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Statistical Analysis Plan

D85 / D236 Interim Analysis

IMMUNOGENICITY AND SAFETY STUDY OF VLA15, A MULTIVALENT RECOMBINANT OSPA BASED VACCINE CANDIDATE AGAINST LYME BORRELIOSIS, IN HEALTHY ADULTS AGED 18 TO 65 YEARS – A RANDOMIZED, CONTROLLED, OBSERVER-BLIND PHASE 2 STUDY.

Protocol: VLA15-201

Confidential

Sponsor: Valneva Austria GmbH

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Approval

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List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
Alum	Al(OH)3, Aluminum Hydroxide
Bb s.l.	Borrelia burgdorferi sensu lato
DSMB	Data Safety Monitoring Board
ELISA	Enzyme-Linked Immunosorbent Assay
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
I.M.	Intramuscular
IA	Interim Analysis
IgG	Immunoglobulin G
MedDRA	Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
OspA	Outer surface protein A
PBS	Phosphate Buffered Saline
PP	Per-protocol
SAE	Serious Adverse Event
SBA	Serum Bactericidal Assay
SCR	Seroconversion Rate
SOP	Standard Operating Procedure
ST	Serotype
TLF	Table, Listing and Figures
WHO	World Health Organization

1. OVERVIEW

1.1 Study Objectives

1.1.1 Primary Objective

- To determine the optimal dose of VLA15 in healthy adults aged 18 - 65 years up to Day 85.

1.1.2 Secondary Objectives

Immunogenicity:

- To assess the immune response of VLA15 in healthy adults aged 18 – 65 years up to Month 12 (i.e. 10 months after the primary vaccination series).

Safety:

- To assess the safety profile of VLA15 in healthy adults aged 18 – 65 years up to Month 12.

1.2 Study Design

This is a randomized, observer-blind (subject, sponsor and investigator/ site staff involved in clinical evaluation of subjects are blinded), placebo controlled, multicenter Phase 2 study (see Figure 1).

In the Run-in phase, a total of 120 subjects aged 18 to 40 years were to be randomized stratified by study site 1:1:1:1 to receive VLA15 90 µg w/ alum, VLA15 135 µg w/ alum, VLA15 180 µg w/ alum, or placebo (30 subjects per treatment group) as intramuscular (I.M.) vaccinations on Days 1, 29 and 57. Dosing was to be adjusted by injection volume (see Table 1).

Table 1: Treatment Groups and Vaccinations

Group	Treatment	Injection Volume [mL]	Days of Vaccination
90 µg	VLA15 90 µg w/ alum	0.50	1, 29, 57
135 µg	VLA15 135 µg w/ alum	0.75	1, 29, 57
180 µg	VLA15 180 µg w/ alum	1.00	1, 29, 57
Placebo	PBS	1.00	1, 29, 57

Two safety visits were to be performed after the first vaccination: a safety phone call at Day 4 (i.e. Visit 1a, three days after the first vaccination) and an in-person visit at Day 8 (i.e. Visit 1b, seven days after the first vaccination). After all subjects enrolled in the Run-in phase completed Visit 4 (Day 85, i.e. 28 days after the third vaccination) a Data Safety Monitoring Board (DSMB) reviewed all available safety data up to Day 85 in a scheduled DSMB meeting and gave the recommendation that all treatment groups were safe and well tolerated so far and could be continued in the Main Study phase based on available safety data. After the DSMB meeting, the two higher dose groups (135 µg and 180 µg of VLA15 w/ alum) were selected for further investigation. No safety concerns associated with any of the VLA15 treatment groups were identified by the independent DSMB.

In the Main Study phase, a total of 450 subjects aged 18 to 65 years will be randomized stratified by study site, age group and baseline *B.b.* s.l. serostatus 2:2:1 to receive 135 µg or 180 µg VLA15 w/ alum (180 subjects each) or placebo (90 subjects), as I.M. vaccinations on Days 1, 29 and 57. Subjects will be enrolled in two age groups (18-49 years and 50-65 years) in a ratio of approximately 2:1.

In both study phases, target is to enroll approximately 10 % or more of subjects that are baseline seropositive for *Borrelia burgdorferi sensu latu* (*Bb s.l.*). This is aimed to be achieved through selection of endemic recruitment areas as well as database searches for *Bb s.l.* seropositive subjects.

1.3 Endpoints

1.3.1 Primary Endpoint

- Geometric Mean Titers (GMTs) for Immunoglobulin G (IgG) against each Outer surface protein A (OspA) serotype ST1 to ST6, determined by Enzyme-Linked Immunosorbent Assay (ELISA) at Day 85.

1.3.2 Secondary Endpoints

Immunogenicity:

- GMTs for IgG against each OspA serotype (ST1 to ST6), determined by ELISA, at Day 1, 29, 57, 180, 236, and Month 12;
- Seroconversion rates (SCRs) for each OspA serotype specific IgG (ST1 to ST6), determined by ELISA, at Day 29, 57, 85, 180, 236, and Month 12;
- Geometric Mean Fold Rise (GMFR) as compared to baseline for IgG against each OspA serotype (ST1 to ST6), determined by ELISA, at Day 29, 57, 85, 180, 236 and Month 12;
- GMTs, SCRs and GMFRs for IgG against each OspA serotype (ST1 to ST6), determined by ELISA, at Day 1, 29, 57, 85, 180, 236, and Month 12, stratified by age group.

Safety:

- Frequency of Serious Adverse Events (SAEs) during the entire study;
- Frequency of related SAEs during the entire study;
- Frequency of Adverse Events of Special Interests (AESIs) during the entire study;
- Frequency of related AESIs during the entire study;
- Frequency of unsolicited Adverse Events (AEs) during the entire study (incl. clinically relevant laboratory parameters);
- Frequency of related unsolicited AEs during the entire study (incl. clinically relevant laboratory parameters);
- Frequency of solicited local and solicited systemic AEs within 7 days after each and after any vaccination.
- Frequency of SAEs, AESIs, solicited and unsolicited AEs during the entire study stratified by age group.

1.4 Sample Size Calculation

The sample size for the Run-in phase has been chosen to allow detection of common AEs with the three initial dose levels. 30 Subjects will provide 95 % confidence that an AE not seen in the Run-in phase would have a true incidence of below 10 %.

The overall group size for the two doses (VLA15 w/ alum 135 µg and VLA15 w/ alum 180 µg) evaluated in the Main Study phase has been selected to provide a sufficient safety database and for determining the optimal dose before advancing the vaccine candidate into Phase 3. Upon completion of the study, the total number of subjects exposed to the dose used for Phase 3 trials would be a minimum of approximately N=210. The database would thus allow 95 % confidence that a given reaction would not be observed at a higher rate than 1:(210/3) rate, i.e. 1.4 %, if it is not observed in the trials preceding Phase 3.

With respect to the primary endpoint, GMTs for ST1-6 specific IgGs on Day 85: In the absence of an established protective titer, sample size calculation is based on somewhat arbitrary differences in GMTs between VLA15 treatment groups, in order to demonstrate which titer levels could be distinguished with the proposed sample size. Titers observed in Phase 1 were used as basis: In the 90 µg w/ alum group (i.e. the lowest dose group used in the present Phase 2 study), a GMT of 61.3 was observed for ST1 (i.e. the serotype with lowest titers in Phase 1) with a Standard Deviation (LOG10) of 0.51. A total of 189 subjects per group (assuming 10 % of the 210 subjects per treatment group are excluded from primary Per-protocol (PP) analysis) will provide 80 % power at a two-sided alpha level of 5 % to distinguish a GMT of 61.3 in one treatment group from a putative higher GMT of 86.1 in another dose group. An approximately 1.5 fold higher titer could thus be distinguished. A 1.5 fold difference in GMTs is often considered a relevant difference in vaccine studies, e.g. when setting non-inferiority boundaries.

The overall sample size of 120 subjects in the placebo group has been selected to allow for the internal validation of both safety and immunogenicity results.

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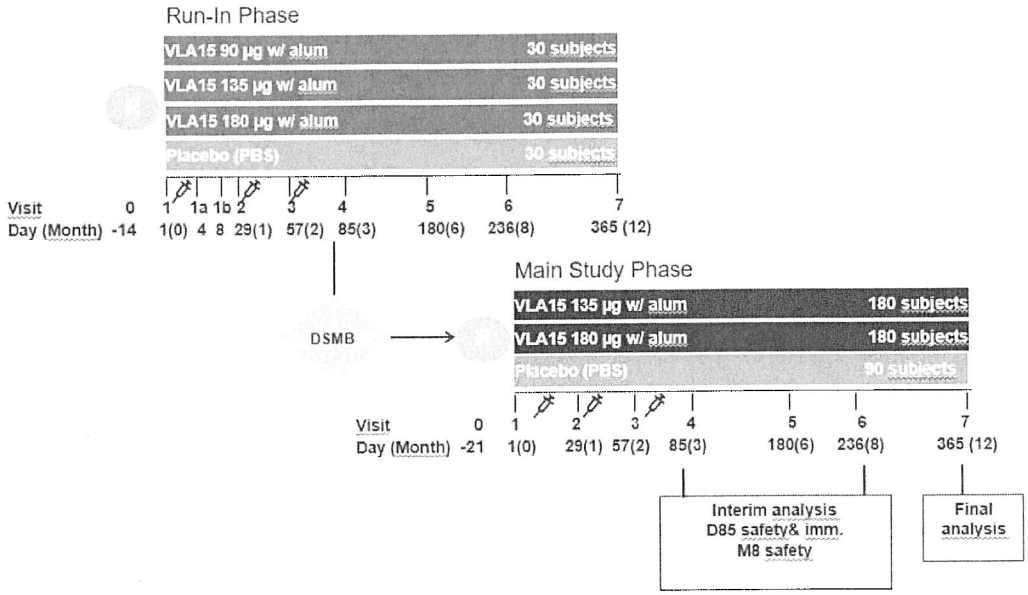
1.5 Flowchart

