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Applicant	Valneva Austria GmbH
Established Name	Chikungunya Vaccine, Live-Attenuated , Absorbed
(Proposed) Trade Name	IXCHIQ
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	A dose of (b) (4) TCID ₅₀ per 0.5 mL of the lyophilized formulation
Dosage Form(s) and Route(s) of Administration	Lyophilized dosage form which is reconstituted with 0.5 mL sterile water for injection
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years and older

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1. Executive Summary

Valneva, the applicant, submitted an original Biologics License Application (BLA), STN 125777/0, of the live-attenuated Chikungunya virus vaccine VLA1553 for active immunization for the prevention of disease caused by Chikungunya virus (CHIKV) in adults 18 years of age and older using an accelerated pathway.

In accordance with the accelerated approval pathway, clinical efficacy was assessed using surrogate immunogenicity endpoints based on the determination of CHIKV-specific neutralizing antibody titers from serum samples collected before and after vaccination, using a micro plaque reduction neutralization test (μ PRNT). A μ PRNT₅₀ ≥ 150 was agreed by FDA as reasonably likely to predict protection. This surrogate of protection was supported with animal experiments including passive transfer of VLA1553-specific human sera. This BLA is supported by three completed clinical studies (VLA1553-101, VLA1553-301 and VLA1553-302) conducted in healthy adults in the United States. Study VLA1553-301 was the pivotal, placebo-controlled, Phase 3 study to evaluate the safety and immunogenicity of VLA1553 (lyophilized formulation) in younger adults (18 to <65 years) and older adults (65 years and above) for 6 months after a single immunization at the recommended dose of (b) (4) 50% tissue culture infectious dose (TCID₅₀). The primary endpoint was proportion of participants with a seroprotective CHIKV antibody level (seroprotection rate; SPR) defined as 50% plaque reduction in a micro plaque reduction neutralization test (μ PRNT₅₀) ≥ 150 for baseline negative participants 28 days post-vaccination. Study VLA1553-302 was a Phase 3 lot-to-lot consistency study to demonstrate manufacturing consistency of three manufacturing lots of VLA1553 (lyophilized formulation) and to expand the safety and immunogenicity assessment in healthy adults (18 to 45 years). Study VLA1553-101 was the first-in-human, dose-finding, Phase 1 study to compare the safety and immunogenicity of VLA1553 (liquid formulation) after a single-dose immunization at three different dosage levels and after re-vaccination at 6 or 12 months in healthy adults (18 to 45 years). This statistical review focuses on studies VLA1553-301 and VLA1553-302.

VLA1553-301

Overall, 4115 participants (3082 VLA1553 and 1033 placebo) were included in the safety population. The per-protocol (PP) population included 362 participants, of which 266 participants were randomized to VLA1553 and 96 participants to placebo. The seroprotection rate was 98.9% (95% confidence interval [CI]: 96.7% to 99.8%) on Day 29 and remained high, with 98.0% and 96.3% of responders (i.e., achieving μ PRNT₅₀ ≥ 150) in the VLA1553 arm on Day 85 and Day 180, respectively. The protocol-specified success criterion that the 95% lower confidence limit of SPR being >70% at Day 29 was met.

Solicited systemic adverse events (AEs) were reported by more participants in the VLA1553 arm than in the placebo arm (1547/3082 [50.2%] and 278/1033 [26.9%] participants, respectively). Solicited injection site AEs were also reported by more participants in the VLA1553 arm than in the placebo arm (463/3082 [15.0%] and 115/1033 [11.1%] participants, respectively).

Up to Day 29, more participants reported unsolicited AEs in the VLA1553 arm than in the placebo arm (687/3082 [22.3%] and 138/1033 [13.4%] participants, respectively). Overall, most unsolicited AEs were of mild or moderate severity.

During the review, updated safety datasets were submitted to BLA 125777/0.57 in response to data standard reviewer's comments. Safety analyses with the updated datasets show that slightly higher percentages (<0.5%) of participants in Study 301 reporting solicited systemic adverse reactions in both treatment groups, and unsolicited adverse events that occurred within 28 days following vaccination were reported in 21.8% of 3082 participants who received VLA1553 versus 13.3% of 1033 participants who received placebo.

In Study VLA1553-301, 361 participants (11.7%) in the IXCHIQ group (n= 3082) reported chikungunya-like adverse reactions (defined as fever $\geq 38^{\circ}\text{C}$ / 100.4°F and one or more of any of the following symptoms: arthralgia or arthritis, myalgia, headache, back pain, rash, lymphadenopathy, or certain neurological, cardiac or ocular symptoms, that occurred with an onset within 30 days after vaccination), including 48 participants (1.6%) who reported severe chikungunya-like adverse reactions. Six (0.6%) participants in the placebo group (n= 1033) reported chikungunya-like adverse reactions, none of which were severe. Fourteen IXCHIQ recipients had prolonged (duration greater than 30 days) chikungunya-like adverse reactions (range 33 days to at least 6 months). Two of the 3082 IXCHIQ recipients experienced serious chikungunya-like adverse reactions.

VLA1553-302

In total, 408 participants vaccinated with VLA1553 (136, 137, and 135 subjects received vaccine from Lot 1, Lot 2, and Lot 3, respectively) were included in the safety analysis set. In the PP population, GMTs on Day 29 were 2556.7 (Lot 1 arm), 2767.7 (Lot 2 arm), and 2613.7 (Lot 3 arm) . The 95% confidence intervals (CIs) for the pairwise GMT ratios were all within the pre-specified acceptance margins of 0.67 to 1.5. Thus, the primary objective of demonstrating lot-to-lot consistency was achieved.

Safety results from study VLA1553-302 were similar to those for the VLA1553 arm from study VLA1553-301. Solicited AEs of injection site reactions were reported by 79 (19.4%) of the 408 participants vaccinated with VLA1553. Solicited AEs of systemic reactions were reported by 233 (57.1%) participants vaccinated with VLA1553. No notable differences between lots were seen in the occurrences of solicited AEs.

Up to Day 29, unsolicited AEs were reported in 102/408 (25.0%) subjects with more subjects in the Lot 1 (38/136 [27.9%] subjects) and Lot 3 arms (42/135 [31.1%] subjects) than in the Lot 2 arm (22/137 [16.1%]). Most unsolicited AEs were graded as mild or moderate.

Conclusion

Study VLA1553-301 and Study VLA1553-302 met the success criteria for the primary immunogenicity endpoints. I defer to the clinical reviewer on the safety assessment of this vaccine.

