Statistical Analysis Plan (SAP)

Protocol Title:	A MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLINDED PIVOTAL STUDY TO EVALUATE SAFETY AND IMMUNOGENICITY OF A LIVE-ATTENUATED CHIKUNGUNYA VIRUS VACCINE CANDIDATE (VLA1553) IN ADULTS AGED 18 YEARS AND ABOVE
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1.0 Approvals

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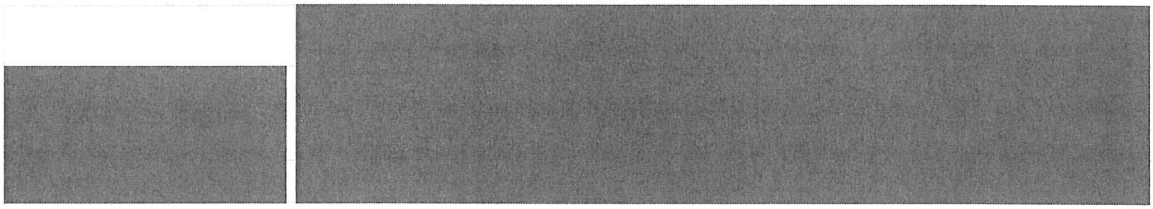
(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

Change History

Version/Date	Change Log
[redacted]	[redacted]



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3.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Valneva Austria GmbH Protocol VLA1553-301.

4.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Endpoints to be Analyzed and the Analysis Sets (Estimands)
- Applicable Study Definitions
- Statistical Methods

This SAP covers the analysis for Part A (Visit 3, Day 29) and Part B (Visit 5, Month 6) of the study.

5.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF). Any further changes to the protocol or CRF may necessitate updates to the SAP.

Final approval of this document will occur prior to database lock and unblinding for the Part A analysis.

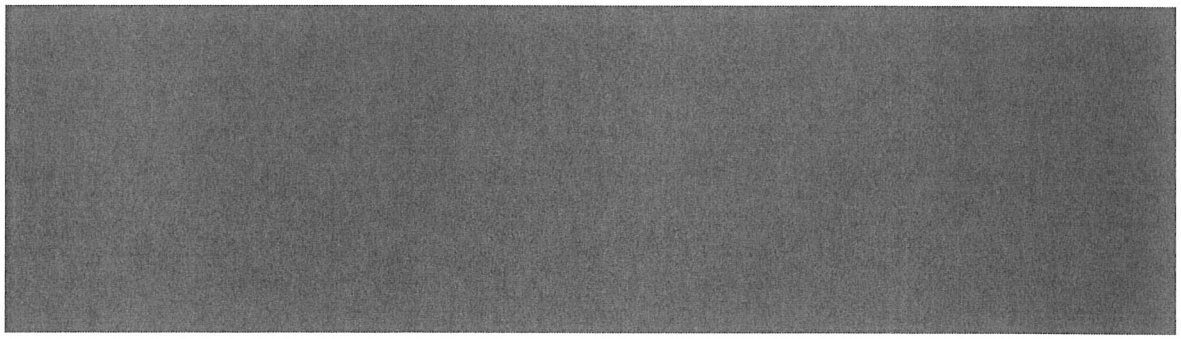
5.1 Changes from Protocol

The distribution scheme shown in **Table 7-1** is different from the protocol planned distribution scheme. This is to reflect the different composition of the immunogenicity subset including 111 subjects ≥65 years instead of 154 subjects as originally planned, and a total of 501 to reflect the actual enrolment. This is to match the updates made in Protocol version 5 to allow for fewer subjects in stratum B of the immunogenicity subset.

Clarifications have been made in the study design section 7.0 to clarify the need to analyze the immunogenicity samples for those subjects included in the immunogenicity elderly population who are not part of the initially defined immunogenicity subset.

The Per Protocol analysis set uses different visit windows to define out of window results than outlined in the protocol schedule of events. This is in order to align the visit windows allowable in this analysis in line with the phase 1 study of this vaccine. The visit windows in the protocol are shown in section 9.2, whilst the windows for the exclusion from the Per Protocol population are outlined in section 10.6.1.

The definition of adverse event of special interest in section 9.7.5 has been updated per FDA feedback for clarification of the anatomical location with cutaneous pruritis. This is not yet reflected in Protocol version 6.0, which is the approved version at time of SAP finalization.



6.0 Study Objectives

6.1 Primary Objectives

- To evaluate the immunogenicity and safety of the final dose of the live-attenuated Chikungunya virus (CHIKV) vaccine candidate (VLA1553) 28 days following vaccination in a population aged 18 years and above after a single immunization.

6.2 Secondary Objectives

- To assess the immunogenicity and safety of the final dose of VLA1553 up to 180 days following vaccination in a population aged 18 years and above after a single immunization.

7.0 Study Design

This is a prospective, randomized, double-blinded, multicenter, pivotal clinical study evaluating the final dose of VLA1553 (1 x10E4 $TCID_{50}$ per 0.5 mL) in comparison to a placebo control. The final dose of VLA1553 or control will be administered as single immunization on Day 1. Overall, approximately 4,060 male and female subjects aged 18 years and above will be enrolled (i.e. ICF signed) in this study. All participants will be healthy adults.

Subjects will be allocated in a 3:1 ratio to VLA1553 (n= approximately 3,045) or control group (n= approximately 1,015). The approximately 4,060 subjects in this study will be stratified into two age strata of subjects aged 18 to 64 years (Stratum A: overall approximately 3,653 subjects) and subjects of 65 years of age or above (Stratum B: overall approximately 407 subjects).

The first enrolled and randomized approximately 346 subjects in Stratum A and 154 subjects in Stratum B will be included in the immunogenicity evaluation and comprise the immunogenicity subset of in total approximately 500 subjects. The immunogenicity subset will be randomly enrolled at approximately 15 pre-selected study sites across the US representative of the whole study population.

Due to the difficulty to enroll elderly subjects of Stratum B (≥65 yrs.), enrollment was opened to all subjects in December 2020 and Stratum B was filled up with either subjects of Stratum A (18 – 64 yrs.) or Stratum B (≥65 yrs.) changing the composition of the immunogenicity subset, but not its total number (refer to Amendment 5 of the Clinical Study Protocol VLA1553-301). Due to study blinding, the exact figures for study arms 1 and 2 are not available for the time being.

Table 7-1 below illustrates the subject distribution scheme.

Table 7-1. Subject Distribution

Study Arm	Study Arm	Stratum	Number of subjects (n)	Immunogenicity evaluation (n)	Dose ($TCID_{50}$/dose)	Injection Volume (mL)
1	VLA1553		3,045		1x 10E4	0.5
		A (18 – 64 yrs.)	2,740	~~260~~ 292*		
		B (≥ 65 yrs.)	305	~~115~~ 83*		
2	Control		1,015		n.a.	0.5
		A (18 – 64 yrs.)	913	~~86~~ 98*		

		B (≥ 65 yrs.)	102	~~39~~ 28*		
		Total N:	**4,060**	**~~500~~ 501***		

Note: * with actually 111 subjects enrolled in Stratum B, we expect approximately 83 subjects receiving VLA1553 and 28 subjects receiving placebo, similarly with 390 Stratum A subjects enrolled into the immunogenicity subset we expect approximately 292 on VLA1533 and 98 on placebo (to be confirmed after unblinding of the study). The changes shown here reflect the updates made in Protocol version 5.

All subjects will be asked to return to the study site at Day 8 (Visit 2), Day 29 (Visit 3) and Day 85 (Visit 4) and Month 6 (Day 180, Visit 5) for immunogenicity sampling. However, immunogenicity analysis and evaluations were only planned to be done in the immunogenicity subset. Due to the addition of non-immunogenicity subset subjects in the Immunogenicity elderly population, some immunogenicity samples will also be evaluated and analyzed for these subjects. In addition, a clinical sample for safety laboratory evaluations will be obtained at all study visits from the immunogenicity subset only. Safety data collection will capture solicited adverse events (AEs) until Day 11 and unsolicited AEs up to Day 180 (Month 6, Visit 5) from all subjects. Adverse events of special interest (AESIs) will be captured from 2 to 21 days post-vaccination. Subjects presenting with acute arthralgia within this time period will be followed-up until resolution and monitored for recurrences until the end of the study. Serious adverse events (SAEs) will also be assessed until the end of the study in all subjects (Month 6, Visit 5).