1.5.1 Study Design

Figure 1: Study Design



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1.5.2 *Study Schedule*

Table 2: Table of Events – Run-in-Phase

Visit	V0	V1	V2	V3	V4	V5	V6	V7	Early Termination (1)
Timing Day (D) Month (M)	D-21	D1	D29 M1	D57 M2	D85 M3	D180 M6	D236 M8	D365 M12	before V7
Time windows	-21 to -1	0	+/- 4	+/- 4	+/- 4	+ 7/- 14	+ 7/ - 14	+/- 14	n/a
Visit type	In-person	In-person	In-person	In-person	In-person	In-person	In-person	In-person	In-person
Informed consent (2)	X								
Inclusion/exclusion criteria	X	X (Review)							
Vaccination delay criteria		X	X	X					
Demographic data	X								
Medical history incl. vaccinations	X	X (3)							
Concomitant medications/ treatments incl. vaccinations	X	X	X	X	X	X	X	X	X
Physical examination (4), ECG	X								
Vital signs (5)	X	X	X	X					
Evaluation of oral body temperature	X	X (6)	X (6)	X (6)					
HIV test [3.5 mL] (7)	X (26)								
Bb s.l. screening test [4mL] (8)	X (26)							X	X
Baseline serology Sample [5.0 mL] (9)	X (26)								
Serum Pregnancy test [3.5 mL] (10)	X (26)								
Urine Pregnancy test (10)		X (11)	X (11)	X (11)	X	X	X	X	X
Clinical chemistry [8.5 mL] (12)	X (26)		X (11)	X (11)	X			X	
Hematology [4 mL] (13)	X (26)		X (11)	X (11)	X			X	
Coagulation blood sample [4.5 mL] (14)	X (26)								
Urinalysis (15)	X		X (11)	X (11)	X			X	
Immunogenicity blood sample. (16)		X (11) [54 mL]	X (11) [27 mL]	X (11) [54 mL]	X [54 mL]	X [27 mL]	X [27 mL]	X [54 mL]	
Randomization (17)		X							
VACCINATION (18)		X	X	X					
Check for AEs following vaccination		X	X	X					
Symptom-driven physical exam (19)		X (20)	X (20)	X (20)	X	X	X	X	X
Inspection of injection site of previous vaccinations			X (21)	X (21)	X				X
Distribute and explain Subject Diary (22)		X	X	X					
Review and collect Subject Diary			X	X	X				X (23)
Distribute and explain Memory Aid					X	X	X		
Review and collect Memory Aid						X	X	X	X (23)
AE/ SAE/ AESI Assessment (24)		X	X	X	X	X	X	X	X
Blood Volume [mL]	33.0 (10); 29.5 (25)	54.0	39.5	66.5	66.5	27.0	27.0	70.5	4.0

[redacted]

Table 3: Table of Events – Main Study Phase

Visit	V0	V1	V2	V3	V4	V5	V6	V7	Early Termination (1)
Timing Day (D) Month (M)	D-21	D1	D29 M1	D57 M2	D85 M3	D180 M6	D236 M8	D365 M12	before V7
Time windows	-21 to -1	0	+/- 4	+/- 4	+/- 4	+ 7/- 14	+ 7/ - 14	+/- 14	n/a
Visit type	In-person	In-person	In-person	In-person	In-person	In-person	In-person	In-person	In-person
Informed consent (2)	X								
Inclusion/exclusion criteria	X	X (Review)							
Vaccination delay criteria		X	X	X					
Demographic data	X								
Medical history incl. vaccinations	X	X (3)							
Concomitant medications/ treatments incl. vaccinations	X	X	X	X	X	X	X	X	X
Physical examination (4), ECG	X								
Vital signs (5)	X	X	X	X					
Evaluation of oral body temperature	X	X (6)	X (6)	X (6)					
HIV test [3.5 mL] (7)	X (26)								
Bb s.l. screening test [4mL] (8)	X (26)							X	X
Baseline serology Sample [5.0 mL] (9)	X (26)								
Serum Pregnancy test [3.5 mL] (10)	X (26)								
Urine Pregnancy test (10)		X (11)	X (11)	X (11)	X	X	X	X	X
Clinical chemistry [8.5 mL] (12)	X (26)		X (11)	X (11)	X			X	
Hematology [4 mL] (13)	X (26)		X (11)	X (11)	X			X	
Coagulation blood sample [4.5 mL] (14)	X (26)								
Urinalysis (15)	X		X (11)	X (11)	X			X	
Immunogenicity blood sample, (16)		X (11) [54 mL]	X (11) [27 mL]	X (11) [54 mL]	X [54 mL]	X [27 mL]	X [27 mL]	X [54 mL]	
Randomization (17)		X							
VACCINATION (18)		X	X	X					
Check for AEs following vaccination		X	X	X					
Symptom-driven physical exam (19)		X (20)	X (20)	X (20)	X	X	X	X	X
Inspection of injection site of previous vaccinations			X (21)	X (21)	X				X
Distribute and explain Subject Diary (22)		X	X	X					
Review and collect Subject Diary			X	X	X				X (23)
Distribute and explain Memory Aid					X	X	X		
Review and collect Memory Aid						X	X	X	X (23)
AE/ SAE/ AESI Assessment (24)		X	X	X	X	X	X	X	X
Blood Volume [mL]	33.0 (10); 29.5 (25)	54.0	39.5	66.5	66.5	27.0	27.0	70.5	4.0

(1) Every effort should be made to have discontinued subjects complete the early termination visit. If the subject is unwilling to perform an ET visit, a phone-call should be made to follow-up on Adverse Events and Concomitant Medications/ Vaccinations. Note: If a subject presents at a regular study visit and informs that it will discontinue the study after this visit, the study visit will not be performed as an ET visit, but as a regular study visit including all events that are described for the respective study visit; but in addition, a Lyme borreliosis screening test will be performed.

(2) Occurs before screening and prior to any study-related procedures.

(3) Symptoms noted at Visit 1 (prior to first vaccination) are not considered AEs but will be recorded as medical history.
(4) Physical examination on the following body systems: general appearance, skin, head/ eyes /ears/ nose/ throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, and neurological system. If applicable, physical examination as well as ECG performed within the study VLA15-202 is acceptable for study VLA15-201 if within the specified visit window.
(5) Vital signs (Systolic and diastolic blood pressure and pulse rate while seated and at rest) to be measured prior to vaccination and in addition prior to discharge in case subject reports any complaints.
(6) To be performed prior to vaccination.
(7) The results of negative HIV tests that were performed up to 30 days before Visit 0 are acceptable (blood: HIV test 3.5 mL). Positive HIV test obtained by ELISA will have to be confirmed by a second method (e.g. Westernblot or PCR).
(8) A commercially available C6 ELISA assay (VlsE ELISA) will be performed (blood: 4 mL). Serum samples that are tested positive will have to be verified by a confirmatory immunoblot. Test results need to be available before randomization and remain valid for 4 weeks.
(9) A baseline serology sample will be taken at the screening visit and might be used for work-up of suspected LB-associated, autoimmune or neuroinflammatory events (e.g. analysis of Rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), etc, as appropriate), (blood: 5.0 mL). If applicable, a baseline serology sample collected at the study site within the study VLA15-202 is acceptable for study VLA15-201 if within the specified visit window.
(10) In women of childbearing potential. A woman is considered of childbearing potential if fertile, following menarche and until becoming post-menopausal unless permanently sterile. A woman that is considered of non-childbearing potential must be e.g. surgically sterilized for at least 3 months prior to Visit 1 (e.g. by hysterectomy, bilateral salpingectomy, bilateral oophorectomy, transcervical sterilization), or postmenopausal for at least one year prior to Visit 1. For serum pregnancy test: tests that were performed in study laboratory within visit window and where results are available at study visit are acceptable.
(11) At vaccination visits, all samples have to be obtained before vaccination. Pregnancy results and urinalysis must be available before vaccination.
(12) Creatinine, sodium, potassium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, CRP (blood: 8.5 mL). Test results of current visit do not need to be available before vaccination. Tests that were performed in study laboratory within visit window and where results are available at study visit are acceptable.
(13) Hemoglobin, hematocrit, erythrocyte count, white blood count, platelets (Ethylenediaminetetraacetic acid [EDTA] blood: 4 mL). Test results of current visit do not need to be available before vaccination. Tests that were performed in study laboratory within visit window and where results are available at study visit are acceptable.
(14) Prothrombin time, aPTT, fibrinogen (blood: 4.5 mL). Tests that were performed in study laboratory within visit window and where results are available at study visit are acceptable.
(15) Standard urine dipstick: pH, specific gravity, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, erythrocytes. Tests that were performed in study laboratory within visit window and where results are available at study visit are acceptable.
(16) Blood will be collected for immunogenicity testing by ELISA and for supportive functional antibody analysis by e.g. growth inhibition assay, surface binding assay or serum transfer experiments (passive protection animal model). *
(17) To be performed by study staff otherwise not involved with study conduct to keep the study observer-blinded (i.e. un-blinded study staff)
(18) Study vaccine has to be administered by study staff otherwise not involved with study conduct to keep the study observer-blinded. Subjects enrolled in the Run-in phase should be observed for at least one hour, subjects enrolled in the Main Study phase should be observed for at least 30 min after vaccination for treatment of any immediate reactions.
(19) Except for Visit 1: Body systems for which the subject reports any symptoms should be evaluated and relevant abnormal findings documented as AEs. At vaccination days the symptom-driven physical exam is to be performed before administration of the vaccination.
(20) If subject has any complaints after vaccination, a second symptom-driven physical examination will be performed by the investigator prior to discharge.
(21) The injection site of previous injections should be evaluated by study staff prior to the next vaccination.
(22) At Visit 1, the subjects will be provided with thermometer and measuring tapes. The subjects will assess solicited local and systemic AEs themselves over a period of seven consecutive days after each vaccination.
(23) Unreturned Subject Diaries/ Memory Aids should be collected at the Early Termination Visit. For Early Terminations prior to Visit 4, the previous injection site should be inspected.
(24) AEs, SAEs and AESIs will be collected throughout study conduct. Symptoms noted at Visit 1 (prior to vaccination) are not considered adverse events but will be recorded as medical history.
(25) Women of non-childbearing potential and male subjects.
(26) If applicable, HIV test, Lyme borreliosis screening test, serum pregnancy test, clinical chemistry tests, hematology tests, and coagulation tests performed at the study site within the study VLA15-202 are acceptable for study VLA15-201 if within the specified visit window. As such, if test results are available, respective blood samples do not need to be collected again for the present study. Similar, if applicable, a baseline serology sample collected at the study site within the study VLA15-202 is acceptable for study VLA15-201 if within the specified visit window.

* Functional antibody analysis will be provided using a serum bactericidal assay.

2. GENERAL CONSIDERATIONS

2.1 Conduct of Analysis

An interim analysis (IA) on safety and immunogenicity data will be conducted in two parts after the last subject completed Visit 6 (i.e. Day 236). The first part (IA Day 85) will be performed after safety data up to Day 85 have been cleaned and immunogenicity samples of Day 1 and 85 have been analyzed. The first part (IA Day 85) will cover safety data up to Visit 4 (Day 85) and ELISA immunogenicity data from Visit 1 (Day 1) and Visit 4 (Day 85). The second part (IA Day 236) will cover safety data up to Visit 6 (Day 236, i.e. six months after the last vaccination).

Data from selected dose groups in the Main Study and data from respective dose groups from the Run-in phase will be pooled for this and all further analyses.

A preliminary immunogenicity analysis was done prior to the IA D 85 as described above. This analysis was described in a separate analysis plan and covered descriptive immunogenicity analysis of selected time points of subjects from the run-in phase only.

A final data analysis will be conducted once the last subject has completed the study, i.e. Visit 7 (Month 12). As part of this analysis, Serum Bactericidal Assay (SBA) results will be analyzed. Those results will only be available for a subset of subjects, that was randomly chosen from the set of subjects from the main phase who have both a Day 1 and Day 85 immunogenicity blood sample.

It is indicated in Section 7, which Tables, Listings and Figures (TLFs) are provided for IA D85 and IA D236.

2.2 Statistical Software and Quality Control

All statistical analyses will be performed using SAS® version 9.3 or higher. Tables, figures and data listings will be generated in Microsoft® Word® as well as PDF® format.