2. CLINICAL AND REGULATORY BACKGROUND

A vaccine efficacy study to demonstrate disease prevention was considered not feasible due to the sporadic epidemic occurrence of symptomatic chikungunya disease and due to ethical concerns of human challenge models. Therefore, the clinical efficacy of VLA1553 was assessed using surrogate immunogenicity endpoints based on the determination of CHIKV-specific neutralizing antibody titers. Upon review of nonclinical data from a nonhuman primate (NHP) passive transfer study under IND 17854, FDA agreed that achieving a neutralizing antibody titer ≥ 150 (as determined by the μ PRNT assay) could be considered reasonably likely to predict a clinical benefit.

On August 11, 2023, FDA issued a Major Amendment acknowledgement letter to the applicant due to a substantial amount of new information in the post-marketing confirmatory trial protocol (b) (4) -402 submitted on July 31, 2023. Therefore, the action due date was extended by three months to November 22, 2023.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The quality of the submission was sufficient for a statistical evaluation.

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues were identified.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

I defer to reviewers from other disciplines.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The statistical review of this BLA comprises two parts: clinical (immunogenicity and safety) data and clinical assay validation. This review focus on the clinical data from the two Phase 3 studies (VLA1553-301 and VLA1553-302).

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following submissions were reviewed:

- STN 125777/0.3 Module 2.5 Clinical Overview
- STN 125777/0.3 Module 2.7 Clinical Summary
- STN 125777/0.3 Module 5 Clinical Study Reports
- STN 125777/0.21 Module 1.2 Cover Letters
- STN 125777/0.37, 125777/0.39, 125777/0.40 Module 1.11 Information Not Covered Under Modules 2 to 5

5.3 Table of Studies/Clinical Trials

Table 1 displays an overview of the clinical trials providing immunogenicity and safety data to support this application.

Table 1. Overview of Clinical Trials

Protocol No.	Study Design	No. of Subjects (By Treatment Group)	Number of Sites, Location Study Status
VLA1553-301	Placebo-controlled, randomized, double-blinded, multicenter	VLA1553 (1×10^4 TCID ₅₀ per 0.5 mL): 3093 Immunogenicity subset: 375 Placebo (0.5 mL): 1035 Immunogenicity subset: 126	43 sites in the United States First participant in: 17-Sep-2020 Last participant out: 15-Oct-2021 Completed
VLA1553-302	Lot-to-lot, randomized, double-blinded, multicenter	VLA1553 (1×10^4 TCID ₅₀ per 0.5 mL): 136, 137, 136 subjects in Lot 1, Lot 2, and Lot 3, respectively	12 sites in the United States First participant in: 22-Feb-2021 Last participant out: 10-Dec-2021 Completed
VLA1553-101	Sentinel dosing: Dose-escalation, open-label, single center Randomized dosing: Three parallel doses, randomized, observer-blinded, multicenter	VLA1553 low dose: 31 (3.2×10^3 TCID ₅₀ per 0.1 mL + re-vaccination at Month twelve 3.2×10^5 TCID ₅₀ per 1 mL) VLA1553 medium dose: 30 (3.2×10^4 TCID ₅₀ per 1 mL + re-vaccination at Month twelve 3.2×10^5 TCID ₅₀ per 1 mL) VLA1553 high dose: 59 (3.2×10^5 TCID ₅₀ per 1 mL + re-vaccination at Month six/twelve 3.2×10^5 TCID ₅₀ per 1 mL)	3 sites in the United States First participant in: 05-Mar-2018 Last participant out: 23-Jul-2019 Completed

Source: Adapted from Table 2.7.3-1 in Clinical Efficacy submitted to BLA 125777/0.3.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: VLA1553-301

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

6.1.1 Objectives

Primary Objective:

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

Secondary Objective:

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

6.1.2 Design Overview

This was a prospective, randomized, double-blinded, multicenter, pivotal clinical study evaluating the single dose of VLA1553 in comparison to a placebo control.

Participants were allocated in a 3:1 ratio to VLA1553 (n=3093) or placebo arm (n=1035). VLA1553 or placebo was administered on Day 1. It was planned to stratify 4060 participants into 2 age strata of participants aged 18 to 64 years (Stratum A: approximately 3653 participants [planned]; 3652 [actual]) and participants of 65 years of age or above (Stratum B: approximately 407 participants [planned]; 463 [actual]).

6.1.3 Population

The study enrolled approximately 4060 healthy adult participants.

6.1.4 Study Treatments or Agents Mandated by the Protocol

All participants received a single intramuscular vaccination in the deltoid region of the arm of the participant with either VLA1553 (1×10^4 TCID₅₀ per 0.5 mL) or placebo (phosphate buffered saline [PBS], 0.5 mL).

6.1.6 Sites and Centers

Forty-three sites in the United States.

6.1.7 Surveillance/Monitoring

Please refer to clinical reviewer's memo.

6.1.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoint:

- Proportion of participants with a seroprotective CHIKV antibody level defined as 50% plaque reduction in a micro plaque reduction neutralization test (μ PRNT₅₀) ≥ 150 for baseline negative participants 28 days post-vaccination.

Success criterion: The lower limit of the 95% CI of the SPR is greater than 70%.

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;
- Proportion of subjects with seroprotective levels (defined as μ PRNT₅₀ ≥ 150 for baseline negative subjects) on Day 8, Day 85 and Month 6 post-vaccination as determined by μ PRNT assay;
- Proportion of subjects with seroconversion at Day 29 and Month 6 as determined by μ PRNT assay (where seroconversion is defined as CHIKV-specific NT of ≥ 20 for baseline negative subjects and >4 -fold rise for baseline positive subjects);
- Fold increase of CHIKV-specific NT determined by μ PRNT 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 μ PRNT assay.

Secondary Endpoints (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 adverse event of special interest (AESI) within 2 to 21 days post-vaccination.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary immunogenicity analysis

The primary immunogenicity analysis compared the SPR against a threshold of 70%. An exact binomial test for the null-hypothesis H_0 : $SPR \leq 70\%$ against the alternative H_1 : $SPR > 70\%$ with a one-sided significance level of 2.5% was applied and exact (Clopper-Pearson) two-sided 95% CIs was calculated.