The overall study design is displayed in **Figure 7-1** below.

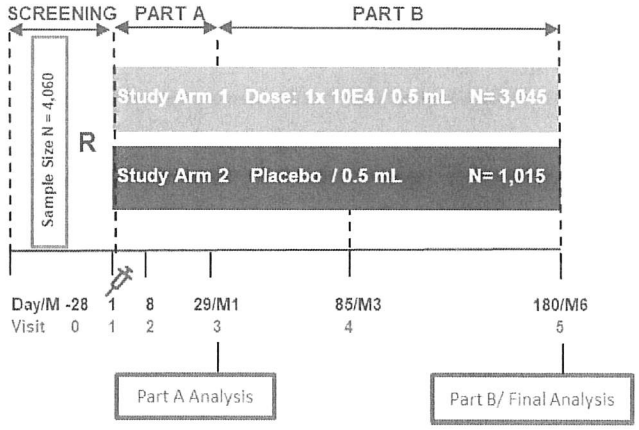


Figure 7-1. Overall Clinical Phase 3 Study Design.

The individual subject participation is approximately 7 months from enrollment to study completion unless prematurely discontinued. The screening period will last up to 1 month (28 days) prior to randomization at Visit 1.

The study is split into 2 parts which will be reported separately:

- Part A: Screening to Visit 3 (Day 29)
- Part B: Visit 4 to Visit 5 (Month 6)

7.1 Sample Size Considerations

The sample size for this study is selected in order to provide a comprehensive safety profile with regards to rare AEs and SAEs. A number of approximately 3,000 VLA1553 vaccinated subjects will allow for the detection of at least one vaccine-related rare event (incidence rate 1/1000) with a probability of 94% in this study.

The sample size of the immunogenicity subset will allow for sufficient statistical power when applying a one-sided exact binomial test with a significance level of 2.5% against a non-acceptance threshold of 70%

on the proportion of subjects with a seroprotective level (defined as Micro Plaque Reduction Neutralization Test [redacted] for baseline negative subjects) at Day 29. A seroprotection rate (SPR) of 80% is assumed, and 200 VLA1553-vaccinated subjects would thus be necessary for a statistical power of 90%. With an expected drop-out/major protocol deviations rate of approximately 10%, 225 subjects vaccinated with VLA1553 need to be allocated to the immunogenicity subset. In order to account for placebo subjects, to achieve a meaningful number of subjects in both age strata, and to enroll sufficient numbers of subjects for a long-term follow-up in a potential subsequent trial, a total of 500 subjects will be enrolled into the immunogenicity subset.

Even if recruitment of elderly subjects (Stratum B) in the IMM population does not achieve the envisaged total of 154 subjects, the analysis of the IMM population will proceed as defined below. In addition, missing subjects of Stratum B in the immunogenicity subset will be filled up with randomly selected subjects of Stratum B from the safety analysis population and an additional analysis will be performed at a later stage for immunogenicity evaluations in the newly defined IMM elderly (eIMM) population.

7.2 Randomization

The approximately 4,060 subjects will be randomized into the two study arms (VLA1553 or Placebo) at a ratio of 3:1 at Visit 1. Randomization will be stratified by age group (18 - 64 years and ≥65 years) and whether the subject is included in the immunogenicity subset.

Randomization will be performed via the IXRS (Interactive Voice/Web Response System). The stratification by age and whether the subject is included in the immunogenicity subset is built in to the IXRS system, so that separate blocks are filled for subjects in each of the four different stratification factor categories. At Day 1 (Visit 1, day of vaccination) eligible subjects will be assigned to VLA1553 or Placebo. Each subject will receive a unique randomization number when he/she is assigned to the study arm. Subjects will be allocated to study arms according to the randomization code.

The first 500 subjects allocated to the immunogenicity subset will be randomized to the study arms via the IXRS across approximately 15 pre-selected study sites across the US and the randomization stratification will ensure an approximate 3:1 randomization in the immunogenicity subset.

The investigational medicinal product (IMP) will be prepared by unblinded study staff in accordance with the information in the IXRS.

7.3 Random selection of subjects to fill up the eIMM population

Missing subjects of Stratum B in the immunogenicity subset will be filled up with randomly selected subjects of Stratum B from the safety analysis population. Additional immunogenicity analyses will be performed using the newly defined IMM elderly population. This analysis will be included in the Part A CSR if all elderly subjects are enrolled in a timely manner to allow the processing of immunogenicity samples within the timeframe of the Part A unblinding and CSR creation, else it will be performed at a later date and filed with the Part B analysis.

To this aim, the following algorithm will be applied. All non-immunogenicity subjects in Stratum B (aged >65) from the 15 sites initially contributing to the immunogenicity subset will be counted, with the number of such subjects noted as N. If there are more than 43 such subjects then these will be considered to make up the IMM elderly population. 43 of these N subjects will then be selected to be included in the new IMM elderly group by a random sampling method. All N subjects will be sorted by subject number and then allocated a random number using the rand(uniform) procedure in SAS. A seed number of 15532021 will be used. The subjects will then be sorted by the randomly allocated value. The 43 subjects will be selected sequentially from this list, while maintaining the approximate 3:1 ratio of treatment arms. Hence the first 11 placebo, and the first 32 active subjects will be added to the eIMM population.

If N is less than 43, then all N subjects will be included in the IMM elderly population. In addition, the additional [43-N] subjects will be selected from the other sites via random sampling using the method above while maintaining as close to the 3:1 ratio as possible for treatment arms.

7.4 Blinding/Unblinding

The study is conducted in a double-blind manner. Investigators, study staff (apart from those designated to randomize subjects and handle the IMP), study participants, biostatistician (except the unblinded independent reporting statistician involved in the Data Safety Monitoring Board [DSMB]), CRAs responsible for monitoring study data and lab staff will all be blinded to treatment allocation.

The randomization assignment is not to be revealed except in emergency cases in which unblinding is necessary for the clinical management of an SAE. In such events, Investigator must either inform the Sponsor before breaking the blind or immediately after unblinding has been performed.

The study will be unblinded for analysis purposes at the end of Part A (after all subjects have completed Visit 3, Day 29), but sites and subjects will remain blinded until the end of study.

8.0 Study Endpoints, Variables and Covariates

8.1 Primary Endpoint

- Proportion of subjects with a seroprotective CHIKV antibody level defined as [redacted] for baseline negative subjects 28 days post-vaccination.