Quality control of SAS® programs will include a review of the whole process of result generation:

- Review of all analysis SAS® programs
- Review of SAS® log for errors, warnings and other notes that could indicate mistakes in the programs
- Review of all tables, listings and figures for completeness and correctness

As additional quality control measure, independent re-programming will be performed as described in SOP SAS04.

2.3 Applicable Standard Operating Procedures

The applicable Standard Operating Procedures (SOPs) of [redacted] or this study are:

STAT01 Statistical Analysis File

STAT03 Statistical Analysis Plan

STAT04 Interim Analysis

[redacted]

STAT05	Randomization and Unblinding
STAT06	Data Review Meeting
STAT07	Report Writing
SAS01	SAS General Principles
SAS04	Handling of Statistical Analyses
SAS06	CDISC- ADaM
SAS07	CDISC - Quality Control

2.4 Blinding and Randomization

Subjects will be allocated to treatment groups via the EDC system. Eligible subjects will be randomized stratified by study site 1:1:1:1 in the Run-in Phase and stratified by study site, age group and baseline *B.b.* s.l. serostatus 2:2:1 in the Main Study Phase according to a randomization list created by a statistician. The study will be an observer-blinded trial, which will be conducted in a blinded manner for the study investigators, the sponsor including laboratory personnel, and the subjects. Only designated study staff who randomize subjects into treatment groups and perform preparation and application of the vaccinations will be unblinded. These unblinded study staff members will not be involved with trial conduct otherwise. An overview of persons who will be unblinded is provided below:

Unblinded:

- Designated study site staff who randomize subjects to treatment groups and are concerned with IMP handling (i.e. perform preparation and application of the study vaccine, maintain drug dispensing log detailing the dates and quantities of IMP administered to each subject). These unblinded study staff members will not be involved with trial conduct otherwise.
- CRAs responsible for monitoring of IMP handling and related data for verifying drug accountability during the study and performing overall drug accountability.
- Statistical team at the CRO performing statistical analyses for generation of safety data tables for the DSMB.
- DSMB members.

Blinded:

- Study participants
- Investigators and other study staff involved in general study conduct and safety assessments.
- All other CRAs (responsible for monitoring study data apart from IMP handling/drug accountability).
- All other sponsor and CRO staff including laboratory personnel at the sponsor's labs for immunogenicity assessments.

General unblinding of sponsor staff and ADMB will be done for the IA Day 85 after confirmation that all subjects performed Visit 6 or, in case of missing V6 visits, after the close of the time window for Visit 6. Interim analyses results will be distributed to selected sponsor representatives.

2.5 Descriptive Analyses

In general, descriptive analyses of continuous variables (summary statistics) will be described with the number of non-missing observations, arithmetic mean, standard deviation (±SD), median, quartiles (Q1 and Q3) and range (minimum and maximum).

Descriptive analyses of continuous immunogenicity variables (i.e. tables for the GMT and GMFR) will be described with the number of non-missing observations, geometric mean, confidence intervals for the geometric mean, standard deviation of logarithmic values, median, quartiles (Q1 and Q3) and range (minimum and maximum).

Categorical variables (frequency statistics) will be described with the number of non-missing observations and percentages (%). Percentages will be calculated on the total number of non-missing observations, if not stated otherwise.

2.6 Center and Country Effect and Stratification Variables

The center and region effect will be taken into account and estimated by adding study site and region, respectively in ANOVA models. Also other covariates will be used as described in Section 5.3.
Furthermore, selected tables will be presented per study site/region and by other stratification factors. A separate column in the List of Tables (Section 7) defines which tables will be stratified by study site, region (Europe vs. United States), *B.b. s.l.* serostatus at Visit 0, and by age group as marked in Section 7.

2.7 Handling Missing Data

Generally, missing values of immunogenicity variables will not be imputed, and the analyses will be limited to observed values. For missing data in AE evaluation (e.g. missing information if serious, medically attended, about severity or causality) a worst case approach will be applied. In case of missing assignment to solicited or unsolicited, this AE will neither be counted in tables for solicited AEs nor in tables for unsolicited AEs but in tables for all AEs.

2.8 Protocol Deviations

Protocol deviations will be reviewed in the Blind Data Review Meeting (BDRM) prior to interim analysis of D85. Deviations will be classified as minor or major deviations, based on the potential influence on the immunogenicity analysis.

Major protocol violations that lead to exclusion of a subject from the PP Population (see Section 2.10.3) will include but are not limited to the following:

- Subjects who received less than three vaccinations
- Subjects who received wrong vaccinations

- Subjects with substantial time window violations on vaccination visits (Visits 2 and 3)
  - Visit 2 (Day 29): +/- 7 days
  - Visit 3 (Day 57): +/- 10 days
- Subjects who fulfil exclusion criteria 2, 8, 9 and 14
- Subjects with other deviations that may affect immune response

Protocol deviation classification will be made on a case by case decision.

2.9 Exclusion of Time Points in the Per-Protocol Analysis

In the PP analysis immunogenicity samples that are outside the predefined time windows described below will be excluded at the respective visit (exclusion of subjects from the PP Population is described in Section 2.8):

- Visit 2 (Day 29): +/- 7 days
- Visit 3 (Day 57): +/- 10 days
- Visit 4 (Day 85): +/- 10 days
- Visit 5 (Day 180): +/- 14 days
- Visit 6 (Day 236): +/- 21 days
- Visit 7 (Day 365): +/- 28 days

2.10 Analysis Populations

2.10.1 Safety Population

The Safety Population includes all subjects who entered into the study and received at least one vaccination. The Safety Population will be used for all safety analyses as well as demographic data. All analyses based on the Safety Population will be carried out using the actual treatment received. Subjects with vaccination errors will be allocated to a treatment group for safety analyses after a case-by-case review in the BDRM; applying the following general rules:

- If a subject received different VLA15 doses at different visits, the minimum dose received will decide the treatment group of the subject for safety analysis;
- If a subject received both VLA15 and placebo, the subject will be analyzed in a VLA15 group (dose decided by the first rule)

2.10.2 Modified Intent-to-Treat (mITT) Population

The mITT population is defined to include all subjects enrolled who received at least one vaccination. Subjects will be analyzed according to the treatment group they had been allocated to, rather than by the actual treatment, they received.

If the Safety and mITT Population are identical (i.e. no mis-randomization) the analysis will be performed for the Safety Population and the mITT Population together, labeled with "Safety/mITT Population".

2.10.3 Per-Protocol (PP) Population

The Per-Protocol (PP) Population will exclude all subjects from the mITT that fulfilled at least one of the major protocol deviation criteria as defined in in Section 2.8. The PP Population will be defined in the BDRM that is conducted before IA Day 85. A second DRM is planned prior to the final analysis to review protocol deviations after the interim analysis.

2.11 Subject Data Listings

All vaccinated subjects will be included in the listings if not stated otherwise. Data listings will include the subject number as identifier (and parameter and/or visit if available) and will be sorted by subject ID (and parameter and/or visit if available). A column showing the treatment group will be shown in all listings. Additionally, a column indicating if a subject is in the PP Population will be shown in all immunogenicity listings.

2.12 Columns in Tables

All tables will be presented by treatment group, i.e. every treatment group will be shown in a separate column. Tables described at overall study information (Section 3),baseline evaluation (Section 4) and safety analysis (Section 6) will show one column per treatment group (i.e. 90 µg, 135 µg, 180 µg and Placebo) a column for the three VLA15 treatment groups pooled and a column for all subjects pooled. Tables defined in Section 5 will show one column for each treatment group. Statistical analyses will pool subjects from both Run-in and Main Study phase.

2.13 Medical Coding

Adverse events, medical history and concomitant procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and concomitant medications and vaccination history will be coded using WHO Drug Reference List and Anatomical Therapeutic Chemical (ATC) Classification System as described in the Coding Guideline.

Events reported in the adverse events log will be combined with solicited symptoms from the diary section. Solicited symptoms will be coded as described in Section 6.1.2.2.

2.14 Changes in the Conduct of the Study or Planned Analysis

Statistical analysis will be conducted as described in this SAP. Any deviations or changes will be described and justified in the CSR.

- It was stated in the protocol that an interim analysis on safety and immunogenicity data will be performed after all subjects have completed Visit 6 (i.e. Day 236, six months after the last vaccination) an that this interim analysis will cover safety and immunogenicity data up to Visit 4 as well as safety data up to Visit 6). This interim analysis will be conducted in 2 parts, a IA Day 85 covering all safety data up to Day 85 and immunogenicity data from Day 1 and Day 85. The second part will cover all safety data up to Day 236 (see Section 2.1). The first part of the Interim Analysis only starts after the last subject completed Visit 6 or the time window for Visit 6 has elapsed.

- The following adjustments concerning statistical analysis as compared to descriptions in the protocol are included in this SAP: The protocol planned to only compare the two dose groups selected for the main phase and the placebo group. However, it was decided to include all dose groups in the comparison. In particular, the pair-wise comparison between the two dose groups selected for the main phase and the placebo group, respectively, will be part of the comparisons that will be performed.
- It was stated in the protocol that all time points up to Day 85 will be included in interim immunogenicity analysis. However, only Day 1 and Day 85 will be analyzed in the IA Day 85. All time points will be analyzed in the Final Analysis.
- Due to optimization of the ELISA assay, the definition for seroconversion for ELISA results was adjusted as compared to the protocol, see Section 5.2.
- Functionality of antibodies will be measured by a Serum Bactericidal Assay (SBA). Analysis of SBA parameters will be described in a separate SAP and is not part of the interim analysis described here.

2.15 Effect of COVID19 on the Interim Analysis

Possible impact of Covid-19 pandemic and respective measures were discussed and it was decided to not implement specific analysis measures for the interim analyses. Subject visits and time points analyzed in the IA D85 were completed before the pandemic started in the respective regions. IA D236 will be partly affected by the pandemic.

In particular, phone calls instead of on-site visits for time points after D85 were allowed and safety data for IA D236 are collected via phone call for a portion of the subjects. For IA Day 236, it will be tabulated and listed whether Visits were performed as a phone call (due to Covid-19) or on site.

The impact and analysis of availability of immunogenicity data and respective impact on trial results will be described in the SAP for Final Analysis.

In general, overviews on missing data, protocol deviations, missed visits, visits out of time-window and changes in study processes due to Covid-19 will be planned in the SAP for final analysis and described in the Final Clinical Study Report.

3. OVERALL STUDY INFORMATION

Analyses will be performed for the Safety Population, mITT Population and PP Population. If the Safety and mITT Populations are identical, the analysis will be performed for the Safety Population and the mITT Population together, labeled "Safety/mITT Population".

3.1 Data Points

The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings:

- Subject overview (Analysis populations, countries)
- Screening failures and reasons
- Randomization
- Violated inclusion/exclusion criteria (will only be listed)
- Study vaccination details
- Visits log
- Attendance status and early termination details
- Protocol deviations
- Visits performed as phone call due to Covid-19 (only applicable for IA D236)

3.2 Definition

- Screening failures are defined as subjects not eligible for study enrolment.

4. BASELINE EVALUATION

Baseline data will be presented for the Safety, mITT and PP Population. If the Safety and mITT Population are identical (i.e. no mis-randomization) the analysis will be performed for the Safety Population and the mITT Population together, labeled with "Safety/mITT Population".