Sample size determination

The sample size for this study was selected to provide a sufficient safety database with regards to rare AEs. Approximately 3000 VLA1553 vaccinated subjects allowed for the detection of at least one vaccine-related rare event (with an incidence rate of 1/1000) with a probability of 94% in this study.

The sample size of the immunogenicity subset allowed 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 antibody level at Day 29. When a seroprotection rate of 80% was assumed, 200 VLA1553-vaccinated subjects would be necessary for 90% statistical power. In order to account for drop-out/major protocol deviations and 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 were enrolled into the immunogenicity subset.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Safety population contained all subjects who entered the study and received one vaccination. Subjects were analyzed as treated. This was the primary analysis set for all safety endpoints.

The Immunogenicity (IMM) population contained all randomized and vaccinated subjects of the immunogenicity subset who were CHIKV seronegative at baseline (defined as μ PRNT₅₀ titer <20) and had at least one evaluable post-baseline titer measurement after vaccination. Subjects were analyzed according to the study arm they had been randomized to.

The Per Protocol (PP) population contained all IMM population subjects who had no major protocol deviations that could impact the immune response. Subjects were analyzed in the PP population according to the study arm they have been randomized to. This was the primary analysis set for all immunogenicity analyses.

In total, 4128 participants were randomized, of whom 3093 and 1035 were randomized to the VLA1553 and placebo arms, respectively (Table 2). The PP population was composed of 362 participants (266 in the VLA1553 arm [including 207 participants of Stratum A (18 to 64 years) and 59 participants of Stratum B (≥ 65 years)], and 96 in the placebo arm [including 73 participants of Stratum A and 23 participants of Stratum B]).

Table 2. Analysis Populations in Study 301

	VLA1553	Placebo	Total
	n (%)	n (%)	n (%)
Randomized population	3093 (100.0)	1035 (100.0)	4128 (100.0)
Safety population ^a	3082	1033	4115
Included in Immunogenicity Subset	375 (12.1)	126 (12.2)	501 (12.1)
Immunogenicity Population (IMM)	344 (11.1)	118 (11.4)	462 (11.2)
Per Protocol Population (PP)	266 (8.6)	96 (9.3)	362 (8.8)

a. Percentages were not included because participants are grouped according to treatment actually received and not randomized treatment.

Source: Adapted from Table 17 in the CSR for Study VLA1553-301.

Reviewer's comments:

1. *There were two data analyses planned for the study:*
 - *Part A included safety and immunogenicity data after all participants have completed Visit 3 (Day 29). Results of the Part A analysis were presented in a previous Clinical Study Report (CSR).*
 - *Part B included safety and immunogenicity data after all participants have completed Visit 5 (Day 180). The CSR submitted to this BLA presented the results of Part B analysis.*

Due to post unblinding protocol deviations review, several changes to the protocol deviation database occurred, leading to changes in the composition of the PP population between Part A and Part B analyses. The PP population presented in the table above was based on Part B analysis. The changes to the PP population were described in an appendix in the statistical analysis plan (SAP) submitted to Section 16.1.9 for Study VLA1553-301. I examined the list of impacted subjects and found that the changes to the PP population would not lead to substantial impact on the primary immunogenicity results that would change the conclusion.

2. *Due to difficult recruitment of elderly subjects during the SARS-CoV-2 pandemic, the applicant additionally defined an elderly immunogenicity population (eIMM), as an extra analysis set. Randomly selected subjects in Stratum B, i.e., subjects ≥ 65 years of age, from the safety analysis population were used to fill up the eIMM population and to reach the originally planned subject number (i.e., 154) in age Stratum B. The eIMM population consisted of 503 subjects (376 in the VLA1553 arm [including 269 subjects of Stratum A and 107 subjects of Stratum B], and 127 in the placebo arm [including 94 subjects of Stratum A and 33 subjects of Stratum B]).*

Overall, 3644/4115 (88.6%) participants completed the Day 180/Month 6 Visit (Part B of the study). A total of 471 of 4115 (11.4%) participants discontinued early from the study; 249 participants were lost to follow-up, 186 withdrew consent, 21 were withdrawn for other reasons, 10 were withdrawn following physician decision, 3 died, and 2 were withdrawn due to AE. The proportion of subjects who discontinued the study in the VLA1553 and placebo groups were similar (11.6% in the VLA1553 group and 10.9% in the placebo group).

Among the safety population, slightly more female participants (2251/4115 [54.7%]) than male participants were included in the study (Table 3); the majority of participants were white (3309/4115 [80.4%]). Mean age of the participants was 45.0 years. A total of 463 elderly participants (≥ 65 years [Stratum B]) were enrolled. Demographic characteristics were well-balanced in treatment and placebo arms. Demographic characteristics were also comparable between the two age strata, and between the immunogenicity and non-immunogenicity subsets.

Table 3. Demographics and Baseline Characteristics in the Safety Population in Study 301

	VLA1553, N= 3082	Placebo N= 1033	Total N=4115
Age (years)			
Mean (std)	45.1 (15.4)	45.0 (15.6)	45.0 (15.5)
Median	45.0	45.0	45.0
Min, Max	18, 88	18, 94	18, 94
Age Group [n (%)]			
≥18 years – 64 years (Stratum A)	2736 (88.8)	916 (88.7)	3652 (88.7)
≥65 years (Stratum B)	346 (11.2)	117 (11.3)	463 (11.3)
Sex n (%)			
Female	1682 (54.6)	569 (55.1)	2251 (54.7)
Male	1400 (45.4)	464 (44.9)	1864 (45.3)
Race n (%)			
White	2456 (79.7)	853 (82.6)	3309 (80.4)
Black or African American	451 (14.6)	122 (11.8)	573 (13.9)
Asian	51 (1.7)	17 (1.6)	68 (1.7)
American Indian or Alaska Native	27 (0.9)	5 (0.5)	32 (0.8)
Native Hawaiian or other Pacific Islander	13 (0.4)	5 (0.5)	18 (0.4)
Other	84 (2.7)	31 (3.0)	115 (2.8)
Weight (kg)			
	87.8 (22.6)	86.4 (21.9)	87.4 (22.4)
Median	85.0	83.6	84.6
Min, Max	38.7, 247.7	43.8, 197.8	38.7, 247.7
Height (cm)			
Mean (std)	169.8 (9.9)	169.9 (9.9)	169.8 (9.9)
Median	169.0	169.0	169.0
Min, Max	128.8, 199.4	133.9, 204.2	128.8, 204.2

Source: Adapted from Tables 13 and 14 in the CSR for Study VLA1553-301.