8.2 Secondary Endpoints

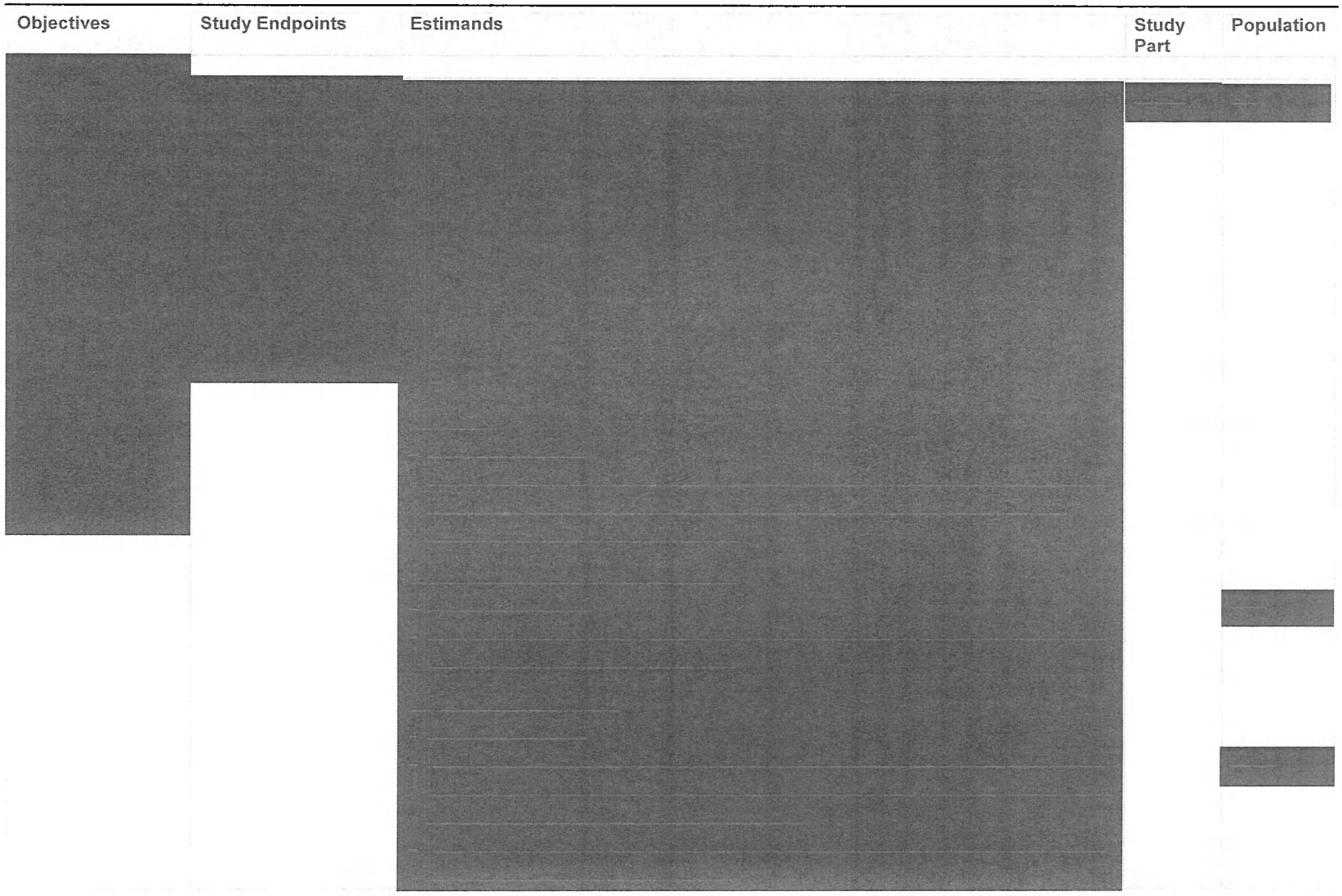
Immunogenicity:

- Immune response as measured by CHIKV-specific neutralizing antibody titers (NTs) on Day 8, Day 29, Day 85 and Month 6 post-vaccination as determined by µPRNT assay;
- Proportion of subjects with seroprotective levels (defined as [redacted] for baseline negative subjects; seroprotective threshold derived from animal passive experiments) on Day 8, Day 85 and Month 6 post-vaccination as determined by µPRNT assay;
- Proportion of subjects with seroconversion at Day 29 and Month 6 as determined by µPRNT assay (seroconversion defined as CHIKV-specific [redacted] for baseline negative subjects and [redacted] for baseline positive subjects);
- Fold increase of CHIKV-specific NT determined by µPRNT assay at Days 8, 29, 85, and Month 6 post-vaccination as compared to baseline;
- Proportion of subjects reaching an at least 4-fold, 8-fold, 16-fold or 64-fold increase in CHIKV-specific NT compared to baseline as measured by µPRNT assay.

Safety:

- Frequency and severity of unsolicited AEs within 28 days post-vaccination;
- Frequency and severity of solicited injection site and systemic reactions within 10 days post-vaccination;
- Frequency, severity and relatedness of any AE during the entire study period;
- Frequency and relatedness of any SAE during the entire study period;
- Frequency and relatedness of any AESI within 2 to 21 days post-vaccination.

The below table links the endpoints to the study objectives, and describes the estimands to be used on the study.



Objectives	Study Endpoints	Estimands	Study Part	Population
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Objectives	Study Endpoints	Estimands	Study Part	Population
[redacted]				

Objectives	Study Endpoints	Estimands	Study Part	Population
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Objectives	Study Endpoints	Estimands	Study Part	Population
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Objectives	Study Endpoints	Estimands	Study Part	Population
[redacted]				

Objectives	Study Endpoints	Estimands	Study Part	Population

9.0 Conventions and Derivations

9.1 Baseline and Change from Baseline

Unless otherwise specified, baseline will be defined as the latest assessment taken prior to the administration of the study drug. All procedures/assessments (apart from AE assessment) taken at Visit 1 are assumed to occur prior to vaccination.

Change from baseline is defined as:

Observed result at nominal time point – observed result at baseline.

9.2 Study Days and Visit Windows

Study day is defined relative to the day of vaccination (Visit 1). Study Day 1 is the day of vaccination (Visit 1).

The scheduled study visits along with the predefined allowable visit window are included in the table below.

Study Part	VISIT	Study Day (Visit Window)
[redacted]	Visit 0 (Screening)	Day -28 to -0 (prior to Visit 1)
	Visit 1	Day 1
	Visit 2	Day 8 (Week 1) [redacted]
	Visit 3	Day 29 (Month 1) [redacted]
	Visit 4	Day 85 (Month 3) [redacted]
	Visit 5	Day 180 (Month 6) [redacted]

Subjects who withdraw from the study prior to completion of the study will attend an Early Termination (ET) Visit where possible. For the purposes of analysis and reporting, each ET visit will be assigned to one of the two study parts. If the ET visit falls within the visit window for a scheduled visit then it will be summarized under that planned visit, unless a scheduled visit already exists within the time window. Otherwise, if a subject has an ET visit but no Visit 3 or later visits then the ET visit will be assigned to Part A, if the subject has an ET visit and a Visit 3 or later visit then the ET visit will be assigned to Part B.

Data will be analyzed according to the visit recorded on the CRF, except in the case of the Immunogenicity analyses on the Per Protocol (PP) population (see Section 10.6.1) and ET visits. Unscheduled visits may be held at any time during the study as necessary, but these will not be included in the analyses of planned visits for Part A. Data at ET visits within the visit window for a scheduled visit will be summarized under the scheduled visit. Data at ET visits outside these visit windows will be listed only and not included in summary tables, except when looking at data across the study as a whole.

Analyses described as being presented at a study day will include all data up to the corresponding visit number. For example an analysis presented at Day 29 will include all data up to the subject's visit 3 timepoint, even if this is after study day 29. Similarly endpoints analyzed up to Day 180 will include all data collected on study, up to their Visit 5 or ET visit.

For the Part B analysis, visit windowing will be explored as a sensitivity analysis of the primary immunogenicity analysis. In these analyses, visits or immunogenicity samples will be assigned to the Visit number of the window they fall into. Hence, any unscheduled visits which fall into the allowed time window for a scheduled visit would be analyzed under that visit. Similarly planned visits which fall into the window for a different planned visit will be analyzed according to the visit window they fall into rather than the recorded visit number. If there are multiple results falling into one visit after re-windowing, then a conservative approach will be taken, and the lower titer value will be used.

9.3 Re-screened Subjects

In this study subjects can be rescreened if they initially fail at screening and randomized into the study.

All available prior/concomitant medications and medical history will be re-entered into the latest applicable ID for a subject that is re-screened.

All other data will be mapped from the original ID to the latest applicable ID for a subject that is re-screened.

9.4 Handling of Duplicate Records

If there is duplicate entry of records into the system for any data then both records will appear in tabulation and analysis datasets and listings but only the first record will be flagged for use in the tables and figures.

9.5 [redacted]

[redacted]

9.6 Immunogenicity Endpoints

Immunogenicity of VLA1553 will be evaluated using µPRNT. The µPRNT leads to a single CHIKV-specific NT value from each sample analyzed, referred to as the $\mu PRNT_{50}$.