4.1 Data Points

The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings:

- Demographic Information (gender, childbearing potential, age [years], race, body height [cm], body weight [kg] and body mass index [kg/m^2])
- Physical examination (will only be listed)
- ECG
- Vaccination history
- Medical History
- Prior/Concomitant Medications
- Prior/Concomitant Procedures
- HIV (will only be listed)

4.2 Definitions

- Baseline for non-immunogenicity analyses is defined as Visit 0.
- Body height will be analyzed in centimeters (cm). Body height documented in inch (in) will be converted to cm using the following rule: height [cm] = height [in] × 2.54.
- Body weight will be analyzed in kg. Body weight documented in pounds (lbs) will be converted to kilogram [kg] using the following rule: weight [kg] = weight [lbs] × 0.45359237

- The Body Mass Index [kg/m^2] will be calculated as (kg/cm^2) × 10,000
- Medications stopped prior (<) to Day 1 (Visit 1) will be considered prior medications, all other medications are considered to be concomitant. Medications with a missing or incomplete end date where it cannot clearly be decided if the end date was before or after Day 1 (Visit 1) will be considered concomitant.
- Procedures stopped prior (<) to Day 1 (Visit 1) will be considered prior procedures, all other procedures are considered to be concomitant. Procedures with a missing or incomplete stop date where it cannot clearly be decided if the stop date was before or after Day 1 (Visit 1) will be considered concomitant.
- Medical history not stopped prior (<) to informed consent will be considered ongoing at study entry, Entries with a missing or incomplete stop date where it cannot clearly be decided if the stop date was before or after informed consent will be considered ongoing at study entry.

5. IMMUNOGENICITY ANALYSIS

All tables and figures will be provided for the PP Population. Specific tables and figures will be repeated for the mITT Population and will also be repeated stratified by baseline *B.b.* s.l. serostatus, region and by age group as marked in the list of TLFs in Section 7. Listings will include all subjects from the mITT Population. IA D85 will cover time points Day 1 (Visit 1) and Day 85 (Visit 4). No immunogenicity analysis will be performed for IA Day 236.

5.1 Data Points

5.1.1 Tables and Listings

The following ELISA information will be analyzed and corresponding details on subject level will be provided in data listings:

Summary tables for categorical immunogenicity variables:

- Immunogenicity blood sample availability by time point
- Immunogenicity results/serostatus (report concentration/negative) by OspA serotype by time point (including baseline serology status)
- Subjects by OspA IgG serostatus at baseline
- SCRs for OspA serotype specific IgG by visit
    - each OspA serotype (separate tables for ST1 to ST6)
    - all six OspA serotypes combined
    - ST1 and ST2 combined
- Subjects Reaching an at least 4-fold or a 10- Fold Increase from Day 1 (Visit 1) in OspA-specific IgG Titer by visit
    - each OspA serotype (separate tables for ST1 to ST6)

Summary tables for continuous immunogenicity variables will be provided:

- GMTs for IgG against each OspA serotype (ST1 to ST6) by visit (separate table for each OspA serotype).

- GMFRs as compared to Visit 1 (Day 1) for IgG against each OspA serotype by visit (separate tables for each OspA serotype)

Correlation Analysis:

- Correlation Analyses for each OspA Specific IgG titer with each other OspA Specific IgG titer, respectively, at Day 85 (15 comparisons in total)

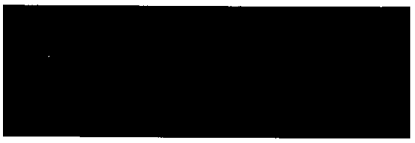
Inferential analysis will be performed as described in Section 5.3. Details are specified in Section 7.

5.1.2 Figures

- Bar charts: OspA-specific IgG antibodies (GMT) including standard deviation vs OspA serotypes by treatment group for each time point separately (y-axis: GMT; x-axis: OspA STs per treatment groups)
- Bar charts Seroconversion Rate:
    - Seroconversion Rate by OspA serotype and treatment group (for each time point separately, y-axis: percentage of subjects, x-axis: OspA STs per treatment groups)
    - Seroconversion Rate for all OspA serotypes combined over time vs. treatment group (y axis: percentage of subjects, x axis: visits per treatment groups)
    - Seroconversion Rate for OspA serotypes ST1 and ST2 combined over time vs. treatment group(y axis: percentage of subjects, x axis: visits per treatment groups)
- Line charts (y-axis: GMT, x-axis: study days): OspA- specific IgG antibodies (GMT) over time vs. treatment group for each ST1-6 separately
- Line charts (y-axis: GMT, x-axis: study days): OspA- specific IgG antibodies (GMT) over time vs. serotype for each treatment group separately
- For each OspA serotype and treatment group: Reverse cumulative distribution curves: percentage of subjects vs. OspA specific
- Scatter plots representing the correlation between OspA IgG antibody GMTs for each combination of two different OspA specific IgG serotypes for all treatment groups pooled.

5.2 Derivations and Definitions

- Baseline for immunogenicity analysis is defined as Visit 1.
- A subject reaches a 4-fold increase if the value at a certain visit after Day 1 is at least 4-times higher than the value at Day 1. 10-fold increase will be derived analogously.
- Baseline OspA IgG seropositive/seronegative for ELISA is defined as follows:
    - ELISA samples scored as "negative" or below the quantitation limit of the ELISA (40 U/mL) will be replaced by 20 U/mL.
    - Subjects with Day 1 (Visit 1) values below the quantitation limit of the ELISA (40 U/mL) and samples scored as "negative" (i.e. replaced by 20 U/mL) will be considered "baseline OspA IgG seronegative" for each serotype.



- Subjects with Day 1 (Visit 1) values of 40 U/mL and above are considered "baseline OspA IgG seropositive" for each serotype.
- Seroconversion is defined as:
    - For subjects that are seronegative at Visit 1 (baseline): a change from seronegative at Visit 1 to seropositive (i.e. antibody titer of ≥40) at a certain time point.
    - For subjects that are seropositive Visit 1 (baseline): a ≥ 4-fold rise in IgG antibody titer from Visit 1.
    - In case of missing values (missing at baseline or current time point), seroconversion is not calculated.

5.3 Inferential analysis

- In general, all statistical tests comparing treatment groups in the immunogenicity analysis will only include the two dose groups chosen for the main phase (i.e. VLA15 135 µg and 180 µg groups) and the placebo group. However, summary measures for 90 µg group will be included in the tables.
- ANOVAs with factors treatment group and study sites will be performed for the comparison between the VLA15 135 µg, 180 µg and Placebo group for each OspA ST1 to ST6 respectively. The primary immunogenicity analysis will be the ANOVA for ELISA GMTs at Day 85 in the PP Population.
- ANOVAs will be performed for GMTs as well as GMFRs at all available time points.
- This will be done using log10 transformed data and taking the anti-log of the resulting point estimates for the least squares means, least squares means differences and the corresponding 95% CIs. Tukey's HSD test will be applied for pair-wise comparisons.
- Sensitivity analyses for GMTs and GMFRs will be performed for ANOVAs with factors study site, treatment group, study site*treatment group, age, and *B.b.* s.l serostatus at baseline.
- Summary tables for the OspA- specific IgG titer against each OspA serotype and summary tables for the geometric mean fold-rise against each OspA serotype will be amended by an overall test (Kruskal-Wallis).
- SCRs will be compared using Fisher-Freeman-Halton tests, a significant overall test will be amended by pair-wise tests (Fisher's exact test). The same will be done for rates of subjects reaching a 4- or 10- fold Increase from Day 1 (Visit 1) in titer.
- A non-parametric correlation analysis (Spearman) between OspA IgG antibodies GMTs for each combination of two different OspA specific IgG types will be performed for Day 85 and VLA15 treatment group separately as well as for all VLA15 treatment groups together (pooled analysis).

6. SAFETY ANALYSIS

Safety Analysis will be performed for the Safety Population. Data from the unscheduled visits will only be listed but not tabulated.

6.1 Adverse Events

Solicited adverse events are documented in the subject diary. Serious solicited AEs are also reported in the Adverse Event Log. Unsolicited adverse events are documented in the AE log.

6.1.1 Data Points

The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings:

- Adverse Events Overview (solicited and unsolicited AEs)
- Adverse Events Overview (solicited and unsolicited AEs) stratified by age group, region and B.b. s.l. serostatus
- Serious Adverse Events (solicited and unsolicited) by SOC and PT
- Medically attended Adverse Events (solicited and unsolicited) by SOC and PT
- Adverse Events (solicited and unsolicited) leading to withdrawal from further vaccination by SOC and PT
- Adverse Events (solicited and unsolicited) leading to withdrawal from study by SOC and PT
- Non-Serious solicited or unsolicited AE by SOC and PT for PTs with Frequency >5% in any treatment group
- Non-Serious solicited or unsolicited AE by SOC and PT for PTs with Frequency >10% in any treatment group

Solicited AE Tables (eCRF Section "Subject Diary")

- Solicited Adverse Events after any vaccination (by symptom, by maximum severity)
- Solicited Adverse Events by Vaccination Period (by symptom, by maximum severity)
- Solicited Adverse Events by Diary Day (overall and by symptom)
- Mean Duration (in days) of solicited Adverse Events
- Greatest Single Diameter (in cm) for Present Erythema, Swelling and Induration
- Body Temperature (in °C) for case of fever

Unsolicited AE Tables (eCRF Section "Adverse Event Log) for specific types of AEs (e.g. any unsolicited AE, any unsolicited SAE)

- Unsolicited Adverse Events by SOC and PT
- Unsolicited Adverse Events by Vaccination Period
- Unsolicited Adverse Event by Maximum Severity (overall and for specific types of AEs)
- Unsolicited Adverse Event by Causality (overall and for specific types of AEs)

The following figures will be provided:

- Bar chart: The number and percentage of subjects with solicited local Adverse Events by symptom and overall, by treatment group and grade for the diary period after each vaccination and for the whole treatment period.

Inferential analysis will be performed as described in Section 6.1.3**Error! Reference source not found.**. Details are specified in Section 7.

6.1.2 *Derivations and Definitions*

6.1.2.1 General Principles for Analysis of Adverse Event

- In general, for tables summarizing solicited AEs, only the Subject Diary will be used. For tables for all AEs (solicited and unsolicited) in general the unsolicited AEs will be taken from the eCRF section "AE-log" and the solicited AEs will only be taken from the eCRF section "Subject Diary".
- Tables showing "severe" events will include events with grade 3 or 4 (or missing grade).
- For tables by maximum severity and worst causality, subjects will only be counted once in highest grading category and events will be counted in each reported grading category.
- Percentages in tables that do not present data by time periods are based on N (treatment group totals).
- For the IA Day 85 all AEs from the eCRF section "Subject Diary" and AEs from the eCRF section "AE log" that started up to Day 85 (Visit4) will be analyzed. It will be stated in the table header that AEs up to Day 85 will be analyzed.
- For the IA Day 236 all AEs from the eCRF section "Subject Diary" and AEs from the eCRF section "AE log" that started up to Day 236 (Visit 6) will be analyzed. It will be stated in the table header that AEs up to Day 236 will be analyzed.
- AEs in the AE log will be considered to have started up to Day 85 if the start date of the AE is before or on study Day 85 (Visit 4). In case of an incomplete start date where it cannot clearly be decided if the AE started up to Day 85 or not, the AE will be considered to have started up to Day 85. The derivation of AEs started before or on Day 236 will be determined analogously.
- For analyzation of non-serious solicited (eCRF section "Subject Diary") and non-serious unsolicited (eCRF section "Adverse Event log") AEs only AEs for which the question "Serious adverse event" was ticked with "no" in the eCRF will be included. Adverse Events will only be included for this analysis if their occurrence by PT in at least one treatment group in the Safety Population is 5% or over 10%, respectively.

