BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA)
STN	125777/0
CBER Received Date	December 22, 2022
PDUFA Goal Date	August 22, 2023
Division / Office	Division of Vaccines and Related Products Applications (DVRPA)/Office of Vaccines Research and Review (OVRR)
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Sixun Yang, MD, PhD
Review Completion Date / Stamped Date	June 28, 2023/November 8, 2023
Supervisory Concurrence	Sheral Patel, MD, Team Leader Andrea Hulse, MD, Branch Chief
Applicant	Valneva Austria GmbH
Established Name	Chikungunya Vaccine, Live-Attenuated
(Proposed) Trade Name	IXCHIQ
Pharmacologic Class	Prophylactic Vaccine
Formulation(s), including Adjuvants, etc.	Lyophilized powder (b) (4) $\log_{10}$ $TCID_{50}$ Live-attenuated Chikungunya La Reunion strain Virus per 0.5 mL) Sterile water
Dosage Form(s) and Route(s) of Administration	Powder and solvent for reconstitution, Intramuscular Injection
Dosing Regimen	Single Dose (0.5 mL after reconstitution) ≥3.0 $\log_{10}$ $TCID_{50}$/0.5ml
Proposed Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by chikungunya virus in individuals 18 years and above
Approved Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by chikungunya virus in individuals 18 years and above who are at increased risk of exposure to chikungunya virus
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

AA	accelerated approval
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transaminase
BLA	Biologics License Application
BNP	brain natriuretic peptide
CBER	Center for Biologics Evaluation and Research
CHIK	chikungunya
CHIKV	chikungunya virus
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ECSA	East/Central/South African lineage (of CHIKV)
eCTD	electronic common technical document
eIMM	elderly immunogenicity population
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GBS	Guillain-Barre syndrome
GCE	genome copy equivalent
GCP	Good Clinical Practice
GMT	geometric mean titer
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	immunoglobulin G
IMM	immunogenicity population
IMP	investigational medicinal product
IND	investigational new drug
iPSP	initial pediatric study plan
IR	information request
IS	injection site
ISE	integrated summary of efficacy
ISS	integrated summary of safety
LB	lower bound
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NHP	non-human primate
NT	neutralizing antibody titer
PP	Per-Protocol
PPAS	Per-Protocol analysis set
PRNT	plaque reduction neutralization assay

PT	preferred term
PVP	pharmacovigilance plan
RCT	randomized clinical trials
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standard MedDRA query
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SOC	System Organ Class
sPP	sensitivity Per-Protocol population
sPP2	sensitivity Per-Protocol 2 population
TND	test negative design
$TCID_{50}$	median tissue culture infectious dose
U.S.	United States
UTMB	University of Texas Medical Branch
VLA1553	Valneva chikungunya vaccine; IXCHIQ
VRBPAC	Vaccines and Related Biological Products Advisory Committee
µNT	microneutralization (assay)
µPRNT	micro-plaque reduction neutralization test
$\mu PRNT_{50}$	The antibody titer to reduce the number of plaques by 50% compared to antibody free virus control in µPRNT

1. EXECUTIVE SUMMARY

Valneva Austria GmbH (the Applicant) submitted a Biologics License Application (BLA) on December 22, 2022, to support licensure of Valneva's chikungunya vaccine (VLA1553), a monovalent live-attenuated vaccine intended as a single-dose immunization for the prevention of disease caused by the chikungunya virus (CHIKV) in adults ≥18 years of age. CHIKV is a mosquito-borne virus that has been identified in over 110 countries in Asia, Africa, Europe and the Americas; approximately 5 million cases of CHIKV infection were reported during the past 15 years. CHIKV infections are symptomatic and result in a rapid onset of high fever and severe disabling arthralgia, and 1.6 to 57% patients experience recurrent or persistent joint pain lasting for months to years post-infection. As no specific antiviral treatments are available, the treatment of chikungunya (CHIK) is supportive and includes rest, fluids, and over-the-counter medications for pain and fever. No vaccine to prevent CHIK has been approved.