Any $\mu PRNT_{50}$ value [redacted] Any subject with a baseline $\mu PRNT_{50}$ [redacted] will be classified as baseline negative; subjects with baseline [redacted] are classed as baseline positive. The upper limit of quantification was determined as [redacted] However, values above [redacted] will be reported in the data, and the reported values will be used in the analysis as they are.

[redacted]

9.6.1 Geometric Mean Titer

The geometric mean titer (GMT) will be calculated as the anti-logarithm of the mean of the log-transformed titer. The geometric standard deviation (GSD) will be calculated as the anti-logarithm transformation of the standard deviation of the log-transformed titer. The 95% confidence interval (CI) will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.

9.6.2 Seroconversion

Seroconversion is defined as a CHIKV-specific [redacted] for baseline negative subjects. Seroconversion for baseline positive subjects is defined as a [redacted] fold increase over baseline.

[redacted]

The seroconversion rate (SCR) is defined as the proportion of subjects meeting the criteria for seroconversion at the relevant study timepoint.

9.6.3 Seroprotection

Seroprotective levels of CHIKV-specific NT are defined as [redacted] at any post-baseline timepoint for baseline negative subjects.

The seroprotection rate (SPR) is defined as the proportion of baseline negative subjects meeting the criteria for seroprotection at the relevant study timepoint.

9.6.4 Fold-Increase in Neutralizing Antibody Titer

The fold-increase from baseline in the CHIKV-specific NT is defined as:

NT result at nominal time point / NT result at baseline.

The fold-increase will be summarized as a continuous endpoint. In addition, the number of subjects reaching pre-specified fold-increase categories of at least 4, 8, 16 and 64-fold increases compared to baseline will be summarized as the number and percentage of subjects in each category.

9.7 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered an investigational product that does not necessarily have a causal relationship with the treatment. All new abnormalities or any exacerbation in intensity or frequency (worsening) of a pre-existing condition during or after vaccination have to be documented as AEs.

Any untoward medical occurrence experienced before vaccine exposure (for example, from the time of signed informed consent up to but not including vaccine exposure) will not be considered an AE and will be described in the medical history.

A subject's death per se is not an event, but an outcome. The event which resulted in the subject's death must be fully documented and reported, regardless of being considered related to treatment or not.

Preexisting diseases that are described in the medical history, and that manifest with the same severity, frequency, or duration after vaccine exposure, will not be recorded as AEs. However, when there is an increase in the severity of a preexisting disease, the event will be recorded as an AE.

There is no definition of treatment-emergent in this study. Any AEs with an onset date prior to the date of vaccination will be raised with data management and should be moved to medical history.

All AEs entered on the CRF will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher. The following information will be documented on the CRF for each AE: severity, causality, outcome, seriousness, medically-attended, action taken to treat AE, start and stop dates.

9.7.1 Adverse Events Severity

- All AEs will be assessed for severity by the Investigator using his/her clinical expertise. Severity will be categorized as Mild (Grade 1), Moderate (Grade 2) or Severe (Grade 3).

If the severity rating for an ongoing AE changes before the event resolves, the AE will not be reported a second time. Instead the original AE report will be revised. For purposes of data capture the highest severity rating during the course of a single AE will be the severity rating entered on the AE CRF. Any AE with missing severity will be classed as severe.

9.7.2 Causality

For AEs, the Investigator will assess the causal relationship between the IMP and the AE using his/her clinical expertise and judgement. Causality will be recorded as Probable, Possible, Unlikely or Not related.

AEs with a causality reported as probable or possible will be considered related to the IMP. AEs with missing causality assessment will be regarded as related unless further specified. All other AEs will be considered as not related to IMP.

9.7.3 Medically Attended Adverse Events

All AEs where subjects are seeking medical care (i.e. doctor's office, emergency service, hospital, but not including use of self-medication). This will be identified by the Investigator and recorded on the CRF.

9.7.4 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death);
- Is life-threatening – defined as an event in which the subject was, in the judgment of the Investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe;
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Is a medically important condition – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. This definition also applies to progression of disease leading to a serious outcome.

All criteria leading to an AE being classified as an SAE will be recorded on the eCRF. AEs graded as potentially life-threatening (Grade 4) as per FDA Guidance on Toxicity Grading Scales will be reported as SAEs and reported as Severe (Grade 3).

9.7.5 Adverse Events of Special Interest

An AESI is an event of scientific and medical concern specific to the Sponsor's product. In addition to nonspecific transient muscle pain and joint pain which may occur after any vaccination, the AESI for VLA1553 include signs and symptoms suggesting an acute stage CHIKV-associated event.

The following cluster of symptoms suggestive of CHIKV infection with or without remissions or exacerbations will receive particular consideration:

1. Fever (≥ 38.0 °C / 100.4 °F measured orally);

AND

2. Acute (poly)arthralgia/arthritis most frequently in the extremities (wrists, ankles and phalanges, often symmetric), back pain and/or neurological symptoms (e.g. confusion, optic neuritis, meningoencephalitis or polyneuropathy) and/or cardiac symptoms (e.g. myocarditis);

OR

One or more of the following signs and symptoms: macular to maculopapular rash (sometimes with cutaneous pruritus (foot plant[1]) and edema of the face and extremities), polyadenopathies;

AND

3. Onset of symptoms 2 to 21 days after vaccination;

AND

4. Duration of event ≥ 3 days.

Any suspected clinical case of CHIKV-associated event shall be referred to a clinical expert, be evaluated according to standard diagnostic procedures and treated according to current medical standard until resolved or stabilized.

All AESI will be identified by Investigator assessment, using the symptoms listed above as a guideline, and will recorded on the CRF. AESI are only captured from 2 to 21 days post-vaccination. Only those AEs identified as AESIs on the CRF will be included in the analysis of AESIs.

All AESIs will be adjudicated by the DSMB to see if the board agree with the investigator decision. Adjudication will be a Y/N flag from the DSMB for each AESI case. This will be added into the database and used for additional reporting.

Additionally, subjects presenting with acute arthralgia within 2 to 21 days post-vaccination will be followed-up until resolution and monitored for recurrences until the end of the study.

9.7.6 Solicited Adverse Events

Solicited AEs are defined only in the first 10 days post-vaccination (until study Day 11). All solicited AEs will be reported by the subject in the Subject eDiary and will be recorded on the AE page of the CRF. The same information on severity and causality will be collected for these events as for the unsolicited AEs and they will be coded in the same way. Only those solicited AEs recorded as such on the AE page of the CRF will be included in the main analysis of solicited AEs.

Any solicited adverse events which are reported on the AE page of the CRF but not reported on the eDiary are flagged as recall events. This flag is used in a sensitivity analysis of the solicited AEs.

9.7.6.1 Injection Site Reactions

Solicited injection site reactions include injection site pain, tenderness, erythema/redness and induration/swelling. The severity for these reactions will be rated based on the FDA Guidance on Toxicity Grading Scales as described in Table 17.2-1 of the Protocol. Any grade 4 injection site reaction should be reported as an SAE and will be reported as Severe (Grade 3) (see Section 9.7.4).

9.7.6.2 Systemic Reactions

Systemic reactions include fever, nausea/vomiting, headache, fatigue, myalgia (muscle pain), arthralgia (joint pain) and rash will be reported in a standardized manner over a period of 10 consecutive days after vaccination.

Severity for systemic reactions will be rated based on the FDA Guidance on Toxicity Grading Scales as described in Table 17.2-2 of the Protocol. Any grade 4 systemic reaction should be reported as an SAE and will be reported as Severe (Grade 3) (see Section 9.7.4).

[1] The update regarding the anatomical location of cutaneous pruritus is included to provide further clarification. This information is not included in the current Protocol Version 6.0. However, this definition will be included in all subsequent CSPs

9.7.7 Duration of AEs

Duration of AEs is calculated as (End date – Onset Date) + 1.

If end date for AE is missing, then for the calculation of the duration the date of study completion/early termination will be used.