6.1.11 Efficacy and Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoints

The study met the success criterion for its primary immunogenicity endpoint against a threshold of 70% on the proportion of participants with a seroprotective level (defined as $\mu\text{PRNT}_{50} \geq 150$ for baseline negative participants) on Day 29. In the PP population, 263/266 (98.9%) participants in the VLA1553 arm on Day 29 reached a seroprotective CHIKV antibody level (Table 4). No meaningful difference in seroprotection rate was observed between Stratum A (98.6% [204/207 participants]) and Stratum B (100.0% [59/59 participants]).

Table 4. Seroprotection Rate for CHIKV-Specific Neutralizing Antibodies on Day 29 (PP Population) in Study 301

	18 to 64 Years (Stratum A)	18 to 64 Years (Stratum A)	≥65 Years (Stratum B)	≥65 Years (Stratum B)	Total	Total
	VLA1553 (N=207)	Placebo (N=73)	VLA1553 (N=59)	Placebo (N=23)	VLA1553 (N=266)	Placebo (N=96)
Participants with Seroprotection [n (%)]	204 (98.6)	0	59 (100.0)	0	263 (98.9)	0
95% CI for Seroprotection Rate	95.8, 99.7	0.0, 4.9	93.9, 100.0	0.0, 14.8	96.7, 99.8	0.0, 3.8

Source: Adapted from Table 18 in the CSR for Study VLA1553-301.

Results obtained in the IMM population were very similar. In the IMM population on Day 29, 321/325 (98.8%) participants in the VLA1553 arm achieved a seroprotective CHIKV antibody level. No meaningful difference in seroprotection rate was observed between the two age strata. In the eIMM population on Day 29, 351/355 (98.9%) participants in the VLA1553 arm achieved a seroprotective CHIKV antibody level.

6.1.11.2 Analyses of Secondary Endpoints

In the PP population, four out of 251 (1.6%) participants in the VLA1553 arm reached the seroprotective CHIKV antibody level on Day 8: two (1.0%) participants of Stratum A (18 to 64 years) and two (3.8%) participants of Stratum B (≥65 years). Seroprotection rates remained high after Day 29, with 241 (98.0%) seroprotected participants in the VLA1553 arm on Day 85 (189 [97.4%] participants of Stratum A [18 to 64 years] and 52 [100.0%] participants of Stratum B [≥65 years]); and 233 (96.3%) seroprotected participants in the VLA1553 arm on Day 180 (Table 5).

Table 5. Seroprotection Rate for CHIKV-Specific Neutralizing Antibodies by Visit (PP Population) in Study 301

	Stratum A VLA1553	Stratum A Placebo	Stratum B VLA1553	Stratum B Placebo	Total VLA1553	Total Placebo
Visit 2 – Day 8 (N^a)	198	70	53	23	251	93
Participants with Seroprotection [n (%)]	2 (1.0)	0	2 (3.8)	0	4 (1.6)	0
95% CI for Seroprotection Rate	0.1, 3.6	0.0, 5.1	0.5, 13.0	0.0, 14.8	0.4, 4.0	0.0, 3.9
Visit 4 – Day 85 (N^a)	194	69	52	22	246	91
Participants with Seroprotection [n (%)]	189 (97.4)	0	52 (100.0)	0	241 (98.0)	0
95% CI for Seroprotection Rate	94.1, 99.2	0.0, 5.2	93.2, 100.0	0.0, 15.4	95.3, 99.3	0.0, 4.0
Visit 5 – Day 180 (N^a)	184	68	58	23	242	91
Participants with Seroprotection [n (%)]	178 (96.7)	0	55 (94.8)	0	233 (96.3)	0
95% CI for Seroprotection Rate	93.0, 98.8	0.0, 5.3	85.6, 98.9	0.0, 14.8	93.1, 98.3	0.0, 4.0

a. Number of µPRNT baseline negative participants (<20) with non-missing titers at the specified time point.

Source: Adapted from Table 21 in the CSR for Study VLA1553-301.

For the VLA1553 arm, GMTs for CHIKV-Specific Neutralizing Antibodies were very similar across age strata, ranging from 3273.7 to 3688.8 on Day 29 in participants of Stratum A and Stratum B, respectively (Table 6). From Day 29 to Day 180, titers decreased but remained significantly higher in the VLA1553 arm, with geometric means of 1083.6 and 752.1 on Day 85 and Day 180, respectively. No notable differences in the GMTs were observed between Stratum A and Stratum B for all the visits.

Table 6. Summary of GMTs for CHIKV-Specific Neutralizing Antibodies by Visit (PP Population) in Study 301

	Stratum A VLA1553	Stratum A Placebo	Stratum B VLA1553	Stratum B Placebo	Total VLA1553	Total Placebo
Visit 2 – Day 8 (N^a)	198	70	53	23	251	93
Geometric Mean (GM)	13.6	10.2	13.4	10.0	13.6	10.2
95% CI for GM	12.22, 15.23	9.92, 10.50	11.05, 16.31	10.00, 10.00	12.36, 14.96	9.94, 10.38
Visit 3 – Day 29 (N^a)	207	73	59	23	266	96
Geometric Mean	3273.7	10.1	3688.8	10.0	3361.6	10.1
95% CI for GM	2860.93, 3746.04	9.89, 10.33	2938.94, 4630.10	10.00, 10.00	2993.83, 3774.45	9.92, 10.25
Visit 4 – Day 85 (N^a)	194	69	52	22	246	91
Geometric Mean	1068.7	10.0	1140.9	10.7	1083.6	10.2
95% CI for GM	934.77, 1221.82	10.00, 10.00	942.97, 1380.31	9.71, 11.78	968.27, 1212.59	9.94, 10.40
Visit 5 – Day 180 (N^a)	184	68	58	23	242	91
Geometric Mean	755.1	10.0	742.8	10.0	752.1	10.0
95% CI for GM	656.01, 869.16	10.00, 10.00	578.36, 954.00	10.00, 10.00	665.91, 849.52	10.00, 10.00

a. Number of μ PRNT baseline negative participants (<20) with non-missing titers at the specified time point.

Source: Adapted from Table 14.2.2.1 in the CSR for Study VLA1553-301.

6.1.11.3 Subpopulation Analyses

All immunogenicity analyses were repeated by age stratum. No notable differences were observed between the two age strata.

6.1.11.4 Exploratory and Post Hoc Analyses

No exploratory and post-hoc analyses were considered in this review.