The BLA included data from three clinical studies evaluating the safety and immunogenicity of VLA1553: a Phase 1 dose escalation study (VLA1553-101), a Phase 3 pivotal effectiveness study (VLA1553-301), and a Phase 3 lot-to-lot consistency study (VLA1553-302); hereafter referred to as Study 101, Study 301, and Study 302, respectively. Immunogenicity data from the two Phase 3 studies were analyzed separately and also pooled in integrated summary of effectiveness (ISE) analyses. Study 101 differed from the Phase 3 studies in the immune assay used to assess seroresponse and in the doses and formulation of VLA1553. Therefore, immunogenicity data from Study 101 were not included in the ISE. As all three studies had similar study populations, definitions of adverse events (AEs), adverse event collection tools, duration of follow-up, and safety data from the three studies were pooled.

In the pivotal trial Study 301, adults ≥18 years of age were enrolled at 43 sites in the United States (U.S.) and randomized 3:1 to VLA1553 or placebo. The primary immunogenicity endpoint was a CHIKV-specific neutralizing antibody titer ≥150 as determined by micro-plaque reduction neutralization test ($\mu PRNT_{50}$) at 28 days postvaccination. The anti-CHIKV titer of ≥150 was selected based on experiments in a non-human primate (NHP) adoptive transfer model, in which the quantity of human anti-CHIKV immune sera needed to prevent viremia in the NHP following wild-type CHIKV challenge was determined. The prevention of viremia following adoptive transfer of anti-CHIKV immune sera and subsequent wild-type CHIKV challenge supports the use of the anti-CHIKV titer as a surrogate endpoint that is reasonably likely to predict a clinical benefit and serves as the basis for approval of the vaccine under the accelerated approval program. All participants in the Per-Protocol (PP) population had a $\mu PRNT_{50}$ titer <20 at baseline. At Day 29, 98.9% (263/266) participants in the VLA1553 group had a CHIKV antibody titer ≥150 compared with no participants in the placebo group. The results met the pre-specified success criterion of a lower bound (LB) of the 95% confidence interval (CI) of >70%. Sensitivity analyses demonstrated that different thresholds for baseline serostatus or different visit windows did not impact immunogenicity outcomes.

Anti-CHIKV neutralizing antibody titer peaked at 28 days postvaccination with a geometric mean titer (GMT) of 3,362, and subsequently decreased to 1,084 and 752 at 84 and 180 days postvaccination, respectively. Seroresponse rates, defined as a percentage of participants who achieved an anti-CHIKV neutralizing antibody titer ≥150 at 28 days postvaccination, remained at 98.0% and 96.3% at 84 days and 180 days postvaccination, respectively. In subgroup analyses by age, sex, race, and ethnicity, no statistically significant differences were observed in terms of GMTs and seroresponse rates 28 days postvaccination.

The lot-to-lot consistency Study 302 demonstrated that the 95% CIs of the anti-CHIKV GMT ratios between any two lots were within 0.67 and 1.5, which met the pre-specified immunogenicity criteria to demonstrate lot consistency.

The integrated effectiveness analyses, which pooled immunogenicity data from Studies 301 and 302 (VLA1553 recipients=655; placebo recipients=103), showed similar seroresponse rates 28 days postvaccination among the pooled populations compared with seroresponse rates reported from Study 301.

In safety analyses from Study 301, solicited adverse reactions were reported by 52.8% (1,628/3,082) and 32.0% (331/1,033) of those who received VLA1553 and placebo, respectively. The most common solicited systemic reactions in VLA1553 and placebo recipients were headache (27.9% vs. 12.4%), fatigue (25.9% vs 11.2%), and myalgia (22.1% vs. 6.8%). Solicited injection site (IS) reactions were reported by 15.0% of VLA1553 recipients and 11.1% of placebo recipients.

Due to the concern that a live, attenuated virus vaccine could result in manifestations of CHIK in recipients, specific symptoms of CHIK were collected as adverse events of special interest (AESIs). In a safety analysis, AESIs that met criteria for CHIK-like illness were reported by 11.7% and 0.6% participants in the VLA1553 and placebo groups, respectively. Most cases of CHIK-like illness were mild or moderate; however, severe CHIK-like illness was reported by 1.6% of VLA1553 recipients and no placebo recipients. Fourteen VLA1553 recipients reported prolonged CHIK-like illness, including events of severe back pain/arthralgia and polyarthralgia that persisted for at least 51 days and 6 months, respectively, postvaccination. Two VLA1553 recipients reported serious CHIK-like illness, including events of myalgia and atrial fibrillation with hypovolemic hyponatremia, which resulted in hospitalization of both participants.