6.1.2.2 Principles for Solicited Adverse Events

Solicited AEs comprise reactions at the injection site or systemic reactions that are typical for vaccinations:

- Solicited local AEs: pain, tenderness, induration/ hardening, swelling and erythema/ redness
- Solicited systemic AEs: headache, myalgia (muscle pain), arthralgia (joint pain), fever (oral body temperature), flu-like symptoms, nausea, vomiting and fatigue
- Solicited AEs are per definition regarded as related to IMP.
- For tables that summarize solicited AEs over several diary days / diary periods from the Subject Diary, the worst severity of all diary days / diary periods is taken as the events severity.
- Percentages in tables for solicited AEs by diary period /diary day are based on the number of subjects with available information (diary completed or symptom present on at least one day). In particular, if a

symptom was not assessed at a certain diary day and the symptom is reported as not present on the other days, the subject is not included in the table of the respective symptom and diary period.

- For the derivation of the duration of solicited Adverse Events by symptom and vaccination period the difference of the first occurrence and the last occurrence of the concerning event in the respective vaccination period will be taken, no matter if the event is continuous or not. Therefore, also the end-date if ongoing after day 6 will be considered. If the AE was ongoing after day 6 but has a missing or incomplete end-date, the date of last attended visit will be used as end date.
- For swelling, redness and induration, the maximum diameter per diary period in cm will be derived as taking the maximum of all diameters reported in that period for that symptom and converting via [cm] = [in] × 2.54.
- The maximum body temperature per diary period for present symptom fever will be derived as taking the maximum temperature of all temperatures reported in that period and converting via [°C] = ([°F] – 32) × 5/9.
- Adverse Events from the Subject Diary will be coded according to the table below:

Event	SOC name	SOC code	PT name	PT code
Arthralgia	Musculoskeletal and connective tissue disorders	10028395	Arthralgia	10003239
Fatigue	General disorders and administration site conditions	10018065	Fatigue	10016256
Fever	General disorders and administration site conditions	10018065	Pyrexia	10037660
Flu like symptom	General disorders and administration site conditions	10018065	Influenza like illness	10022004
Headache	Nervous system disorders	10029205	Headache	10019211
Myalgia	Musculoskeletal and connective tissue disorders	10028395	Myalgia	10028411
Nausea	Gastrointestinal disorders	10017947	Nausea	10028813
Vomiting	Gastrointestinal disorders	10017947	Vomiting	10047700
Erythema/Redness	General disorders and administration site conditions	10018065	Injection site erythema	10022061
Induration/Hardening	General disorders and	10018065	Injection site	10022075

	administration site conditions		induration	
Pain	General disorders and administration site conditions	10018065	Injection site pain	10022086
Swelling	General disorders and administration site conditions	10018065	Injection site swelling	10053425
Tenderness	General disorders and administration site conditions	10018065	Injection site pain	10022086

6.1.2.3 Principles for Unsolicited Adverse Events

- AEs in the AE log will be coded using the MedDRA version that is current at time point of data snapshots for the interim analysis. The version used will be indicated in the respective tables and listings and will be documented in the CSR.
- Adverse events in the AE log will be considered related if the causality to IMP is reported as "probable" or "possible" (or missing causality)
- An AE in the AE-log is considered as "leading to withdrawal from further vaccination" if for "action taken on IMP", "second dose not administered" or "third dose not administered" is ticked.
- An AE in the AE-log is considered as "leading to withdrawal from study" if in section "other action taken" the question "Withdrawn from study", is answered with "yes".
- Percentages in tables for unsolicited events or all events (solicited and unsolicited) over the whole study are based on N (treatment group totals).
- For presentation of AEs by vaccination period, unsolicited AEs will be assigned as follows:
    - 1st vaccination period: AE with start date/time at or after date/time of 1st vaccination and before date/time of 2nd vaccination. If no AE start time is given, the AE is included if the start date is at or after the date of 1st vaccination and before the date of 2nd vaccination. If no 2nd vaccination was administered, the date 28 days after the 1st vaccination will be used instead.
    - 2nd vaccination period: AE with start date /time at or after date/time of 2nd vaccination and before date/time of 3rd vaccination. If no AE start time is given, the AE is included if the start date is at or after the date of 2nd vaccination and before the date of 3rd vaccination. If no 3rd vaccination was administered, the date 28 days after the 2nd vaccination will be used instead.
    - 3rd vaccination period: AE with start date /time at or after date/time of 3rd vaccination and not later than 28 days after the 3rd vaccination.
    - If a subject did not receive a certain vaccination, the respective vaccination period will not be defined.

6.1.3 Inferential Analysis for Adverse Events

95% confidence intervals according to Altman will generally be provided for all AE rates. Differences between the four treatment groups will be assessed for significance using Fisher's exact (Fisher-Freeman-Halton) test, whereby a significant overall test will be amended by pair-wise tests.

It is stated in detail in Section 7 for which tables such comparisons will be made.

6.2 Laboratory Parameters

Laboratory data from scheduled visits will be tabulated. Listings will include results from unscheduled visits and scheduled visits.

6.2.1 Analysis of Fibrinogen

It was detected that Site 03 uses a different Fibrinogen test than the other participating sites at Visit 0. Site 03 reported that their local laboratory does not have a basic Fibrinogen test. Instead, all screened subjects were tested using "Fibrinogen FDP" since this was the closest match. All remaining sites are using the basic Fibrinogen test. It was decided by the sponsor to continue using "Fibrinogen FDP" at site 03 because several subjects had already performed Visit 0 and it was deemed more informative to be compare the later Fibrinogen values of the subjects to the baseline value than to the values at other sites . A comparison of Fibrinogen FDP between site 03 and the basic Fibrinogen test of the other participating sites is not possible. The parameter Fibrinogen at site 03 will be analyzed as "Fibrinogen FDP" separately.

6.2.2 Data Points

The following parameters are assessed in the study and will be included in the statistical analysis:

- Hematology
  - Hemoglobin
  - Hematocrit
  - Erythrocyte count
  - White blood count
  - Platelets
- Coagulation
  - Prothrombin time
  - Activated partial thromboplastin time
  - Fibrinogen
  - Fibrinogen FDP
- Clinical Chemistry
  - Creatinine
  - Sodium
  - Potassium
  - Calcium
  - Aspartate aminotransferase

- Alanine aminotransferase
- Alkaline phosphatase
- Bilirubin
- C-reactive protein

- Urinalysis
  - Specific gravity
  - pH
  - Leukocytes
  - Nitrite
  - Protein
  - Glucose
  - Ketones
  - Urobilinogen
  - Bilirubin
  - Erythrocytes

The following variables will be analyzed descriptively by time point:

- Absolute values (summary statistics for hematology and clinical chemistry)
- Absolute change from Visit 0 (summary statistics for hematology and clinical chemistry)
- Number of subjects with values above/below normal range (for hematology, clinical chemistry and coagulation)
- Urinalysis results (frequency statistics)
- Abnormal pH and specific gravity values (frequency statistics)
- Subjects with values reaching grading by severity (for parameters with grading defined in Section 6.3.2.1)

One set of data listings will show graded laboratory parameters and parameters outside normal range (hematology, coagulation and clinical chemistry)

6.2.3 *Derivations and Definitions*

6.2.3.1 Severity Grading

For statistical analysis, laboratory assessments will be graded according to the grading scale provided below. In particular, all values lying in the range of the severity grades will be assigned to the respective grade and all abnormal values that were not assigned in this way will be labelled "Grade 0". All values that neither lie in the range of a severity grade nor are abnormal will not be assigned to a grade.

Table 4: Grading Scale for Abnormal Laboratory Assessments

	Mild (Grade 1)[1]	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)[2]
Hematology Parameters				
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hematocrit	Outside normal range[3]			
Erythrocyte count	Outside normal range[3]			
WBC (Leucocytes) Increase - cell/mm³	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC (Leucocytes) Decrease - cell/mm³	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Neutrophils Decrease - cell/mm³	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Platelets Decreased - cell/mm³	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Clinical Chemistry Parameters				
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	<125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	>150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – /Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	<3.1
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	<7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	>12.0
AST – increase by factor	1.1 – 2.5 x ULN[4]	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
ALT – increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Alkaline phosphatase – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
CRP	Outside normal range[3]			

[1] In case local laboratory normal ranges and absolute Grade 1 limits overlap, Grade 1 limits will prevail, i.e. the value will be classified as Grade 1 abnormality even if it is within local laboratory normal ranges. Values between the local laboratory normal ranges and absolute Grade 1 limits will be reported as no abnormality (Grade 0).

[2] The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia unsolicited AE if the subject had a new seizure associated with the low sodium value.

[3] As neither the FDA Scale nor the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (December 2004) provide any grading for Hematocrit, Erythrocyte count, , Monocytes, Basophils, ESR and CRP, these will only be analyzed as "outside normal range", as determined by local laboratory standards without further differentiation.

[4] "ULN" is the upper limit of the normal range.

If a laboratory value lies between two grades (e.g. after conversion to the unit used for grading the value has several decimal places), the higher grade will be assigned to the value.

6.2.3.2 Conversion of Units

Conversion of laboratory parameters from a study site specific laboratory unit into the unit to be used in the statistical analysis for severity grading (Section 6.3.2.1) or for summary tables will be performed via the following formula:

Value in unit for severity grading or for analysis = value in study site specific unit * conversion factor

Parameter	Standard Unit/ Unit for Analysis
Clinical chemistry	
Alanine Aminotransferase	U/L
Alkaline Phosphatase	U/L
Aspartate Aminotransferase	U/L
Bilirubin	µmol/L
C Reactive Protein	nmol/L
Calcium	mmol/L
Creatinine	µmol/L
Potassium	mmol/L
Sodium	mmol/L
Coagulation	
Fibrinogen	g/L
Fibrinogen FDP	g/L
Activated partial thromboplastin time	s
Hematology	
Erythrocyte count	T/L
Hemoglobin	g/L

Leukocytes	G/L
Lymphocytes	G/L
Platelets	G/L

Prothrombin Time will be analyzed using the reported unit (i.e. in seconds or percent).

6.3 Lyme borreliosis Screening

Lyme borreliosis screening will be analyzed at baseline and will be used as stratification factor. Complete analysis of all time points will be performed for Final Analysis.