6.1.12 Safety Analyses

Solicited AEs were collected up to Day 11 after vaccination. Solicited systemic AEs were reported by more participants in the VLA1553 arm than in the placebo arm (1547/3082 [50.2%] and 278/1033 [26.9%] participants, respectively, in Table 7). The most common solicited systemic AE was headache (969/3082 [31.4%] participants in the VLA1553 arm and 151/1033 [14.6%] in the placebo arm). Most events were of mild or moderate severity.

Table 7. Solicited Systemic Adverse Events (Safety Population) in Study 301

-	VLA1553 (N=3082) n (%)	Placebo (N=1033) n (%)	Total (N=4115) n (%)
Any Solicited Systemic Adverse Events	1547 (50.2)	278 (26.9)	1825 (44.3)
Headache	969 (31.4)	151 (14.6)	1120 (27.2)
Fatigue	879 (28.5)	130 (12.6)	1009 (24.5)
Myalgia	735 (23.8)	76 (7.4)	811 (19.7)
Arthralgia	520 (16.9)	50 (4.8)	570 (13.9)
Fever	414 (13.4)	8 (0.8)	422 (10.3)
Nausea	345 (11.2)	58 (5.6)	403 (9.8)
Rash	70 (2.3)	5 (0.5)	75 (1.8)
Vomiting	58 (1.9)	10 (1.0)	68 (1.7)

Source: Adapted from Table 33 in the CSR for Study VLA1553-301.

Reviewer's comment:

The applicant's solicited safety analyses were based on data collected in the case report form (CRF) rather than e-Diary. For example, 47 additional subjects reported any solicited systemic AEs based on e-Diary data but were not counted in the 1825 subjects presented in the table above. In the IR response submitted to BLA 125777/0.39, the applicant clarified that only those solicited AEs recorded on the AE page of the CRF were included in the main analysis of solicited AEs. A post hoc review of events collected in e-Diary only (but not recorded in the CRF) was carried out by the applicant, which resulted in 24 subjects being included in the analysis and the remaining 47 subjects excluded. Nevertheless, if those 47 subjects were included in the analysis, any solicited systemic adverse event rates in both groups would have been only minimally impacted (~1%).

Solicited injection site AEs were also reported by more participants in the VLA1553 arm than in the placebo arm (463/3082 [15.0%] and 115/1033 [11.1%] participants, respectively, in Table 8). The most common solicited injection site AE was tenderness (328/3082 [10.6%] participants in the VLA1553 arm and 84/1033 [8.1%] in the placebo arm).

Table 8. Solicited Injection Site Adverse Events (Safety Population) in Study 301

-	VLA1553 (N=3082) n (%)	Placebo (N=1033) n (%)	Total (N=4115) n (%)
Any Solicited Injection Site Adverse Events	463 (15.0)	115 (11.1)	578 (14.0)
Tenderness	328 (10.6)	84 (8.1)	412 (10.0)
Pain	191 (6.2)	38 (3.7)	229 (5.6)
Erythema/Redness	46 (1.5)	15 (1.5)	61 (1.5)
Induration	44 (1.4)	8 (0.8)	52 (1.3)
Swelling	21 (0.7)	8 (0.8)	29 (0.7)

Source: Adapted from Table 36 in the CSR for Study VLA1553-301.

Up to Day 29, more unsolicited AEs were reported in the VLA1553 arm than in the placebo arm (687/3082 [22.3%] and 138/1033 [13.4%] participants, respectively, in Table 9). Overall, most unsolicited AEs were graded as mild or moderate. Twenty-four of 4115 (0.6%) participants (18/3082 [0.6%] in the VLA1553 arm and 6/1033 [0.6%] in the placebo arm) experienced at least one unsolicited AE that was graded severe. Unsolicited AEs were more frequently considered related to the vaccination in the VLA1553 arm than in the placebo arm (290/3082 [9.4%] and 39/1033 [3.8%] participants, respectively).

Table 9. Unsolicited Adverse Events in Study 301

-	VLA1553 (N=3082) n (%)	Placebo (N=1033) n (%)	Total (N=4115) n (%)
Any Unsolicited Adverse Events up to Day 29	687 (22.3)	138 (13.4)	825 (20.0)
Mild	503 (16.3)	93 (9.0)	596 (14.5)
Moderate	166 (5.4)	39 (3.8)	205 (5.0)
Severe	18 (0.6)	6 (0.6)	24 (0.6)
Any Related Unsolicited Adverse Events up to Day 29	290 (9.4)	39 (3.8)	329 (8.0)
Mild	212 (6.9)	32 (3.1)	244 (5.9)
Moderate	73 (2.4)	7 (0.7)	80 (1.9)
Severe	5 (0.2)	0	5 (0.1)

Source: Adapted from Table 39 in the CSR for Study VLA1553-301.

During the review process, the data standard reviewer Brenda Baldwin requested the applicant to remap some adverse events in the raw datasets, which resulted in a few AEs being removed from the unsolicited AE into the solicited AE category. The updated safety datasets were submitted to BLA 125777/0.57. Table 10 shows the percentage of participants in Study 301 reporting solicited systemic adverse reactions based on updated safety datasets. Unsolicited adverse events that occurred within 28 days following vaccination were reported in 21.8% of 3082 participants who received VLA1553 versus 13.3% of 1033 participants who received placebo.

Table 10. Percentage of Participants with Solicited Systemic Adverse Events (Based On Updated Safety Datasets) in Study 301

-	VLA1553 (N=3082) (%)	Placebo (N=1033) (%)
Headache	31.6	14.7
Fatigue	28.5	12.7
Myalgia	23.9	7.4
Arthralgia	17.2	4.9
Fever	13.5	0.9
Nausea	11.2	5.6
Rash	2.3	0.5
Vomiting	1.9	1.0

Source: Adapted from Table 1 in the PI.