Serious adverse events (SAEs) were reported by 1.5% and 0.8% of VLA1553 and placebo recipients, respectively. With the exception of the SAEs of CHIK-like illness above, none of the remaining SAEs were considered related to vaccine.

Safety of VLA1553 was assessed in the U.S. in an integrated analysis of 4,643 healthy participants from the three clinical studies, of whom 3,610 and 1,033 participants received VLA1553 and placebo, respectively (all placebo recipients were from Study 301). The study populations among the three studies were generally similar except that Studies 101 and 302 did not include participants older than 45 years of age. The safety profile of the three studies was similar in terms of incidences of solicited adverse reactions and unsolicited AEs. Among VLA1553 recipients, a numerically higher incidence of SAEs was reported in older participants: 3.5% of VLA1553 recipients ≥65 years of age vs. 1.2% of VLA1553 recipients 18 through 64 years of age. In the placebo group, 1.7% of participants ≥65 years of age and 0.7% of participants 18 through 64 years of age reported SAEs.

In conclusion, the immunogenicity data from Studies 301 and 302 indicate that a single intramuscular injection of VLA1553 is likely effective in preventing disease caused by CHIKV based on the surrogate endpoint of seroresponse rates; however, postmarketing confirmatory studies will be needed to confirm clinical benefit. The overall reactogenicity profile of the to-be-licensed dose of VLA1553 is acceptable. However, the frequency and severity of AESIs of CHIK-like illness associated with VLA1553 administration, including severe, serious, and/or prolonged events, and atypical presentations such as cardiac events warrant the following: (1) restricting the indication of the vaccine to individuals 18 years of age and older who are at increased risk of exposure to CHIKV; (2) inclusion of information on the risk of severe or

prolonged CHIK-like illness in Section 5 (Warnings and Precautions) of the Prescribing Information; (3) enhanced postmarketing surveillance to include expedited reporting (arthritis/arthralgia, cardiac events, and spontaneous abortion), a summary and analysis in periodic safety reports, and dedicated AE questionnaires; and (4) a postmarketing requirement (PMR) to include evaluation of severe CHIK-like illness (including typical and atypical presentations and cases that result in hospitalization) and prolonged arthralgia in approximately 10,000 individuals who receive VLA1553 compared with individuals in the control group in an individual-level randomized, observer-blind, controlled trial conducted across multiple centers in an endemic country (see Section 11.6.2).

Reviewer comment: *CHIK-like illness is described as CHIK-like adverse reactions in the package insert (PI). CHIK-like adverse reactions in the PI are synonymous with the CHIK-like illness in this review.*

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1 below summarizes the demographic representation of study participants who enrolled in the pivotal Study 301 and were randomized to VLA1553 or placebo. A total of 4,115 participants were enrolled in the study, including 3,082 participants in the VLA1553 group and 1,033 participants in the placebo group.

Table 1. Participant Demographics, Study 301

Characteristic	VLA1553 N=3082	Placebo N=1033
Age	-	-
≥65 years	346 (11.2)	117 (11.3)
18-64 years	2736 (88.8)	916 (88.7)
Sex	-	-
Female	1682 (54.6)	569 (55.1)
Male	1400 (45.4)	464 (44.9)
Race	-	-
American Indian or Alaska Native	27 (0.9)	5 (0.5)
Asian	51 (1.7)	17 (1.6)
Black or African American	451 (14.6)	122 (11.8)
Native Hawaiian or other Pacific Islander	13 (0.4)	5 (0.5)
Other	84 (2.7)	31 (3.0)
White	2456 (79.7)	853 (82.6)
Ethnicity	-	-
Hispanic or Latino	545 (17.7)	177 (17.1)
Not Hispanic or Latino	2498 (81.1)	840 (81.3)
Not reported	34 (1.1)	14 (1.4)
Unknown	5 (0.2)	2 (0.2)

Source: Adapted from Table 13 (page 88) and Table 14 (page 89) of the clinical study report of VLA1553-301

The demographic characteristics of the evaluable immunogenicity population (PP population used for primary immunogenicity analyses; see Section 6.1.10) of 266 participants exposed to VLA1553 79.7% were White, 57.9% female, and 90.6% non-Hispanic/non-Latino ethnicity. The younger age group (18 to 64 years of age) represented 77.8% of the total evaluable immunogenicity population exposed to VLA1553, while participants ≥65 years of age represented 22.2% of the total.