If end date for SAE is missing, then for calculation of duration the date of overall study completion (date last subject had their end of study visit) will be used.

9.7.8 AEs at end of study

Per the CSP version 6.0 only SAE information should be collected after the end of study for a subject. If a subject has an updated record for an AE that is not an SAE after end of study their AE details will be set to the status that would have been present at end of study.

9.8 Missing Data

All statistical analysis will generally be based on observed values, missing values will not be imputed. Missing severity and causality will be handled as described in Section 9.7.1 and Section 9.7.2 respectively.

In case of > 5% of missing values for the primary immunogenicity analysis, a separate sensitivity analysis will be performed where multiple imputation methods will be applied in order to evaluate the possible impact of missing values on these results. Further details are specified in Section 12.5.

9.9 Handling of Missing or Incomplete Dates

Missing or partial dates will not be imputed, except to determine the timing of AEs or concomitant medications in relation to VLA1553/Placebo dosing.

Untoward medical occurrences with missing or partial start dates will be considered AEs unless the partial start date indicates that the event began prior to vaccination with VLA1553/Placebo, e.g. if the month and/or year are before the month of Visit 1.

Medications with incomplete end dates will only be considered prior if the partial end date indicates that the medication was stopped prior to dosing, e.g. if the month and/or year are before the month of Visit 1. All other medications with missing or incomplete end dates will be considered concomitant.

10.0 Analysis Sets

10.1 Safety Population

The Safety population contains all subjects who entered into the study and received one vaccination. Subjects will be analyzed as treated. This will be the primary analysis set for all safety endpoints.

10.2 Immunogenicity Subset

10.3 The immunogenicity subset is defined as all subjects who were initially enrolled into the immunogenicity evaluation group, regardless of any other factors. Non Immunogenicity Subset

The non immunogenicity subset is defined as all subjects who were initially enrolled and randomized into the study and are not in the immunogenicity subset.

Both the immunogenicity and non immunogenicity subset will be compared in this study in Part B in response to EMA questions to demonstrate the comparability of the two group of subjects in their

demographic and baseline characteristics. This comparison will be performed on the defined Randomized Population.

10.4 Immunogenicity Population

The Immunogenicity (IMM) population contains all randomized and vaccinated subjects of the immunogenicity subset who were CHIKV seronegative at baseline (defined as $\mu PRNT_{50}$ [redacted] and have at least one evaluable post-baseline titer measurement after vaccination. Subjects will be analyzed according to the study arm they had been randomized to, rather than by the actual treatment they received.

This population will be used for sensitivity analyses of the immunogenicity endpoints.

10.5 Immunogenicity Elderly Population

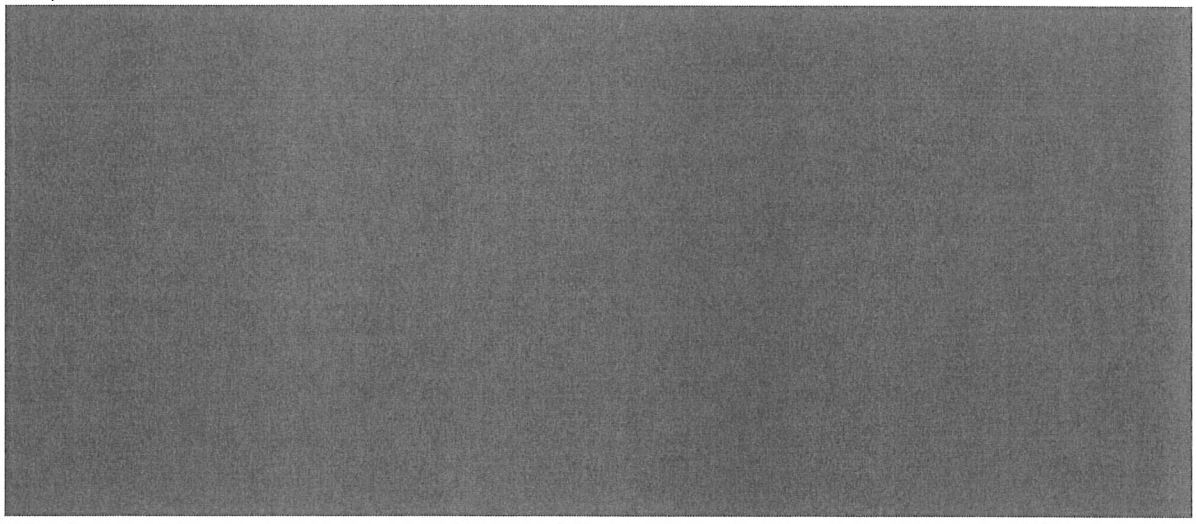
As the composition of the IMM population differs from that originally planned in the CSP v4.0 due to recruitment problems, an additional statistical analysis will be performed at a later stage to enhance the number of subjects for which immunogenicity data are available. For this analysis, randomly selected subjects of Stratum B, i.e. subjects ≥65 years of age, will be used to arrive at the originally planned numbers of subjects for this age stratum and to perform the specified immunogenicity analyses.

This analysis will be included in the Part A CSR if all elderly subjects are enrolled in a timely manner to allow the processing of immunogenicity samples within the timeframe of the Part A unblinding and CSR creation, else it will be performed at a later date and filed with the Part B analysis.

Therefore, the Immunogenicity elderly (eIMM) population is defined to include all randomized and vaccinated subjects of the IMM subset who receive a vaccination, are CHIKV seronegative at baseline and have a non-missing post-baseline immunogenicity sample, as well as the randomly selected elderly subjects (Stratum B) of the safety analysis population to achieve 154 (see section 7.3). Subjects will be analyzed according to the study arm they had been allocated to, rather than by the actual treatment they received. This population will be used for sensitivity analyses of the immunogenicity endpoints.

10.6 Per Protocol Population

The PP population contains all IMM population subjects who have no major protocol deviations that could impact the immune response. Subjects will be analyzed in the PP population according to the study arm they have been randomized to.



The final decisions on whether any protocol deviation could impact immune response and thus lead to exclusion from the PP population will be made by the Sponsor on a case by case basis in a blinded manner (prior to study unblinding).

This will be the primary analysis set for all immunogenicity analyses.

The same PP population will be defined for both Part A and Part B analysis, and if excluded from the PP population, the subject as a whole will not be included in the PP analysis for either Part A or Part B. In addition subjects may be excluded from the PP analysis at specified visits only. As an example, some major Protocol Deviations may occur post Day 29, such as certain prohibited concomitant medication. In this instance the immunogenicity results after the occurrence of the protocol deviation will be removed from the PP analysis; the relevant subject remains in the PP population.

As the PP population encompasses the definition of the IMM Population, missing Visit 1 immunogenicity samples have also been deemed a major PD at the time of Part A analysis reporting due to the need for a sample to satisfy the requirement of whether the subject is CHIKV seronegative at baseline and to compare titers to baseline.

10.6.1 Exclusion of Time Points in Per Protocol Analysis

In the PP analysis of immunogenicity, samples with extensive time window deviations will be excluded from the analysis, even if the subject may remain in the PP population. Any scheduled immunogenicity sample collected outside of the visit windows defined in the table below will be excluded from the PP analysis.

Due to the fast onset of titer generation after immunization with VLA1553 and the long-term persistence of the titer without significant decrease over one year, the following protocol deviations related to time window deviations are classified as "minor protocol deviations" and do not exclude these subjects from the PP population (except for Visit 3 out of window as defined in section 10.6).

Study Part	VISIT	Study Day (Visit Window)
[redacted]	Visit 0 (Screening)	Day -28 to -0 (prior to Visit 1)
	Visit 1	Day 1
	Visit 2	Day 8 (Week 1) [redacted]
	Visit 3	Day 29 (Month 1) [redacted]
	Visit 4	Day 85 (Month 3) [redacted]
	Visit 5	Day 180 (Month 6) [redacted]

Sample testing issues may also lead to exclusion from the PP analysis for particular timepoints.