In this study, AESI was defined as an event of scientific and medical concern specific to the sponsor's product, which included signs and symptoms suggesting an acute stage CHIKV-associated event. In total, 11 participants met the criteria of AESI: 10/3082 (0.3%) and 1/1033 (0.1%) participants in the VLA1553 and placebo arms, respectively. FDA further requested the applicant to conduct an analysis on chikungunya-like reactions using a less specific definition: fever $\geq 38^{\circ}\text{C}$ / 100.4°F and one or more of any of the following symptoms: arthralgia or arthritis, myalgia, headache, back pain, rash, lymphadenopathy, or certain neurological, cardiac or ocular symptoms, that occurred with an onset within 30 days after vaccination. Overall, 361 participants (11.7%) in the IXCHIQ group (n= 3082) reported chikungunya-like adverse reactions, including 48 participants (1.6%) who reported severe chikungunya-like adverse reactions. Six (0.6%) participants in the placebo group (n= 1033) reported chikungunya-like adverse reactions, none of which were severe. Fourteen IXCHIQ recipients had prolonged (duration greater than 30 days) chikungunya-like adverse reactions (range 33 days to at least 6 months). Two of the 3082 IXCHIQ recipients experienced serious chikungunya-like adverse reactions.

Overall, 83 SAEs were experienced in 54/4115 (1.3%) participants during the study (46/3082 [1.5%] participants in the VLA1553 arm and 8/1033 [0.8%] participants in the placebo arm). The most frequent SAE was infections and infestations (9/3082 [0.3%] participants in the VLA1553 arm and 3/1033 [0.3%] participant in the placebo arm). Two SAEs reported in the VLA1553 arm were considered related to the vaccination. Three participants died during the study (2/3082 [0.1%] participants in the VLA1553 arm and 1/1033 [0.1%] participant in the placebo arm). Two spontaneous abortions and one fetal death were reported in the VLA1553 arm and considered not related to the vaccination by the investigator.

6.2 Trial #2: VLA1553-302

A randomized, double-blinded Phase 3 study to demonstrate lot-to-lot consistency of three lots of a live-attenuated chikungunya virus vaccine candidate (VLA1553) in healthy adults aged 18 to 45 years

6.2.1 Objectives

Primary Objective: To demonstrate lot-to-lot manufacturing consistency of the single dose of the live-attenuated CHIKV vaccine candidate (VLA1553) in a healthy CHIKV-naïve population aged 18 to 45 years.

Secondary Objectives:

To evaluate immunogenicity and safety of VLA1553 up to 180 days following vaccination in a healthy population aged 18 to 45 years after a single immunization.

6.2.2 Design Overview

Subjects were block-randomized in a 1:1:1 ratio into the 3 study arms to receive 1 of 3 lots of VLA1553 as a single intramuscular vaccination on Day 1 (Visit 1). All subjects were asked to return to the study site at Day 8 (Visit 2), Day 29 (Visit 3), Day 85

(Visit 4), and Month 6 (Day 180, Visit 5) for immunogenicity sampling. Safety data collection was planned to capture solicited AEs until Day 11 and unsolicited AEs up to Day 180 (Month 6, Visit 5) from all subjects. Overall, approximately 402 subjects were to be enrolled into the study with 134 subjects per VLA1553 lot.

6.2.3 Population

The study population comprised subjects 18 to 45 years of age, who met all inclusion criteria and none of the exclusion criteria and provided written informed consent.

6.2.4 Study Treatments or Agents Mandated by the Protocol

All subjects received a single vaccination in the deltoid region of the arm with VLA1553 (1×10^4 TCID₅₀ per 0.5 mL) from one of the 3 lots.

6.2.6 Sites and Centers

Twelve sites in the USA.

6.2.7 Surveillance/Monitoring

Please refer to Dr. Sixun Yang's clinical review memo.

6.2.8 Endpoints and Criteria for Study Success

Primary immunogenicity Endpoint:

Geometric mean titer (GMT) of CHIKV-specific neutralizing antibodies determined by the μ PRNT assay on Day 29 post-vaccination in subjects who tested negative for CHIKV antibodies (as determined by (b) (4) at baseline.

Success Criterion: the 95% CIs for the pair-wise ratios of the GMTs were all between 0.67 and 1.5.

Secondary Immunogenicity Endpoints:

- Immune response as measured by CHIKV-specific neutralizing antibody titers on Day 8, Day 85 and Month 6 post-vaccination;
- Proportion of subjects with seroprotective levels (defined as μ PRNT₅₀ ≥ 150 for baseline negative subjects) on Day 8, Day 29, Day 85 and Month 6 post-vaccination;
- Proportion of subjects with seroconversion at Day 29 and Month 6 as determined by μ PRNT assay (seroconversion defined as CHIKV-specific NT of ≥ 20 for baseline negative subjects and >4 -fold for baseline positive subjects);
- Fold increase of CHIKV-specific NT determined by μ PRNT 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 μ PRNT assay.

Secondary Safety Endpoints:

- 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 and severity of any AE during the entire study period;
- Frequency and severity of any SAE during the entire study period;
- Frequency and severity of any AESI within 2 to 21 days post-vaccination.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Primary immunogenicity analysis

The primary immunogenicity analysis was pairwise comparisons of the GMTs in the PP population at Day 29 between VLA1553 Lots 1, 2, and 3 by analysis of covariance (ANCOVA), using Lot as a fixed effect and study center as a covariate. The ANCOVA model was applied to the log-transformed (natural log base) μ PRNT values of the 3 lots and the 95% CIs for the pair-wise ratios of the GMTs were obtained by taking the anti-log of the resulting 95% CIs for the least square means differences. If these 3 pairwise 95% CIs for GMT ratios were all between 0.67 and 1.5, lot consistency would be demonstrated.

Sample size determination

A total of 393 randomized subjects (i.e., 131 per lot) would ensure that the three pairwise comparisons had an overall power of approximately 90% based on a two-sided significance level of 5%, an assumed standard deviation (SD) of 0.32 (on a log10 scale), and equivalence margins of 0.67 and 1.5 for the GMT ratios, while accounting for an assumed drop-out rate of 10%.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

In total, 409 subjects were randomized, of whom 136, 137, and 136 were randomized to the VLA1553 Lot 1, Lot 2, and Lot 3 arms, respectively. One subject in the VLA1553 Lot 3 arm did not receive vaccination (Table 11).

Table 11. Analysis Populations in Study 302

-	VLA1553 LOT 1	VLA1553 LOT 2	VLA1553 LOT 3	Total
-	n (%)	n (%)	n (%)	n (%)
Randomized population	136 (100)	137 (100)	136 (100)	409 (100)
Vaccinated (Safety Analysis Set)	136 (100)	137 (100)	135 (99.3)	408 (99.8)
Per-Protocol Analysis Set (PP)	122 (89.7)	118 (86.1)	122 (89.7)	362 (88.5)

Source: Adapted from Table 16 in the CSR for Study VLA1553-302.