6.4 Other Safety Parameters

The following information will be analyzed descriptively and corresponding details on the subject level will be provided in data listings:

- Systolic blood pressure by time point incl. measurements after vaccinations (summary statistics)
- Diastolic blood pressure by time point incl. measurements after vaccinations (summary statistics)
- Pulse rate by time point incl. measurements after vaccinations (summary statistics)
- Body temperature by time point (summary statistics)

The following information will only be listed:

- Physical Examination
- Pregnancy Test
- Injection Site Inspection
- Assessment after Vaccination
- Vaccination delay criteria

7. LIST OF TABLES, DATA LISTINGS AND FIGURES

7.1 List of Tables

7.1.1 Overall Study Information

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Table 14.1.1.1.2:	Subjects by Treatment Groups, Country and Overall (Safety Population)	
Table 14.1.1.1.3:	Subjects by Visit (Safety Population)	For IA Day 236: It will be displayed whether Visits were performed as phone call or on site due to Covid-19
Table 14.1.1.1.4:	Subject Attendance Status and Early Termination Details (Safety Population)	
Table 14.1.1.1.5:	Vaccination Details (Safety Population)	
Table 14.1.1.1.6:	Protocol Deviations by Deviation Type (Safety Population)	
Table 14.1.1.1.7:	Number of Screening Failures and Reason	
Table 14.1.1.2.x:	Repeat Table 2-6 for mITT Population	
Table 14.1.1.3.x:	Repeat Table 2-6 for PP Population	

7.1.2 Baseline

No	Legend	Content/Comment
Table 14.1.2.1.1:	Summary Table of Demographic Data (Safety Population)	Stratified by age group, region and *B.b. s.l.* serostatus
Table 14.1.2.1.2:	ECG Results at Screening (Safety Population)	
Table 14.1.2.1.3:	Medical History by SOC and PT (Safety Population)	
Table 14.1.2.1.4:	Medical History Ongoing at Visit 1 by SOC and PT (Safety Population)	
Table 14.1.2.1.5:	Prior Medications by ATC Level 2 and ATC Level 3 (Safety Population)	
Table 14.1.2.1.6:	Concomitant Medications by ATC Level 2 and ATC Level 3 (Safety Population)	
Table 14.1.2.1.7:	Prior Procedures by SOC and PT (Safety Population)	
Table 14.1.2.1.8:	Concomitant Procedures by SOC and PT (Safety Population)	

Table 14.1.2.1.9:	Vaccination History by ATC Level 3 (Safety Population)	
Table 14.1.2.2.x:	Repeat all tables for mITT Population	
Table 14.1.2.3.x:	Repeat all tables for PP Population	

7.1.3 Immunogenicity

No	Legend	Content/Comment
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Table 14.1.3.1.2:	ELISA: Number of Immunogenicity Results by OspA Serotype (PP Population)	
Table 14.1.3.1.3:	ELISA: Number and Percentage of Subjects Stratified by OspA IgG Serostatus at Baseline (Visit 1) by Serotype (PP Population)	Stratified by region and age group
Table 14.1.3.1.4:	ELISA: GMTs for OspA ST1-specific IgG by Visit (PP Population)	Stratified by age group, region and *B.b. s.l.* serostatus To be repeated for mITT population (without stratification)
Table 14.1.3.1.5:	ELISA: GMTs for OspA ST2-specific IgG by Visit (PP Population)	Stratified by age group, region and *B.b. s.l.* serostatus To be repeated for mITT population (without stratification)
Table 14.1.3.1.6:	ELISA: GMTs for OspA ST3-specific IgG by Visit (PP Population)	Stratified by age group, region and *B.b. s.l.* serostatus To be repeated for mITT population (without stratification)
Table 14.1.3.1.7:	ELISA: GMTs for OspA ST4-specific IgG by Visit (PP Population)	Stratified by age group, region and *B.b. s.l.* serostatus To be repeated for mITT population (without stratification)
Table 14.1.3.1.8:	ELISA: GMTs for OspA ST5-specific IgG by Visit (PP Population)	Stratified by age group, region and *B.b. s.l.* serostatus To be repeated for mITT population (without stratification)
Table 14.1.3.1.9:	ELISA: GMTs for OspA ST6-specific IgG by Visit (PP Population)	Stratified by age group, region and *B.b. s.l.* serostatus To be repeated for mITT population (without stratification)
Table 14.1.3.1.10:	ELISA: GMFRs (as compared to Day 1) for OspA ST1-specific IgG by Visit (PP Population)	Stratified by age group
Table 14.1.3.1.11:	ELISA: GMFRs (as compared to Day 1) for OspA ST2-	Stratified by age group

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Table 14.1.3.1.12:	ELISA: GMFRs (as compared to Day 1) for OspA ST3-specific IgG by Visit (PP Population)	Stratified by age group
Table 14.1.3.1.13:	ELISA: GMFRs (as compared to Day 1) for OspA ST4-specific IgG by Visit (PP Population)	Stratified by age group
Table 14.1.3.1.14:	ELISA: GMFRs (as compared to Day 1) for OspA ST5-specific IgG by Visit (PP Population)	Stratified by age group
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[redacted]

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Table 14.1.3.1.27:	ELISA: Subjects Achieving a >=4 or >=10-fold increase from Day 0 (Visit 1) in OspA ST4-specific IgG Titer by visit (PP Population)	
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Table 14.1.3.1.30:	ELISA:ANOVA (Factors: Treatment Group, Study Site) for GMT of OspA ST1-specific IgG by Visit (PP Population)	To be repeated for mITT population
Table 14.1.3.1.31:	ELISA:ANOVA (Factors: Treatment Group, Study Site) for GMT of OspA ST2-specific IgG by Visit (PP Population)	To be repeated for mITT population
Table 14.1.3.1.32:	ELISA:ANOVA (Factors: Treatment Group, Study Site) for GMT of OspA ST3-specific IgG by Visit (PP Population)	To be repeated for mITT population
Table 14.1.3.1.33:	ELISA:ANOVA (Factors: Treatment Group, Study Site) for GMT of OspA ST4-specific IgG by Visit (PP Population)	To be repeated for mITT population
Table 14.1.3.1.34:	ELISA:ANOVA (Factors: Treatment Group, Study Site) for GMT of OspA ST5-specific IgG by Visit (PP Population)	To be repeated for mITT population
Table 14.1.3.1.35:	ELISA:ANOVA (Factors: Treatment Group, Study Site) for GMT of OspA ST6-specific IgG by Visit (PP Population)	To be repeated for mITT population
Table 14.1.3.1.36:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMT of OspA ST1-specific IgG at Day 85 (PP Population)	To be repeated for mITT population
Table 14.1.3.1.37:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMT of OspA ST2-specific IgG at Day 85 (PP Population)	To be repeated for mITT population
Table 14.1.3.1.38:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMT of OspA ST3-specific IgG at Day 85 (PP Population)	To be repeated for mITT population
Table 14.1.3.1.39:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMT of OspA ST4-specific IgG at Day 85 (PP Population)	To be repeated for mITT population

[redacted]

Table 14.1.3.1.40:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMT of OspA ST5-specific IgG at Day 85 (PP Population)	To be repeated for mITT population
Table 14.1.3.1.41:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMT of OspA ST6-specific IgG at Day 85 (PP Population)	To be repeated for mITT population
Table 14.1.3.1.42:	ELISA: ANOVA (Factors: Treatment Group, Study Site) for GMFR from Day 1 of OspA ST1-specific IgG by Visit (PP Population)	
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Table 14.1.3.1.49:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMFR of OspA ST2-specific IgG at Day 85 (PP Population)	
Table 14.1.3.1.50:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMFR of OspA ST3-specific IgG at Day 85 (PP Population)	
Table 14.1.3.1.51:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMFR of OspA ST4-specific IgG at Day 85 (PP Population)	
Table 14.1.3.1.52:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMFR of OspA ST5-specific IgG at Day 85 (PP Population)	

[redacted]

Table 14.1.3.1.53:	ELISA: ANOVA (Factors: Treatment Group, Study Site, Study Site*Treatment Group, Age group, and B.b. s.l serostatus at baseline) for GMFR of OspA ST6-specific IgG at Day 85 (PP Population)	
Table 14.1.3.1.54:	ELISA: Correlation Analysis for GMTs of OspA Specific IgG for ST1 vs ST2 by Visit (PP Population)	
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Table 14.1.3.1.57:	ELISA: Correlation Analysis for GMTs of OspA Specific IgG for ST1 vs ST5 by Visit (PP Population)	
Table 14.1.3.1.58:	ELISA: Correlation Analysis for GMTs of OspA Specific IgG for ST1 vs ST6 by Visit (PP Population)	
Table 14.1.3.1.59:	ELISA: Correlation Analysis for GMTs of OspA Specific IgG for ST2 vs ST3 by Visit (PP Population)	
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Table 14.1.3.1.65:	ELISA: Correlation Analysis for GMTs of OspA Specific IgG for ST3 vs ST6 by Visit (PP Population)	
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7.1.4 Safety

No	Legend	IA D85	IA D236	Content/Comment
Table 14.1.4.1:	Summary Table of Adverse Events (solicited and unsolicited) (Safety Population)	X	X	Including statistical test • Any AE, related AE, severe AE, related

				severe AE, SAE, related SAE, medically attended AE, related medically attended AE, AE leading to withdrawal from study, AE leading to withdrawal from further vaccination • Any solicited AE, severe solicited AE, solicited local AE, severe solicited local AE, solicited systemic AE, severe solicited systemic AE • Any unsolicited AE, related unsolicited AE, severe solicited AE, related severe solicited AE, unsolicited SAE, medically attended unsolicited AE, related medically attended unsolicited AE, unsolicited AE leading to withdrawal from study, unsolicited AE leading to withdrawal from further vaccination, AE of special interest, related AE of special interest
Table 14.1.4.2:	Summary Table of Adverse Events by Age group (solicited and unsolicited) (Safety Population)	X	X	Including statistical test Content see table 14.1.4.1
Table 14.1.4.3:	Summary Table of Adverse Events by Region (solicited and unsolicited) (Safety Population)	X	X	Including statistical test Content see table 14.1.4.1
Table 14.1.4.4:	Summary Table of Adverse Events by B.b. s.l. serostatus (solicited and unsolicited) (Safety Population)	X	X	Including statistical test Content see table 14.1.4.1
Table 14.1.4.5:	Summary Table of Adverse Events (solicited and unsolicited) by Vaccination Period (Safety Population)	X	X	Including statistical test Content see table 14.1.4.1
Table 14.1.4.6:	Subjects with Solicited and Unsolicited Serious	X	X	Including statistical test