10.7 [redacted]

10.8 [redacted]

10.9 Randomized Population

The randomized population contains all enrolled and randomized subjects in the study.

[redacted]

11.0 Analyses Part A and Part B

11.1 Planned Analysis Timepoints

There are 2 planned data analyses on this study:

- Part A includes safety and immunogenicity data after all subjects have completed Visit 3 (Day 29).
- Part B includes safety and immunogenicity data after all subjects have completed Visit 5 (Month 6).

Individual study parts will be analyzed sequentially.

The study will be unblinded for Part A analysis once the final subject has completed Visit 3 and database lock for Part A has occurred (blind will be maintained for study sites and subjects) and Part B final report will be submitted for Biologics License Application (BLA) filing.

The analyses to be done at each study part are specified within each section of the statistical methods part of this SAP.

For the Part A analysis, data up to and including Visit 3 (Day 29) or ET if earlier will be kept for all subjects, for the Part B analysis all data will be kept for all subjects. All AEs and concomitant medications with a start date up to and including the date of the cutoff visit for each subject will be included in the analysis. Any record with a start date prior to the cutoff which has a stop date recorded after the cutoff visit for the analysis will be classed as ongoing for the relevant study part.

11.2 Data Safety Monitoring Board

An independent unblinded DSMB will be utilized for this study. The DSMB will meet to review accumulating safety data on a regular basis until all subjects have received the vaccination at Day 1 and until all subjects have completed Visit 2 or 3. In addition, the DSMB will periodically review accruing safety information throughout the study, as applicable. Additional meetings of the DSMB may be called at the discretion of the Sponsor, e.g. to address any safety concerns arising during the conduct of the study.

The DSMB will ad hoc review cases of SAEs, AESIs and severe (Grade 3) solicited AEs. The DSMB will periodically review listings and summary tabulations of SAEs, Deaths, Solicited AEs, Unsolicited AEs.

A DSMB charter including a detailed description will be prepared. A separate DSMB table and listing shell document will also be created which will specify the outputs to be produced for review at these meetings.

12.0 Statistical Methods

Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous variables will generally be summarized using the number of observations (n), mean, Standard Deviation (SD), median, 25th quartile (Q1), 75th quartile (Q3), minimum and maximum. Summaries of CHIKV-specific NT values will present the number of observations (n), GMT, GSD, median, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean, GSD, median, Q1, and Q3 to a further decimal place, and the SD and GSD to two additional decimal places.

Where relevant, estimates will be presented with 95% two-sided CIs.

All statistical analysis will generally be based on observed values, missing values will not be imputed. In case of > 5% of missing values for the primary immunogenicity analysis, a separate sensitivity analysis will be performed where multiple imputation methods will be applied in order to evaluate the possible at impact of missing values on these results. Further details are given in Section 12.5.3.2

For the analyses of each study part, all available data will be included, regardless of the subject status during that part of the study. For example, if a subject discontinued the study in part A, they would still be included in any summaries of Part A timepoints in Part B.

Unless otherwise specified, all data collected during the trial will be presented in the subject data listings.

All analyses will use SAS version 9.4 or higher.

12.1 Subject Disposition

The number and percentage of subjects screened, randomized and vaccinated in the study will be presented. The number and percentage of subjects who withdrew from the study prematurely during each part and a breakdown of the corresponding reasons for early termination and discontinuation will be presented for the Safety and IMM populations.

Tabulations of the number and percentage of subjects included in each analysis set will be provided. Reasons for exclusion from each analysis set will not be tabulated, but will be listed.

The number and percentage of subjects in the study at each timepoint will also be presented.

A tabulation of the number and percentage of subjects randomized at each center will be presented.

12.2 Protocol Deviations

The study specific Protocol Deviation Guidance Document defines all important protocol deviations.

Per PRA processes, protocol deviations data will be entered into our system of record (PSO). The study team and the Sponsor will conduct on-going reviews of the deviation data from PSO and the resulting set of evaluable subjects throughout the study, adjusting the deviation criteria as seems appropriate. The evaluable subjects set must be finalized at the post-freeze data review meeting (or earlier), prior to the database lock for each part of the study.

Protocol deviations will be classified into major or minor protocol deviations based on their possible impact on the study results in a blind data review meeting prior to the database snapshots at each study part. Major deviations are those which will lead to exclusion from the Per Protocol analysis set.

A tabulation of the number and percentage of protocol deviations by deviation types and deviation category will be provided for each study part on the Safety population, and repeated on the IMM and elMM populations at Part B. A by-subject listing of all protocol deviations will be presented for the Safety population.

In addition, a separate table and listing of COVID-19 specific protocol deviations will be produced.

12.3 Prior and Concomitant Medications

Prior and concomitant medications, categorized by ATC level 2 and preferred term (PT) according to WHODrug (Version B3 Sep2020 or later), will be summarized separately. The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each medication group and subgroup. Each concomitant medication will be coded to a single ATC code, taking into account the indication for the use of the medication as documented on the CRF.

The summary of prior medications will include any medication with a stop date prior to vaccination (Day 1). Prior medications with a stop date more than 14 days prior to vaccination will not be included in the summary table, but will be listed. Concomitant medications are those with a start or end date on or after date of vaccination.

Prior medication summary will be repeated on the Randomized population stratified by immunogenicity versus non-immunogenicity subset.

The concomitant medication summaries for each study part will be cumulative, so the summary for each part of the study will contain any concomitant medications taken during previous study parts.

12.4 Demographic and Baseline Characteristics

Demographic characteristics to be summarized will include gender, ethnicity, race, age at screening (years), age group (18 – 64 years, ≥65 years), height (cm), weight (kg) and body mass index (BMI) (kg/m^2).

Medical history will be summarized by system organ class (SOC) and PT using the current version of MedDRA.

A separate summary of vaccination history at baseline will be provided.

All demographic and baseline summaries will be provided on the Safety population. Additionally, the summary of demographic characteristics will be presented for the IMM, IMM Elderly and PP populations and an additional summary on the Safety population with demographics stratified by age stratum. All demographic and baseline data will be listed.

Demographic and baseline summaries will be repeated on the Randomized population stratified by immunogenicity versus non-immunogenicity subset.

12.5 Immunogenicity Analyses

12.5.1 Hypothesis Testing Strategy and Multiplicity

A formal hypothesis test is defined for the primary immunogenicity analysis, using a one-sided significance level of 2.5%. There will be no adjustment for multiplicity for any immunogenicity endpoints.

12.5.2 Sub-group Analyses

All immunogenicity analyses will be repeated by age stratum.

12.5.3 Primary Immunogenicity Endpoint

The primary immunogenicity endpoint is the proportion of subjects with a seroprotective CHIKV antibody level (defined as [redacted] for baseline negative subjects) 28 days post-vaccination.

The primary immunogenicity analysis will compare the SPR against a non-acceptance threshold of 70%. An exact binomial test for the null-hypothesis H0: SPR ≤70% against the alternative H1: SPR >70% with a one-sided significance level of 2.5% will be applied and exact (Clopper-Pearson) two-sided 95% CIs will be calculated. This will be presented for the PP population.

12.5.3.1 Pooling of Sites

Separate summaries by site are not planned.

12.5.3.2 Sensitivity Analyses

All primary and secondary immunogenicity analyses will be repeated on the IMM and eIMM populations.

Additionally, if there are >5% of missing values out of the number of subjects in the PP population on Day 29 for the primary immunogenicity analysis of seroprotection on Day 29, a separate sensitivity analysis will be performed applying multiple imputation methods. The multiple imputation is based on the missing at random assumption. Treatment group and age group and whether seroprotection is achieved on Day 8 will be used to impute the missing Day 29 seroprotection responses. A seed number of 15532021 will be used. The MI procedure in SAS will be used with the MONOTONE LOGISTIC statement for the imputation, and the imputation will be repeated 500 times. The proportions and 95% CI for the SPR in each treatment group and the difference between proportions and associated 95% CIs will be estimated for each imputed data set as in the primary analysis, and the results will be combined using the MIANALYZE procedure in SAS to produce an overall estimate.