Overall, 394/408 (96.6%) subjects completed the Day 29 Visit (Part A of the study) and 364/408 (89.2%) subjects completed the Day 180/Month 6 Visit (Part B of the study). A total of 44 of 408 (10.8%) subjects discontinued from the study; 30 subjects were lost to

follow-up, 13 withdrew consent, and 1 subject was withdrawn for other reasons. The proportion of subjects who discontinued the study among three lots were similar (11.0%, 12.4% and 8.9% in Lots 1-3, respectively).

Slightly more female subjects (223/408 [54.7%]) than male subjects participated in the study; the majority of subjects were white (315/408 [77.2%]). As shown in Table 12, there were no notable differences in the demographic and baseline characteristics between arms in the safety analysis set (SAF). Demographics and baseline characteristics were also balanced in the PP analysis set.

Table 12. Demographics and Baseline Characteristics in the Safety Population in Study 302

	VLA1553 LOT 1 N=136	VLA1553 LOT 2 N=137	VLA1553 LOT 3 N=135	Total N=408
Age (years)				
Mean (std)	33.2 (7.03)	33.2 (7.78)	33.2 (7.43)	33.2 (7.40)
Median	34.0	34.0	34.0	34.0
Min, Max	18, 45	18, 45	18, 45	18, 45
Sex n (%)				
Female	75 (55.1)	76 (55.5)	72 (53.3)	223 (54.7)
Male	61 (44.9)	61 (44.5)	63 (46.7)	185 (45.3)
Race n (%)				
White	103 (75.7)	106 (77.4)	106 (78.5)	315 (77.2)
Black or African American	21 (15.4)	22 (16.1)	19 (14.1)	62 (15.2)
Asian	6 (4.4)	5 (3.6)	7 (5.2)	18 (4.4)
American Indian or Alaska Native	4 (2.9)	1 (0.7)	0	5 (1.2)
Native Hawaiian or other Pacific Islander	0	1 (0.7)	0	1 (0.2)
Other	2 (1.5)	2 (1.5)	3 (2.2)	7 (1.7)
Weight (kg)				
Mean (std)	86.0 (23.9)	86.8 (22.7)	85.8 (22.1)	86.2 (22.9)
Median	83.3	85.0	83.3	84.0
Min, Max	49.2, 204.5	45.8, 171.4	45.5, 157.9	45.5, 204.5
Height (cm)				
Mean (std)	170.8 (9.0)	171.3 (9.8)	171.4 (9.7)	171.2 (9.5)
Median	170.2	170.5	172.5	170.7
Min, Max	142.2, 189.5	149.9, 197.0	148.6, 194.0	142.2, 197.0

Source: Adapted from Table 13 in the CSR for Study VLA1553-302.

6.2.11 Immunogenicity Analyses

Primary Immunogenicity Endpoint

In the PP analysis set, GMT on Day 29 were 2556.7 (Lot 1 arm), 2767.7 (Lot 2 arm) and 2613.7 (Lot 3 arm), respectively. The 95% CIs for all the pairwise GMT ratios among the

3 lots were in the defined equivalence margins of 0.67 and 1.5 (Table 13), meeting the success criterion for lot consistency.

Table 13. GMTs for CHIKV-Specific Neutralizing Antibodies at Day 29 (PP Analysis Set) in Study 302

	VLA1553 LOT 1 (N=122)	VLA1553 LOT 2 (N=118)	VLA1553 LOT 3 (N=122)
GMT	2556.7	2767.7	2613.7
95% CI for GMT	2055.63, 3179.80	2310.25, 3315.65	2128.06, 3210.17
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1
GMT ratio	1.08	0.94	1.02
95% CI for GMT ratio	0.81, 1.44	0.71, 1.26	0.77, 1.36

Source: Adapted from Table 17 in the CSR for Study VLA1553-302.

6.2.12 Safety Analyses

Table 14 shows that solicited systemic AE rates were similar across the 3 arms (73/136 [53.7%] subjects in the Lot 1 arm, 78/137 [56.9%] subjects in the Lot 2 arm, and 82/135 [60.7%] subjects in the Lot 3 arm). Solicited injection site AE rates were also similar across the 3 arms (23/136 [16.9%] subjects in the Lot 1 arm, 30/137 [21.9%] subjects in the Lot 2 arm, and 26/135 [19.3%] subjects in the Lot 3 arm).

Table 14. Summary of Solicited Adverse Events (Safety Analysis Set) in Study 302

	VLA1553 LOT 1 (N=136) n (%)	VLA1553 LOT 2 (N=137) n (%)	VLA1553 LOT 3 (N=135) n (%)	Total (N=408) n (%)
Any Solicited Systemic Adverse Events	73 (53.7)	78 (56.9)	82 (60.7)	233 (57.1)
Mild	56 (41.2)	60 (43.8)	61 (45.2)	177 (43.4)
Moderate	12 (8.8)	15 (10.9)	18 (13.3)	45 (11.0)
Severe	5 (3.7)	3 (2.2)	3 (2.2)	11 (2.7)
Any Solicited Injection Site Adverse Events	23 (16.9)	30 (21.9)	26 (19.3)	79 (19.4)
Mild	21 (15.4)	29 (21.2)	26 (19.3)	76 (18.6)
Moderate	2 (1.5)	1 (0.7)	0	3 (0.7)
Severe	0	0	0	0

Source: Adapted from Table 35 in the CSR for Study VLA1553-302.

Table 15 shows that unsolicited AEs were reported in 102/408 (25.0%) subjects with more subjects in the Lot 1 (38/136 [27.9%] subjects) and Lot 3 arms (42/135 [31.1%] subjects) than in the Lot 2 arm (22/137 [16.1%]). Most unsolicited AEs were graded as mild or moderate. Overall, 63/408 (15.4%) subjects experienced at least one unsolicited AE that was considered related to the vaccination, with slightly more subjects in the Lot 3 arm (29/135 [21.5%] subjects) than in the Lot 1 (20/136 [14.7%] subjects) and Lot 2 arms (14/137 [10.2%] subjects).