Subgroup analyses of vaccine effectiveness (although limited by small numbers of participants in some subgroups) did not indicate meaningful differences in immune seroresponse rates by age, sex, race, or ethnic group.

The overall safety database includes 3,610 participants exposed to VLA1553, with 90.4% participants 18 to 64 years of age, 9.6% participants ≥65 years of age; 46.8% male and 53.2% female; and 16.8% Hispanic/Latino, 79.4% White, 14.7% African American, 2.5% other racial groups, 2.0% Asian, 0.9% American Indian or Alaska Native, and 0.4% Native Hawaiian or Other Pacific Islander.

In safety analyses, reported rates of SAEs after VLA1553 vaccinations were numerically higher in older participants (≥65 years of age) compared with younger participants (18-64 years of age); however, a similar pattern was observed in the placebo group. No clinically meaningful difference was observed between the older and younger subgroup in solicited adverse reactions, unsolicited AEs and AESIs. No clinically meaningful differences in the occurrence of solicited adverse reactions, unsolicited AEs, AESIs or SAEs were observed by sex, race or ethnicity subgroups.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

CHIK is a mosquito-borne disease caused by CHIKV, an alphavirus first isolated in 1953. Although there is only one serotype for CHIKV, phylogenetic analyses reveal three distinct CHIKV lineages: the West African, Asian, and East/Central/South African (ECSA) lineages. The ECSA lineage includes the Indian Ocean lineage (IOL) subgroup, now recognized as a strain of ECSA. CHIK is an emerging global health threat with at least five million cases of CHIKV infection reported during the past 15 years. CHIKV often causes sudden large outbreaks affecting 33-75% of the population in areas where the virus is circulating; up to 97% of infected individuals are symptomatic (CDC, 2022); however, another study shows >80% CHIKV infected individuals are asymptomatic (Yoon, 2020). Depending on the study report, approximately 2% to 57% patients developed chronic or recurrent arthralgia (Suhrbier, 2012). A study in post-epidemic CHIK on Reunion Island showed that 36% patients developed persistent joint pain over 15 months (15.5% with moderate and 1.2% with severe joint pain) (Sissoko, 2009). Recent evidence suggests that the lineages may differentially activate inflammatory responses in mouse models (Teo, 2015) and vary in virulence and cross-protective ability in mice and nonhuman primates (Langsjoen, 2018) and differ in transmissibility by competent mosquitoes (Tsetsarkin, 2007).

The highest risk of CHIKV infection is in tropical and subtropical regions of Africa, Southeast Asia, and parts of the Americas where CHIKV-carrying mosquitos are endemic. However, because of environmental, epidemiological, ecological, and social factors, such as global warming, land use and industry, and population movement due to migration, tourism, and cross-border trade, CHIKV has spread to new geographical areas causing a rise in global prevalence.

CHIKV was rarely identified in U.S. travelers prior to 2006. Between 2006-2013, an average of 28 cases per year were reported in U.S. travelers who had returned from Asia, Africa, or the Indian Ocean. In 2014, CHIK cases were reported among U.S. travelers returning from affected areas in the Americas, and the first cases of local transmission in Florida, Texas, Puerto Rico, and the U.S. Virgin Islands were reported (CDC, 2023).

CHIKV infections typically present in three stages that differ in clinical features and treatment. During the acute stage, clinical symptoms appear 4 to 7 days post-infection and manifest as rapid onset of high fever, transient maculopapular rash and multiple mild to severe arthralgia/arthritis episodes. This is followed by a subacute stage and then chronic stage of disease leading to impaired quality of life in some people due to persistent incapacitating rheumatic symptoms up to months and years after infection (Simon, 2015; Couderc, 2009; Suhrbier, 2012). Viremia in the acute stage may lead to death; however, mortality due to CHIKV infection is low with an estimated rate of 0.07%. On the contrary, morbidity is high and may lead to significant, long-term disability (Kumar, 2021).