12.5.4 Secondary Immunogenicity Endpoints

12.5.4.1 Comparison of Geometric Mean Titer

A summary of the NTs in each study arm will be presented at all post-baseline timepoints (Day 8, Day 29, Day 85 and Day 180) for the PP, IMM and eIMM populations. Two-sided 95% CIs will be presented for the GMT in each study arm at each timepoint.

The GMT will be compared between VLA1553 and placebo groups using an analysis of covariance (ANCOVA) model including treatment group and age stratum as factors. Estimates of treatment differences in GMT and associated 95% CIs will be presented.

Day 1 will also be presented, but CI and inferential statistics will not be provided as all subjects in PP, IMM and eIMM will be seronegative at baseline (Day 1),), hence by definition have a value of 10 imputed for analysis and there is no variation to calculate a meaningful CI or the ANCOVA model.

A line plot of the GMT at each study timepoint will be produced by treatment group in the PP population.

A reverse cumulative distribution plot of the proportion of subjects by titer value will be produced. This will be done for the by arm, and will include both Day 29 and Day 180. This plot will be repeated by age strata.

12.5.4.2 Seroprotection Rate

The number and percentage of subjects meeting the criteria for seroprotection will be presented for each study timepoint, including baseline (Day 1). The denominator for the percentage will be the number of baseline negative subjects with non-missing NT values at each timepoint. Two-sided exact (Clopper-Pearson) 95% CIs for the SPR will be presented for post-baseline visits.

The VLA1553 and placebo groups will be compared using Fisher's Exact test for post-baseline visits. In addition, the difference in proportion between the two treatment groups, and exact (Clopper-Pearson) two-sided 95% CIs for the difference in treatment groups will be presented.

This summary will be repeated by titer threshold, evaluating the number of baseline negative subjects meeting the criteria $\mu PRNT_{50} \geq x$, where x takes the values [redacted]

Bar charts of the percentage of subjects meeting the seroprotective criteria will be produced by study visit and treatment group.

12.5.4.3 Seroconversion Rate

The SCR rate will be summarized similarly to the SPR, but will only be presented on Days 29 and 180.

12.5.4.4 Fold-increase in Neutralizing Antibody Titer

A descriptive summary of the continuous fold-increase in CHIKV-specific NT from baseline will be produced for all post-baseline timepoints. This summary will include n, mean, SD, median, Q1, Q3 and range.

In addition, a categorical summary of subjects reaching at least 4-fold, 8-fold, 16-fold, and 64-fold increase in $\mu PRNT_{50}$ compared to baseline will be produced for all post-baseline timepoints. Two-sided Clopper-Pearson 95% CIs for the percentages will be presented.

12.5.5 Other Immunogenicity Endpoints

For those subjects who are baseline positive only, the proportion of subjects who meet the seroconversion criterion at each timepoint will be summarized descriptively and listed. The proportion of baseline positive subjects reaching at least 4-fold, 8-fold, 16-fold and 64-fold increase in NT values from baseline will be summarized in a similar way. The NT values and the continuous fold-increase for baseline positive subjects will be summarized descriptively. The Safety population will be used for these analyses.

12.5.6 [redacted]

12.5.7 [redacted]

12.6 Safety Analyses

12.6.1 Adverse Events

Safety tabulations will include both solicited AEs and unsolicited AEs, unless otherwise specified. Number and proportion of subjects, plus number of events in each category will generally be presented. Two-sided exact (Clopper-Pearson) 95% CIs will be provided for overall AE rates in the summary AE table, and by SOC and PT. Differences between the study arms will be assessed for significance using Fisher's exact test for overall rates.

Summaries of AEs categorized by SOC and PT coded according to the MedDRA dictionary will be produced. Within these summaries counting will be by subject not event and subjects are only counted once within each SOC or PT.

Where AEs are presented by severity (Mild, Moderate, Severe), SOC and PT, subjects with multiple events within a particular body system or preferred term will be counted once under the category of their most severe event within that SOC or PT.

In summaries of AEs which are categorized by relationship to IMP, SOC and PT, AEs with a causality reported as probable or possible will be considered related to the IMP. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most drug-related event within that SOC or PT.

All AE tables of secondary AE analyses will be produced by age group in addition to the total of both age groups combined.

All AE tabulations will be presented for the Safety population.

All AEs recorded on the CRF will be listed.

12.6.1.1 Secondary Adverse Event Analyses

The following tabulations will be produced to analyze the secondary safety endpoints:

- All unsolicited AEs up to study Day 29 will be presented by SOC and PT, as well as summaries by SOC, PT and severity. Treatment groups will be compared using Fisher's exact test (Part A);
- Solicited injection site and systemic reactions within 10 days post-vaccination by PT (Parts A, B);
- Solicited injection site and systemic reactions within 10 days post-vaccination by PT and severity (Parts A, B);
- All AEs during the entire study period by SOC and PT (Parts A, B);
- All AEs during the entire study period by SOC, PT and severity (Parts A, B);
- All Related AEs during the entire study period by SOC and PT (Parts A, B);
- SAEs by SOC and PT during entire reporting period (Parts A, B);
- Related SAEs by SOC and PT during entire reporting period (Parts A, B);
- AESI within 2 to 21 days post-vaccination by SOC and PT (Part A);
- AESI for ongoing events from Part A (Part B)
- Related AESI within 2 to 21 days post-vaccination by SOC and PT (Part A);

12.6.1.2 Other Adverse Event Analyses

The following tables will also be presented for the specified study part:

- AE summary table showing the overall number and percentage of subjects with any AE, any related AE, any severe AE, any related severe AE, any solicited AE, any severe solicited AE, any related solicited AE, any related severe solicited AE, any solicited injection site reaction, any severe solicited injection site reaction, any solicited systemic AE, any severe solicited systemic AE, any unsolicited AE, any related unsolicited AE, any severe unsolicited AE, any related severe unsolicited AE, any SAEs, any related SAEs, any related solicited SAE, any related unsolicited SAE, any AESI as assessed by the investigator, any AESI as assessed by the DSMB, any related AESI as assessed by the investigator, any medically attended AE, any related medically attended AE, any related medically attended solicited AE, any related medically attended unsolicited AE, any AE leading to withdrawal from study, any unsolicited AE leading to withdrawal from study and any solicited AE leading to withdrawal from study. For each study arm 95% CIs will be presented for

percentages. Differences between the study arms will be assessed for significance using Fisher's exact test (Parts A, B);

- AE summary table as above, split by whether the subject was seropositive or seronegative at baseline (Parts A, B);
- Unsolicited related AEs up to Day 29 by SOC and PT (Part A);
- Unsolicited related AEs up to Day 29 by SOC, PT and maximum severity (Part A);
- Solicited injection site and systemic reactions within 10 days post-vaccination by PT excluding recall data (Parts A, B);
- Solicited related injection site and systemic reactions (Parts A, B);
- Solicited related injection site and systemic reactions by maximum severity (Parts A, B);
- AESI by SOC, PT and maximum severity (Part A);
- Related AESI by SOC, PT and maximum severity (Part A);
- Solicited local and systemic AEs tabulated by subject diary day up to Day 11. This tabulation will be based on onset day of the AE. If not possible to assign a day due to partial onset date then it will be assumed to be Day 1 (Parts A, B);
- Summary of duration of solicited local and systemic reactions. Summary statistics for duration of solicited reaction (days) will be presented by symptom in each study arm (Parts A, B);
- Maximum fever temperature post-vaccination up to Day 11, for subjects who experienced fever (Parts A, B);
- Unsolicited AEs by SOC and PT (Parts A, B);
- Unsolicited related AEs by SOC, PT (Parts A, B);
- Any unsolicited related severe AE by SOC and PT (Parts A, B);
- Any AE occurring at a frequency of at least 10% in at least one study arm by PT (Parts A, B);
- Any AE occurring at a frequency of at least 1% in at least one study arm by PT (Parts A, B);
- Any related AE occurring at a frequency of at least 10% in at least one study arm by PT (Parts A, B);
- Any related AE occurring at a frequency of at least 1% in at least one study arm by PT (Parts A, B);
- Any medically attended AE by SOC, PT (Parts A, B);
- Any medically attended AE by SOC, PT and Maximum Severity (Parts A, B);
- Any AE leading to withdrawal from study by SOC and PT (Parts A, B);

AE rates will be plotted in forest plots by treatment group for all AEs, severe (related) AEs, related AEs, SAEs and AESIs. Radar plots will be produced for subjects with solicited AEs, displaying the maximum severity of any AEs within each of the categories of solicited reaction.