Table 15. Unsolicited Adverse Events Up to Day 29 in Study 302

	VLA1553 LOT 1 (N=136) n (%)	VLA1553 LOT 2 (N=137) n (%)	VLA1553 LOT 3 (N=135) n (%)	Total (N=408) n (%)
Any Unsolicited Adverse Events up to Day 29	38 (27.9)	22 (16.1)	42 (31.1)	102 (25.0)
Mild	25 (18.4)	17 (12.4)	32 (23.7)	74 (18.1)
Moderate	10 (7.4)	5 (3.6)	10 (7.4)	25 (6.1)
Severe	3 (2.2)	0	0	3 (0.7)
Any Related Unsolicited Adverse Events up to Day 29	20 (14.7)	14 (10.2)	29 (21.5)	63 (15.4)
Mild	17 (12.5)	12 (8.8)	21 (15.6)	50 (12.3)
Moderate	3 (2.2)	2 (1.5)	8 (5.9)	13 (3.2)
Severe	0	0	0	0

Source: Adapted from Table 42 in the CSR for Study VLA1553-302.

Overall, 5 SAEs were reported by 5/408 (1.2%) subjects during the study (3/136 [2.2%] subjects in the Lot 1 arm and 2/137 [1.5%] subjects in the Lot 2 arm). None of the SAEs were assessed as related to the vaccination. There was 1 AESI comprising of two events in 1 subject classified as related to VLA1553. No subjects died during the study. Two spontaneous abortions were reported and considered unlikely related to the vaccination by the investigator.

7. INTEGRATED OVERVIEW OF EFFICACY

The applicant pooled the safety and efficacy data of VLA1553 across the Phase 1 trial (VLA1553-101, including groups with different dose levels) and Phase 3 trials (VLA1553-301 with one VLA1553 arm and one placebo arm, and VLA1553-302 with three different VLA1553 lots). An overview of the analyzed participants is provided in Table 16.

Table 16. Analysis Populations in the pooled analyses

	VLA1553 N	Placebo N	Total N
Screened	3622	1035	4657
Randomized	3602	1035	4637
Sentinels	20	0	20
Vaccinated (among randomized/sentinels)	3610	1033	4643
Per Protocol Analysis Set (PPAS)	656	103	759

Source: Adapted from Table P.1.1 in the VLA1553 Pooled Analysis report of Safety and Immunogenicity.

A pooled analysis (Table 17) of immunogenicity data collected from the two pivotal studies VLA1553-301 and VLA1553-302 at Day 1, Day 29, Day 85, and Day 180 was conducted. The analysis population was per-protocol analysis set (PPAS), which was

defined as all participants who were seronegative (defined as μ PRNT₅₀ value <20) at baseline without major protocol deviation. Overall, SPR was 98.3% at Day 29 in VLA1553-vaccinated subjects and remained at 97.7% on Day 85 and 96.4% on Day 180.

Table 17. Seroprotection Rates, and GMTs, as Determined by μ PRNT Assay, in the Pooled Data of the Pivotal Studies VLA1553-301 and VLA1553-302 (PPAS)

Treatment	VLA1553	Placebo
PPAS	N=656	N=103
Seroprotection Rate n/Nm ^a (%) [95%CI]		
28 days	644/655 (98.3) [97.0; 99.1]	0/103 (0.0) [0.0; 3.6]
3 months	597/611 (97.7) [96.2; 98.6]	1/98 (1.0) [0.2; 5.6]
6 months	582/604 (96.4) [94.5; 97.6]	0/98 (0.0) [0.0; 3.8]
GMT [95%CI]		
28 days	2954.1 [2,729.5; 3197.3]	10.1 [9.9; 10.4]
3 months	956.0 [887.9; 1029.2]	10.4 [9.8; 11.1]
6 months	735.3 [682.0; 792.7]	10.0 [10.0; 10.0]

a. n:number of subjects achieving seroprotection. Nm: number of non-missing observations.

Source: Adapted from Table 2.5-1 in the study report for ISE.

Reviewer's comment:

The analysis population for integrated summary of efficacy (ISE) was based on PPAS, which differs from the PP population used for the primary analysis in the two pivotal studies. In the IR response submitted to BLA 125777/0.40, the applicant explained that the main difference is that PPAS included 36 additional subjects (7 in the placebo group and 29 in the VLA1553 group with Day 29 assay results available) from the non-immunogenicity subset in Study VLA1553-301. Including or excluding these 36 subjects would not have any major impact on the SPR and GMT results.

8. INTEGRATED OVERVIEW OF SAFETY

Table 18 summarizes occurrence of solicited AEs pooling all three studies. In the VLA1553 arm, 51.1% of participants reported systemic AEs; in the placebo arm, 26.9% of participants reported systemic AEs. As for local AEs, 15.2% and 11.1% of participants reported at least one event in the VLA1553 arm and in the placebo arm, respectively. The majority of local AEs were mild.

Table 18. Summary of Solicited Adverse Events in the pooled analyses

	VLA1553 (N=3610) n (%)	Placebo (N=1033) n (%)
Any Solicited Systemic Adverse Events	1843 (51.1)	278 (26.9)
Mild	1353 (37.5)	242 (23.4)
Moderate	401 (11.1)	32 (3.1)
Severe	82 (2.3)	1 (0.1)
N/A - Diary Only	7 (0.2)	3 (0.3)
Any Solicited Injection Site Adverse Events	549 (15.2)	115 (11.1)
Mild	518 (14.3)	110 (10.6)
Moderate	26 (0.7)	5 (0.5)
Severe	1 (0.0)	0 (0.0)
N/A - Diary Only	4 (0.1)	0 (0.0)

Source: Compiled from Tables P.3.8, P.3.10, P.3.16, P.3.18 in the safety tables for ISS.

Table 19 provides a summary of unsolicited AEs with onset within 180 days after single vaccination. Overall, 31.6% and 23.9% of participants in the VLA1553 arm and placebo arm reported any unsolicited AE, respectively. There were two related SAEs in the three studies combined. Four spontaneous abortions and one fetal death were reported in the VLA1553 arm and considered not related to the vaccination by the investigator.

Table 19. Summary of Unsolicited Adverse Events in the pooled analyses

	VLA1553 (N=3610) n (%)	Placebo (N=1033) n (%)
Any unsolicited AE	1140 (31.6)	247 (23.9)
Any related unsolicited AE	420 (11.6)	48 (4.6)
Any serious AE	52 (1.4)	8 (0.8)
Any related serious AE	2 (0.1)	0 (0.0)

Source: Adapted from Tables P.3.1 in the safety tables for ISS.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

Study VLA1553-301 and Study VLA1553-302 met the success criteria for the primary immunogenicity endpoints. I defer to the clinical reviewer on the safety assessment of this vaccine.