Although CHIKV infection is self-limited and characterized mainly by severe joint pain and myalgia, rare, atypical presentations of CHIK do occur. Atypical CHIK manifestations that have been reported during outbreaks include cardiac and neurological complications such as arrhythmias, myocarditis, dilated cardiomyopathy, heart failure, encephalitis, meningitis, and Guillain–Barré Syndrome (Traverse, 2021; Cotella, 2021; Alvarez, 2017; de Lima Cavalcanti, 2022).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Neither CHIK-specific treatments nor vaccines to prevent CHIK are currently available. Current treatment of CHIK is supportive and includes rest, adequate fluid intake, and over-the-counter medications for relief of pain during the acute, subacute, and chronic phases of infection.

2.3 Safety and Efficacy of Pharmacologically Related Products

Two other chikungunya vaccines are currently in late phase clinical development. No safety concerns have been observed with these investigational products.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N/A

2.5 Summary of Pre- and Post-submission Regulatory Activity

2.5.1 Pre-submission Regulatory Activities

Clinical development of IXCHQ was conducted under IND 17854. Table 2 summarizes key regulatory activities related to the clinical development program.

Table 2. Key Regulatory Activities During Clinical Development Program

Date	Regulatory Activity	Comments
March 15, 2017	PTS 3183, Pre-IND meeting	None
December 5, 2017	IND 17854 submitted	None
December 21, 2018	Fast Track Designation Granted	None
March 28, 2019	Type C Meeting post conduct of VLA 1553-101, to discuss clinical development	Discussed potential for licensure via the Accelerated Approval (AA) pathway and challenges for confirmatory study to verify the clinical benefit.
November 8, 2019	VRBPAC meeting to discuss pathways for development and licensure of Chikungunya vaccines	VRBPAC recommended using anti-CHIKV titer that completely prevented viremia and fever in NHP adoptive transfer model as a surrogate endpoint to support licensure via AA. During discussions of the VRBPAC recommendation with CHIKV vaccine developers, there was a concern to include fever as a component of the endpoints in NHP studies because fever is not consistently observed in NHPs after CHIKV challenge. CBER agreed to not include fever in the endpoints in NHP studies.
February 24, 2020	End-of-Phase 2 Meeting	CBER conceptually agreed with AA licensure pathway and requested lot-consistency equivalence bounds of (0.67, 1.5) for GMT ratios.
March 29, 2021	Reached agreement with FDA on surrogate end point for use in pivotal Phase 3 trials	CBER accepted an anti-CHIKV $\mu PRNT_{50}$ titer ≥150 as a surrogate endpoint to support licensure via AA. Refer to Non-Clinical Review for details.
July 6, 2021	Breakthrough Therapy Designation (BTD) Granted	BTD was granted based on anti-CHIKV $\mu PRNT_{50}$ titer ≥150 achieved in VLA1553 vaccinated participants.

Date	Regulatory Activity	Comments
December 7, 2021	Agreement on initial pediatric study plan (iPSP)	None
April 1, 2022	PreBLA meeting WRO issued	Rolling submission was granted.

2.5.2 Post-submission Regulatory Activities

Table 3 summarizes requests that were critical for the clinical review of this BLA.