	Adverse Events by SOC and PT (Safety Population)			
Table 14.1.4.7:	Subjects with Solicited and Unsolicited Related Serious Adverse Events by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.8:	Subjects with Solicited and Unsolicited Medically Attended Adverse Events by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.9:	Subjects with Solicited and Unsolicited Related Medically Attended Adverse Events by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.10:	Subjects with Solicited and Unsolicited Adverse Events Leading to Withdrawal from Further Vaccination by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.11:	Subjects with Solicited and Unsolicited Adverse Events Leading to Withdrawal from Study by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.12:	Subjects with any Non-Serious AE by SOC and PT for PTs with Frequency >5% in any Treatment Group (eCRF Section 'AE Log' for Unsolicited AEs and 'Subject Diary' for Solicited AEs, Safety Population)	X	X	Including statistical test
Table 14.1.4.13:	Subjects with any Non-Serious AE by SOC and PT for PTs with Frequency >10% in any Treatment Group (eCRF Section 'AE Log' for Unsolicited AEs and 'Subject Diary' for Solicited AEs, Safety Population)	X	X	Including statistical test
Table 14.1.4.14:	Subjects with Solicited Adverse Events after any Vaccination (Safety Population)	X		Including statistical test
Table 14.1.4.15:	Subjects with Severe Solicited Adverse Events after any Vaccination by Symptom (Safety Population)	X		Including statistical test
Table 14.1.4.16:	Subjects with Solicited Local Adverse Events after any Vaccination by Symptom (Safety Population)	X		Including statistical test
Table 14.1.4.17:	Subjects with Solicited Local Adverse Events after any Vaccination by Symptom and Age Group (Safety Population)	X		Including statistical test
Table 14.1.4.18:	Subjects with Solicited Local Adverse Events after any Vaccination by Symptom and Region (Safety Population)	X		Including statistical test
Table 14.1.4.19:	Subjects with Solicited Local Adverse Events after any Vaccination by Symptom and *B.b. s.l.* serostatus (Safety Population)	X		Including statistical test
Table 14.1.4.20:	Subjects with Solicited Systemic Adverse Events after any Vaccination by Symptom (Safety Population)	X		Including statistical test
Table 14.1.4.21:	Subjects with Solicited Systemic Adverse Events after any Vaccination by Symptom and Age Group	X		Including statistical test

	(Safety Population)			
Table 14.1.4.22:	Subjects with Solicited Systemic Adverse Events after any Vaccination by Symptom and Region (Safety Population)	X		Including statistical test
Table 14.1.4.23:	Subjects with Solicited Systemic Adverse Events after any Vaccination by Symptom and *B.b. s.l.* serostatus (Safety Population)	X		Including statistical test
Table 14.1.4.24:	Subjects with Solicited Adverse Events after any Vaccination Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.25:	Subjects with Solicited Local Adverse Events after any Vaccination by Symptom Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.26:	Subjects with Solicited Local Adverse Events after any Vaccination by Symptom and Age Group Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.27:	Subjects with Solicited Local Adverse Events after any Vaccination by Symptom and Region Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.28:	Subjects with Solicited Local Adverse Events after any Vaccination by Symptom and *B.b. s.l.* serostatus Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.29:	Subjects with Solicited Systemic Adverse Events after any Vaccination by Symptom Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.30:	Subjects with Solicited Systemic Adverse Events after any Vaccination by Symptom and Age Group Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.31:	Subjects with Solicited Systemic Adverse Events after any Vaccination by Symptom and Region Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.32:	Subjects with Solicited Systemic Adverse Events after any Vaccination by Symptom and *B.b. s.l.* serostatus Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.33:	Subjects with Solicited Adverse Events by Vaccination Period (Safety Population)	X		Including statistical test
Table 14.1.4.34:	Subjects with Solicited Local Adverse Events by Symptom and by Vaccination Period (Safety Population)	X		Including statistical test
Table 14.1.4.35:	Subjects with Solicited Systemic Adverse Events by Symptom and by Vaccination Period (Safety Population)	X		Including statistical test

Table 14.1.4.36:	Subjects with Solicited Adverse Events by Vaccination Period Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.37:	Subjects with Solicited Local Adverse Events by Vaccination Period Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.38:	Subjects with Solicited Systemic Adverse Events by Vaccination Period Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.39:	Subjects with Solicited Local Adverse Events by Symptom and Vaccination Period Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.40:	Subjects with Solicited Systemic Adverse Events by Symptom and Vaccination Period Classified by Maximum Severity (Safety Population)	X		Including statistical test
Table 14.1.4.41:	Subjects with Solicited Adverse Events by Diary Day (Safety Population)	X		Including statistical test
Table 14.1.4.42:	Subjects with Solicited Local Adverse Events by Diary Day (Safety Population)	X		Including statistical test
Table 14.1.4.43:	Subjects with Solicited Systemic Adverse Events by Diary Day (Safety Population)	X		Including statistical test
Table 14.1.4.44:	Greatest Diameter for Present Local Reactions after each Vaccination, by Symptom (Safety Population)	X		
Table 14.1.4.45:	Maximum Fever after each Vaccination (Safety Population)	X		
Table 14.1.4.46:	Number of Days with Local Solicited AE by Diary Period (Safety Population)	X		
Table 14.1.4.47:	Number of Days with Systemic Solicited AE by Diary Period (Safety Population)	X		
Table 14.1.4.48:	Subjects with Unsolicited Adverse Events by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.49:	Subjects with Related Unsolicited Adverse Events by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.50:	Subjects with Severe Unsolicited Adverse Events by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.51:	Subjects with Related Severe Unsolicited Adverse Events by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.52:	Subjects with Adverse Events of Special Interest by SOC and PT (Safety Population)	X	X	Including statistical test
Table 14.1.4.53:	Subjects with Related Adverse Events of Special Interest by SOC and PT (Safety Population)	X	X	Including statistical test

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Table 14.1.4.54:	Subjects with at least one Unsolicited Adverse Event by Maximum Severity (Safety Population)	X	X	Including statistical test
Table 14.1.4.55:	Subjects with at least one Medically Attended Unsolicited Adverse Event by Maximum Severity (Safety Population)	X	X	Including statistical test
Table 14.1.4.56:	Subjects with at least one Adverse Event of Special Interest by Maximum Severity (Safety Population)	X	X	Including statistical test
Table 14.1.4.57:	Subjects with at least one Unsolicited Adverse Event by Causality (Safety Population)	X	X	Including statistical test
Table 14.1.4.58:	Subjects with at least one Medically Attended Unsolicited Adverse Event by Causality (Safety Population)	X	X	Including statistical test
Table 14.1.4.59:	Subjects with at least one Adverse Event of Special Interest by Causality (Safety Population)	X	X	Including statistical test
Table 14.1.4.60:	Absolute Values for Hematology Parameters by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.61:	Absolute Values for Clinical Chemistry Parameters by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.62:	Absolute Changes from Baseline for Hematology Parameters by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.63:	Absolute Changes from Baseline for Clinical Chemistry Parameters by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.64:	Subjects with Hematology Parameters Outside Normal Range by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.65:	Subjects with Clinical Chemistry Parameters Outside Normal Range by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.66:	Subjects with Coagulation Parameters Outside Normal Range by Parameter (Safety Population)	X	X	
Table 14.1.4.67:	Urine Laboratory Results by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.68:	Subjects with Abnormal pH and Specific Gravity Values by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.69:	Subjects Reaching Severity Grading for Hematology Parameters by Parameter and Visit (Safety Population)	X	X	
Table 14.1.4.70:	Subjects Reaching Severity Grading for Clinical Chemistry Parameters by Parameter and Visit (Safety Population)	X	X	

Table 14.1.4.71:	Systolic Blood Pressure [mmHg] by Visit (Safety Population)	X	X	
Table 14.1.4.72:	Diastolic Blood Pressure [mmHg] by Visit (Safety Population)	X	X	
Table 14.1.4.73:	Pulse Rate [beats/min] by Visit (Safety Population)	X	X	
Table 14.1.4.74:	Oral Temperature [C] by Visit (Safety Population)	X	X	

7.2 List of Data Listings

7.2.1 Overall Study Information

No	Legend	Content
Listing 16.2.1.1.1:	Subject overview	Subject ID, Country, Site Name, Study Part, Date of signed informed consent, Subject eligible to be randomized, Reason not randomized, Planned Treatment, Actual Treatment, Safety/mITT Population, Reason not in Safety/mITT Population, PP Population, Reason not in PP Population
Listing 16.2.1.1.2:	Screening Failure with Reason	Subject ID, Withdrawal of consent, In/Ex criteria not met, Other reason screening failure, Specification of other reason for screening failure
Listing 16.2.1.1.3:	In/Exclusion Criteria that were not Met	Subject ID, Visit, Criterion ID not met, Criterion description
Listing 16.2.1.1.4:	Study Vaccination (Vaccinated Subjects)	Subject ID, Group, Visit, Vaccination administered, Reason if not Administered, Date, Time, Kit number, Location, Other location (specification/reason)
Listing 16.2.1.1.5:	Visit Log (Vaccinated Subjects)	Subject ID, Group, Visit, Visit performed, Visit Date, Reason visit not performed, Deviation from time window [days], Reason outside time window, Age, Reason for unscheduled visit, Type of contact (ET visit)
Listing 16.2.1.1.6:	Missed Visits, Missed Vaccinations, Early Terminations: Part I (Vaccinated Subjects)	Subject ID, Group, Visit attendance, All vaccinations administered, Primary reason treatment discontinuation, Other reason for treatment discontinuation, AE Term (treatment discontinuation), Reason for recommended withdrawal (treatment discontinuation), Individual stopping criteria, AE Term (stopping criteria)
Listing 16.2.1.1.7:	Missed Visits, Missed Vaccinations, Early Terminations: Part II (Vaccinated Subjects)	Subject ID, Group, Is the primary reason for treatment discontinuation the same as for early termination, Primary reason for early termination, Other reason for early termination, AE Term (early termination), Reason for recommended withdrawal (early termination), Death date, Primary cause of death, Date of ET, Last attended scheduled visit before ET

Listing 16.2.1.1.8:	Protocol Deviations (Vaccinated Subjects)	Subject ID, Group, PD Category, PD Description, Severity, Reason for classification
Listing 16.2.1.1.9:	Visits Performed as Phone Call Due to Covid-19 (Vaccinated Subjects)	Subject ID, Group, Visit, Visit performed, Visit Date, Reason visit not performed, Deviation from time window [days], Reason outside time window, Age, Reason for unscheduled visit, Type of contact (ET visit) Only applicable for IA D236

7.2.2 Baseline

No	Legend	Content
Listing 16.2.1.2.1:	Demographics (Vaccinated Subjects)	Subject ID, Group, Gender, Childbearing potential, Reason no childbearing potential (other), Year of birth, Age at Screening [years], Age group, Race (other), Body height [cm], Body weight [kg], BMI [kg/m2]
Listing 16.2.1.2.2:	Physical Examination at Screening (Vaccinated Subjects)	Subject ID, Group, Visit, Physical examination performed, Reason not performed, Examination Date
Listing 16.2.1.2.3:	ECG (Vaccinated Subjects)	Subject ID, Group, ECG performed, Date, Reason ECG not performed, ECG Result, ECG clinically relevant
Listing 16.2.1.2.4:	HIV Test (Vaccinated Subjects)	Subject ID, Group, Test performed, Reason test not performed, Date, Result
Listing 16.2.1.2.5:	Medical History (Vaccinated Subjects)	Subject ID, Group, Condition, MedDRA PT (MedDRA 22.1), MedDRA SOC (MedDRA 22.1), Start Date, End Date, Ongoing at study entry
Listing 16.2.1.2.6:	Prior Medications (Vaccinated Subjects)	Subject ID, Group, Medication or therapy, Start Date, End Date, ATC term level 2 (WHODRUG GLOBAL B3 September 1 2019), ATC term level 3 (WHODRUG GLOBAL B3 September 1 2019), Dose Unit, Dose Form, Frequency, Route, Indication category, Indication
Listing 16.2.1.2.7:	Concomitant Medications (Vaccinated Subjects)	Subject ID, Group, Medication or therapy, Start Date, End Date, ATC term level 2 (WHODRUG GLOBAL B3 September 1 2019), ATC term level 3 (WHODRUG GLOBAL B3 September 1 2019), Dose Unit, Dose Form, Frequency, Route, Indication category, Indication
Listing 16.2.1.2.8:	Prior Procedures (Vaccinated Subjects)	Subject ID, Group, Procedure, Start Date, CP ongoing at study end, End Date, Indication category, Indication, MedDRA PT (MedDRA 22.1 English), MedDRA SOC (MedDRA 22.1 English)
Listing 16.2.1.2.9:	Concomitant Procedures (Vaccinated Subjects)	Subject ID, Group, Procedure, Start Date, CP ongoing at study end, End Date, Indication category, Indication, MedDRA PT (MedDRA 22.1 English), MedDRA SOC (MedDRA 22.1 English)
Listing 16.2.1.2.10:	Vaccination History (Vaccinated Subjects)	Subject ID, Group, Date of Vaccination, Vaccination (indication or trade name), ATC term level 3 (WHODRUG GLOBAL B3 September 1 2019)