A histogram showing the frequency of different AE durations will be produced for the solicited AEs of Fever and Arthralgia, by severity. The x-axis will include the duration in days, with the y-axis measuring frequency. Severity will be marked by colors within each bar.

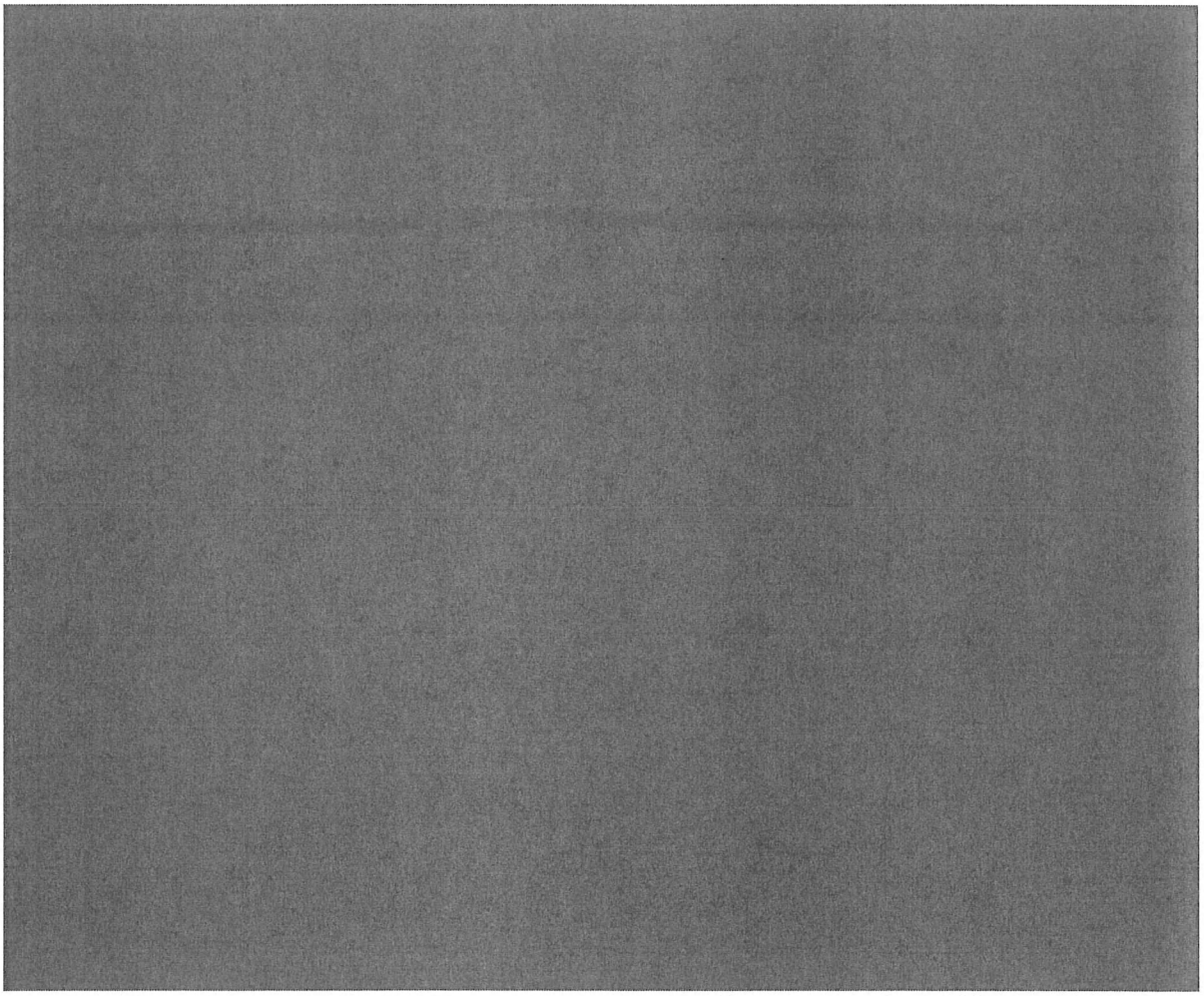
Subject AE and diary data will be listed. Separate listings will be produced for the following AE categories: severe solicited AEs; severe unsolicited AEs; AEs of Arthralgia or Arthritis; AESI.

12.6.2 Laboratory Data

Safety laboratory values will be assessed for all subjects at baseline, and for the immunogenicity subset post-baseline. Laboratory values will be evaluated according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Food and Drug Administration). Clinically significant laboratory values will be documented as AEs.

Changes in laboratory values from study entry will be analyzed descriptively for clinical chemistry, hematology, coagulation and urinalysis. System International units will be used for all laboratory parameters. The rate of subjects with urinalysis results according to the test manufacturer's results categories will be calculated overall and by visit. Baseline values will be summarized separately for subjects in the safety population and subjects in the immunogenicity subset.

The rates of subjects with laboratory assessments with maximum postbaseline grade falling into the grade 0 vs. 1 through 4 will be calculated. Shift tables of laboratory results by grade will be presented for the maximum postbaseline grade. For urinalysis parameters, shift tables of laboratory results by whether normal or abnormal will be produced by timepoint.



12.6.3 Vital Signs

Vital signs will be summarized descriptively at each study timepoint they are collected, including screening, Day 1 pre-vaccination and Day 1 post-vaccination. Change from baseline values will be summarized for the post-vaccination timepoint. Vital signs parameters to be summarized include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (bpm) and body temperature (°C).

All vital sign data will be included in a by-subject listing.

12.6.4 Physical Examinations

A summary table of hand stiffness results by timepoint and change from baseline by timepoint will be presented.

Due to certain sites initially performing the hand stiffness test incorrectly (measuring >0 cm where no stiffness was seen), a second summary of hand stiffness results will be presented to limit the impact of the incorrect results. In cases where hand-stiffness was measured incorrectly, sites were instructed to remain consistent within subjects, and hence the change from baseline remains valid. In this sensitivity summary, results from subjects whose measurements were done incorrectly will be excluded from the summary statistics at each timepoint, but will be included in the change from baseline summaries at each post-baseline timepoint. Subjects measured incorrectly were identified by Notes to File from each affected site.

All physical examination and hand stiffness data will be listed. Physical examination findings will be flagged for clinical significance in the listing.

13.0 References

Food and Drug Administration, C. f. B. E. a. R. "Guidance for Industry: Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

14.0 Important Protocol Deviation Identification Listings

In order to help identify protocol deviations which would lead to exclusion from the PP population, listings of concomitant medications, protocol deviations, and subject visits outside of time window will be produced at the time of database freeze for Part A. Protocol Deviations were assessed on an ongoing basis until completion of Part B.

15.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Classification
BLA	Biologics License Application
BMI	Body Mass Index
CI	Confidence Interval
CHIKV	Chikungunya Virus
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
eIMM	Immunogenicity Elderly

ET	Early Termination
GCE	Genome Copy Equivalents
GMT	Geometric Mean Titer
GSD	Geometric Standard Deviation
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IMM	Immunogenicity
IMP	Investigational Medicinal Product
IXRS	Interactive Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NT	Neutralizing Titer
PP	Per Protocol
PT	Preferred Term
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SD	Standard Deviation
SOC	System Organ Class
SPR	Seroprotection Rate
WHODrug	World Health Organization Drug Dictionary
µPRNT	Micro Plaque Reduction Neutralization Test