Table 3. Key Information Requests for Clinical Review

Information Request Number	Date Sent	Date Received	Topic
7	January 30, 2023	February 10, 2023	Case report forms (CRFs) and a tabular listing with electronic common technical document (eCTD) links to each CRF
10	February 7, 2023	February 15, 2023	Financial Disclosure and subgroup analyses of vaccine effectiveness in study VLA1553-301
13	February 10, 2023	February 15, 2023	Follow-up on Information Request #7, Amendment 7/CRFs/ Table of Participants with Narrative or CRF
15	February 19, 2023	February 22, 2023	Financial Disclosure using provided shell tables 1, 2, and 3
18	March 3, 2023	March 14, 2023	VLA1553-301 and VLA1553-302 immunogenicity/ AE-hand stiffness/spontaneous abortions
21	March 21, 2023	March 23, 2023	Clinical data corrections/ tabular format with eCTD hyperlinks
23	March 28, 2023	March 30, 2023	ISS/ subgroup analyses of adverse events
24	March 28, 2023	April 4, 2023, and April 7, 2023	eDiaries for VLA1553-301 and VLA-1553-302
25	March 28, 2023	April 7, 2023	Datasets
31	April 14, 2023	April 21, 2023	AEs/Participant 1 clarification all reported AESI cases were non-viremic/Participant 2- atrial fibrillation
34	April 27, 2023	May 4 and May 10, 2023	Safety data regarding cardiac-related adverse events
35	May 1, 2023	May 5, 2023	AEs of natural CHIKV infection in pregnant women, harm to fetus/newborn /transmission of the wild- type virus from mother to infant through breast milk.
36	May 4, 2023	May 11, 2023	Clinical/Statistics (eDiary, Protocol Deviations, datasets)
38	May 5, 2023	May 9, 2023	Rationale for conducting an observational study to verify clinical benefit of VLA1553
40	May 8, 2023	May 12, 2023	Integrated efficacy summary: Per-Protocol population (PP) and Per-Protocol analysis set population (PPAS)
41	May 11, 2023	May 22, 2023	AESI analyses
43	May 18, 2023	May 26, 2023	Clinical data analyses/ neutropenia, leukopenia, and lymphopenia
49	June 2, 2023	June 8, 2023	AESI analyses
53	June 15, 2023	June 16, 2023	Individual Laboratory Measurements
65	July 13, 2023	July 19, 2023	AESI analyses

Information Request Number	Date Sent	Date Received	Topic
66	July 17, 2023	July 20, 2023	AE causality assessment
83	September 15, 2023	October 13, 2023	Labeling
87	September 29, 2023	October 13, 2023 October 27, 2023	Prolonged AESI analyses
93	October 20, 2023	October 25, 2023	Confirmatory study Protocol (b) (4) -404

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This BLA was submitted in electronic common technical document (eCTD) format. Data sources include protocols, reporting and analysis plans, study reports, the integrated summaries of efficacy and safety, and data sets (in both Study Data Tabulation Model and Analysis Data Model formats).

Detailed requests regarding submission of clinical content and format were provided to the Applicant through pre-BLA written responses. However, the Applicant did not provide several of the requested items at the time of initial submission of the Clinical package. Examples of items requested at the time of pre-BLA and were missing, or not addressed adequately, at the time of original submission of the clinical package included the following:

1. Case report forms (CRFs) for death, non-fatal serious adverse events (SAEs), adverse events of special interest (AESIs) and adverse events (AEs) leading to discontinuation. and the tabulations of these events were not provided. The Applicant provided the information during the review cycle.
2. The integrated summary of safety (ISS) and integrated summary of efficacy (ISE) were not well organized. Additionally, while individual studies were presented in the ISS and ISE, integrated narratives focusing on analyses of the pooled data were limited, which required multiple IRs for additional information and clarifications from the Applicant during the review cycle.
3. Datasets were found to contain many inconsistencies and errors, which required corrections and clarifications from the Applicant during the review cycle.

3.2 Compliance with Good Clinical Practices and Submission Integrity

In Section 2.5.1.4 of the Clinical Overview, the Applicant states that “the clinical studies of VLA1553 were conducted in compliance with Good Clinical Practice (GCP) and the clinical development program of VLA1553 follows the recommendations of the FDA “Guidance for Industry – General Principles for the Development of Vaccines to Protect Against Global Infectious Disease” (FDA-2011-D-0855) and the EMA “Guideline on Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005).”

Additionally, Section 5.2 in each of the clinical study reports (CSR) for Studies 101, 301 and 302 states that the studies were conducted in accordance with “current International Council for Harmonization/Good Clinical Practice (ICH/GCP) guidelines, and with the applicable national and local regulatory requirements”. Section 5.2 of the CSRs for Studies 301 and 302 states the following: “This study was conducted in accordance with the Note for Guidance on Good Clinical Practice ICH Harmonized Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); United States FDA Code of Federal Regulations (Title 21 Parts 50, 56, 312), the general guidelines

indicated in the Declaration of Helsinki; and all applicable national regulatory requirements governing clinical studies."