7.2.3 *Immunogenicity*

No	Legend	Content
Listing 16.1.3.1:	ELISA: Immunogenicity Results Part 1 (Treated Subjects)	Subject number, Planned Treatment (mITT), Sample excluded from PP analysis, Visit, Date of visit, Time of visit, Sample drawn, Reason for not drawn, Sample ID, Worklist ID, Antigen, IgG titer [U/mL] (measured), Sample Status, IgG titer [U/mL] (analysis), Fold increase from Day 0, ELISA Seroconversion since V1
Listing 16.1.3.2:	ELISA: Immunogenicity Results Part 2 (Treated Subjects)	Subject number, Planned Treatment (mITT), Sample excluded from PP analysis, Visit, Date of visit, Time of visit, Seroconversion for all six serotypes ST1-6, Seroconversion for ST1 and ST2

7.2.4 *Safety*

No	Legend	Content
Listing 16.2.1.4.1.1:	Unsolicited Adverse Events Part I (Vaccinated Subjects)	Patient ID, Group, Adverse Event, MedDRA PT (MedDRA 22.1), MedDRA SOC(MedDRA 22.1), Start date, Start time, Study day of onset, Onset after vacc., Onset (relative to previous vacc.) [days], End Date, End time, Duration of AE [days]
Listing 16.2.1.4.1.2:	Unsolicited Adverse Events Part II (Vaccinated Subjects)	Patient ID, Group, Adverse Event, Event considered as AESI, Specialist work-up performed, Medically attended, Serious adverse event, SAE criteria, Severity, Causality, Action taken on IMP, Action taken general, Outcome
Listing 16.2.1.4.1.3:	Related Unsolicited Adverse Events Part I (Vaccinated Subjects)	See Listing 16.2.1.4.1.1
Listing 16.2.1.4.1.4:	Related Unsolicited Adverse Events Part II (Vaccinated Subjects)	See Listing 16.2.1.4.1.2
Listing 16.2.1.4.1.5:	Severe Unsolicited Adverse Events Part I (Vaccinated Subjects)	See Listing 16.2.1.4.1.1
Listing 16.2.1.4.1.6:	Severe Unsolicited Adverse Events Part II (Vaccinated Subjects)	See Listing 16.2.1.4.1.2
Listing 16.2.1.4.1.7:	Serious Adverse Events Part I (Vaccinated Subjects)	See Listing 16.2.1.4.1.1
Listing 16.2.1.4.1.8:	Serious Adverse Events Part II (Vaccinated Subjects)	Patient ID, Group, Adverse Event, Type of AE, Event considered as AESI, Specialist work-up performed, Medically attended, Serious, SAE criteria, Severity, Causality, Action taken on IMP, Action taken general, Outcome
Listing 16.2.1.4.1.9:	Medically Attended Adverse Events Part I (Vaccinated Subjects)	See Listing 16.2.1.4.1.1
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Listing 16.2.1.4.1.11:	Adverse Events Resulting in Death Part I (Vaccinated Subjects)	See Listing 16.2.1.4.1.1
Listing 16.2.1.4.1.12:	Adverse Events Resulting in Death Part II (Vaccinated Subjects)	See Listing 16.2.1.4.1.8
Listing 16.2.1.4.1.13:	Adverse Events Leading to Withdrawal from Further Vaccination (Vaccinated Subjects)	Patient ID, Group, Adverse event term, MedDRA PT (MedDRA 22.1), MedDRA SOC(MedDRA 22.1), Severity, Causality, Start date, Withdrawn from further vacc. after vacc., Onset (relative to previous vacc.) [days], Estimated Duration of AE (incl. missing stop date) [days]
Listing 16.2.1.4.1.14:	Adverse Events Leading to Withdrawal from the Study (Vaccinated Subjects)	Patient ID, Group, Adverse event term, MedDRA PT (MedDRA 22.1), MedDRA SOC(MedDRA 22.1), Severity, Causality, Start date, Withdrawn from study after vacc., Onset (relative to previous vacc.) [days], Estimated Duration of AE (incl. missing stop date) [days]
Listing 16.2.1.4.1.15:	Adverse Events with Missing Assessment (eCRF Section "AE log") Part I (Vaccinated Subjects)	See Listing 16.2.1.4.1.1
Listing 16.2.1.4.1.16:	Adverse Events with Missing Assessment (eCRF Section "AE log") Part II (Vaccinated Subjects)	See Listing 16.2.1.4.1.8
Listing 16.2.1.4.1.17:	Solicited Adverse Events by Diary Day (Vaccinated Subjects)	Patient ID, Group, Symptom, Present after vaccination, Serious, Medically attended, Taken any medication due to symptom, Withdrawn from further vaccination, Withdrawn from study, Time point, Symptom ongoing after Day 6, Meets FDA Toxicity Grading Scale, Grade per diary day (incl. not present), Size [cm], Oral body temperature [°C]
Listing 16.2.1.4.1.18:	Severe Solicited Adverse Events by Diary Day (Vaccinated Subjects)	See Listing 16.2.1.4.1.17
Listing 16.2.1.4.1.19:	Solicited Adverse Events with Missing Assessments by Diary Day (Vaccinated Subjects)	See Listing 16.2.1.4.1.17
Listing 16.2.1.4.1.20:	Solicited Adverse Events by Diary Period (Vaccinated Subjects)	Patient ID, Group, Symptom, Present after vaccination, Serious, Medically attended, Taken any medication due to symptom, Withdrawn from further vaccination, Withdrawn from study, Onset (relative to previous vacc.) [days], Stop day (relative to previous vacc.) [days], Maximum severity (grade 0-4 and n/p)
Listing 16.2.1.4.1.21:	Severe Solicited Adverse Events by Diary Period (Vaccinated Subjects)	See Listing 16.2.1.4.1.21
Listing 16.2.1.4.2.1:	Hematology Values Outside Normal Range or Meeting FDA Grading Scale for Lab Assessments	Patient ID, Group, Visit, Date, Time, Parameter, FDA Grading, Result, Unit, Lower Limit, Upper Limit, Result (converted), Unit (converted), Lower limit (converted), Upper limit (converted), Out of normal

	(Vaccinated Subjects)	range, Clinically relevant, Likely cause (if available)
Listing 16.2.1.4.2.2:	Clinical Chemistry Values Outside Normal Range or Meeting FDA Grading Scale for Lab Assessments (Vaccinated Subjects)	See Listing 16.2.1.4.2.1
Listing 16.2.1.4.2.3:	Coagulation Values Outside Normal Range (Vaccinated Subjects)	Patient ID, Group, Visit, Date, Parameter, Result, Unit, Lower Limit, Upper Limit, Result (converted), Unit (converted), Lower limit (converted), Upper limit (converted), Out of normal range, Clinically relevant, Likely cause (if available)
Listing 16.2.1.4.2.4:	Urinalysis Values Outside Normal Range (Vaccinated Subjects)	Patient ID, Group, Visit, Date, Time, Test, Result, Clinically relevant, Likely cause (if available)
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Listing 16.2.1.4.3.2:	Physical Examination (Vaccinated Subjects)	Patient ID, Group, Visit, Specifier, Examination Date, Examination Time, Type of physical examination, Physical examination performed, Reason physical examination/observation not performed
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Listing 16.2.1.4.3.6:	Lyme Borreliosis Screening (Vaccinated Subjects)	Patient ID, Group, Visit, Date, Sample analysis performed, Reason not collected/performed, Result (C6 ELISA assay), Confirmatory immunoblot performed, Reason conf. immunoblot not done, IgM Result (Immunoblot), IgG Result (Immunoblot), *B.b. s.l.* serostatus
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7.3 List of Figures

7.3.1 Immunogenicity

No	Legend	Comment
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Figure 14.1.3.3:	Bar Chart: ELISA OspA- Specific IgG Antibodies (GMT) by OspA Serotype and Treatment Group, Day 57 (PP Population)	Content: Not in scope of interim analyses
Figure 14.1.3.4:	Bar Chart: ELISA OspA- Specific IgG Antibodies (GMT) by OspA Serotype and Treatment Group, Day 85 (PP Population)	
Figure 14.1.3.5:	Bar Chart: ELISA OspA- Specific IgG Antibodies (GMT) by OspA Serotype and Treatment Group, Day 180 (PP Population)	Content: Not in scope of interim analyses
Figure 14.1.3.6:	Bar Chart: ELISA OspA- Specific IgG Antibodies (GMT) by OspA Serotype and Treatment Group, Day 236 (PP Population)	Content: Not in scope of interim analyses
Figure 14.1.3.7:	Bar Chart: ELISA OspA- Specific IgG Antibodies (GMT) by OspA Serotype and Treatment Group, Day 365 (PP Population)	Content: Not in scope of interim analyses
Figure 14.1.3.8:	Bar Chart: ELISA Seroconversion Rate by OspA Serotype and Treatment Group at Day 29 (PP Population)	Content: Not in scope of interim analyses
Figure 14.1.3.9:	Bar Chart: ELISA Seroconversion Rate by OspA Serotype and Treatment Group at Day 57 (PP Population)	Content: Not in scope of interim analyses
Figure 14.1.3.10:	Bar Chart: ELISA Seroconversion Rate by OspA Serotype and Treatment Group at Day 85 (PP Population)	
Figure 14.1.3.11:	Bar Chart: ELISA Seroconversion Rate by OspA Serotype and Treatment Group at Day 180 (PP Population)	Content: Not in scope of interim analyses
Figure 14.1.3.12:	Bar Chart: ELISA Seroconversion Rate by OspA Serotype and Treatment Group at Day 236 (PP Population)	Content: Not in scope of interim analyses
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[redacted]

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7.3.2 Safety

Safety figures about solicited AEs will be only provided for IA Day 85.

No	Legend
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8. SHELLS OF TABLES, DATA LISTINGS AND FIGURES

For this analysis, no table shells or mock tables are produced, but analysis drafts of TLFs were generated based on dummy group allocation (dummy randomization list) and dummy immunogenicity data. These drafts were reviewed by the sponsor prior to SAP finalization and database snapshot.