (including LD) recorded in the database will be displayed according to the WHODrug Dictionary and will be descriptively listed by vaccine group and for all participants in the safety population.

6.5. Other Summaries and Analyses

6.5.1. Adverse Events

For all of the AEs categorized in Section 3.1.1.3, each individual AE will be categorized by MedDRA and descriptively summarized by vaccine group.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers (Section 3.5.1). For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the active vaccine and placebo groups in the percentage of participants reporting the events, based on the Miettinen and Nurminen method, will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups 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. AE displays will be sorted in descending order of point estimates of risk difference within each SOC. There are no Tier 1 events identified for this vaccine as of now.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

7. INTERIM ANALYSES

No interim analysis is planned. Data will be summarized after the last visit of the last participant.

8. REFERENCES

1. Newcombe RG. Two-sided intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
CBER	Center for Biologics Evaluation and Research (United States)
CI	confidence interval
CRF	case report form
e-diary	electronic diary
FDA	Food and Drug Administration (United States)
ICD	informed consent document
ICD-10	International Classification of Diseases, 10th Revision
ID	identification
IRT	interactive response technology
LD	Lyme disease
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
OspA	outer surface protein A
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
US	United States
VLA15	6-valent OspA-based Lyme disease vaccine
WHO	World Health Organization

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