3.3 Financial Disclosures

In total, 452 investigators participated in conducting the three studies, Study 101 (25 investigators), Study 301 (303 investigators), and Study 302 (124 investigators), in this application. Of these investigators, there was one investigator not certified regarding the absence of financial interests and/or arrangements. This investigator's financial disclosure was unsigned in the study site's electronic system.

The Applicant explained that this investigator, an Assistant Coordinator who was listed in FDA Form 1572 in Study Site 54 under Study 302, was not certified with due diligence. The Assistant Coordinator was not delegated to informed consent processes, treatment of participants, or the assessment of safety, including the final review of the eDiary. The Applicant stated that they had not made any direct payments to the Assistant Coordinator.

Reviewer comment: *The Applicant did not submit Form 3455 because all 451 investigators submitted financial disclosure and Form 3454 stated that none of the 451 investigators had financial interests or arrangements. However, the number of financial disclosed forms signed by individual investigators did not match the number of investigators listed in Form 3454. We issued an additional IR to the Applicant for clarification and the Applicant submitted their response to STN125777/0.13 on February 22, 2023, which adequately addressed the discrepancy.*

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The product reviewer did not identify any significant chemistry, manufacturing and controls (CMC) issues. Please refer to the product review for details.

4.2 Assay Validation

The assay validation reviewer did not identify any significant assay issues. Please refer to the assay validation review for details.

Reviewer comment: *A* (b) (4) *assay was performed for the analysis of Phase 1 sera. The* (b) (4) *assay was not validated. The μPRNT$_{50}$ assay used in Phase 3 trials was validated.*

4.3 Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer did not identify any significant issues.

A passive transfer study was performed in NHPs using human anti-CHIKV immune sera collected from a Phase 1 study (NCT03382964). The clinical review of this Phase 1 study is in the Appendix at the end of this review. Sera obtained between days 14 and 180 postvaccination were pooled to generate 8 serum pools representing varying anti-CHIKV neutralizing antibody titers. In the passive transfer study, 40 CHIKV-naïve (b) (4) macaques were administered human anti-CHIKV immune sera from the 8 serum pools (n=5 per group) and 6 CHIKV-naïve (b) (4) macaques were administered non-immune control serum by intravenous injection. One day after the transfers, serum samples were obtained from the macaques to determine pre-

challenge anti-CHIKV neutralizing antibody titers by $\mu PRNT_{50}$ assay. Animals were challenged with 100 times the 50% animal infectious dose of wild-type CHIKV strain La Réunion 2006-OPY1, corresponding to 7,000–10,000 Plaque Forming Units. Animal monitoring included assessment of wild type CHIKV-induced viremia by RT-qPCR through 14 days after challenge. Data from the animal studies using macaques were analyzed by logistic regression to determine the threshold $\mu PRNT_{50}$ titer that is considered reasonably likely to predict a clinical benefit. The anti-CHIKV neutralizing antibody titer ≥150 prior to wild-type CHIKV challenge in the macaques was accepted by CBER as the surrogate endpoint to support licensure via AA.

Please refer to the toxicology review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

VLA1553 elicits CHIKV-specific neutralizing antibody responses against CHIKV. Although the exact mechanism of protection is unknown, immune responses induced by vaccination with VLA1553 that protect humans against CHIK is thought to be mediated by CHIKV-specific neutralizing antibodies.

4.5 Statistical

The statistical reviewer verified the key results of the Applicant's analyses of the immunogenicity and safety data. Please refer to the CBER statistical reviewer's memo for details.

4.6 Pharmacovigilance

The pharmacovigilance plan (PVP) includes the following safety concerns:

- Important identified risk: Chikungunya-like adverse reactions, including vaccine associated arthralgia
- Important potential risks: Neutropenia and leukopenia, and cardiac events
- Other potential risks: Adverse pregnancy outcomes such as spontaneous abortion; autoimmune or inflammatory disorders; frail adults with acute or progressive, unstable, or uncontrolled clinical conditions, e.g., cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions; long-term safety; and interaction with other vaccines

In addition to routine pharmacovigilance, the safety concerns of arthritis/arthralgia, cardiac events, and spontaneous abortion will be further evaluated in the postmarket setting with enhanced pharmacovigilance activities, which include expedited reporting (regardless of seriousness or label status), a summary and analysis in periodic safety reports, and dedicated adverse event questionnaires. The Applicant will further evaluate neutropenia and leukopenia with a dedicated adverse event questionnaire and information on this risk will be included in the United States Prescribing Information (USPI). Safety in pregnancy will be further evaluated in a dedicated pregnancy safety study, which will be performed as a PMC in the Chikungunya endemic area of Brazil. In addition, the Applicant will conduct a voluntary postmarketing safety study of 5,000 U.S. travelers for medically attended adverse events of special interest, including pregnancy outcomes. The Applicant's PVP is acceptable. Please refer to PVP review for details.

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

5.1 Review Strategy

The Applicant submitted three clinical studies evaluating the safety and immunogenicity of VLA1553: a dose-escalation study (Study 101), a pivotal effectiveness study (Study 301) and a lot-consistency study (Study 302). Studies 301 and 302 are considered essential to support the proposed indication and usage and are reviewed in detail and documented in Sections 6.1 and 6.2, respectively. Study 101 was a dose-escalation study of dose-levels and formulations that were different from the to-be-marketed dose and formulation. The review of Study 101 is summarized in Appendix A at the end of the review.

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

This clinical review considered the following documents submitted to the BLA, as listed by eCTD module:

- STN125777/0.3, Module 1.3 (Financial Certification and Disclosure)
- STN125777/0.3, Module 1.9 (Pediatric Assessment Plan)
- STN125777/0.3, Module 1.14 (Labeling)
- STN125777/0.3, Modules 2.2, 2.5 and 2.7 (Introduction, Clinical Overview, and Clinical Summary)
- STN125777/0.3: Module 5.3.1 (Reports of Biopharmaceutic studies: VLA1553-302)
- STN125777/0.3, Module 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication: VLA1553-101 and VLA1553-301)
- STN125777/0.3, Module 5.3.5.3 (Reports of Analyses of Data from More than One Study: ISS and ISE)
- STN125777/0.3, Module 5.3.5.4 (Other Study Reports: PASS-Post-marketing safety study protocol, and (b) (4) -402-Post-marketing confirmatory trial protocol)
- STN125777/0.7, Module 5.3.1.2 and 5.3.5.1 (Response to case narrative request)
- STN125777/0.9, Module 5.3.5.1_Responses to IR#13-Case Narratives and CRFs
- STN125777/0.10, Module 1.11.3_Responses to IR#10-Financial disclosure and immunogenicity subgroup analyses
- STN125777/0.12, Module 1.11.3_Responses to IR#14-Datasets
- STN125777/0.13, Module 1.3.4_Responses to financial certification and disclosure
- STN125777/0.19, Module 1.11.3_Responses to IR#18 & 19-Pre-existing anti-CHIK and cross-neutralization data
- STN125777/0.20, Module 5.3.1.2 and 5.3.5.1_Responses to IR#14-Datasets
- STN125777/0.21, Module 1.2_Applicant's correction of errors in statistical analyses
- STN125777/0.22, Module 5.3.1.2 and 5.3.5.1_Responses to IR#21-Clnical data tables
- STN125777/0.23, Module 1.2_Response to IR#14-Datasets
- STN125777/0.24, Module 1.11.3_Responses to IR#23-ISS
- STN125777/0.25, Module 1.11.3_Responses to IR#23-Safety subgroup analyses in ISS population
- STN125777/0.31, Module 1.11.3_Responses to IR#31_AESIs
- STN125777/0.35, Module 1.11.4_Responses to IR#34_Atrial fibrillation in VLA1553-101
- STN125777/0.36, Module 1.11.3_Responses to IR#35-Adverse pregnancy outcomes following natural CHIKV infection
- STN125777/0.37, Module 1.11.3_Responses to IR#38-Rationale not conducting randomized placebo controlled confirmatory trials
- STN125777/0.38, Module 1.11.3_Responses to IR#34-Cardiac disorder SMQ analyses
- STN125777/0.40, Module 1.11.3_Responses to IR#36_ISE analyses
- STN125777/0.43, Module 1.11.3_Responses to IR#41_Re-analyses of AESIs

- STN125777/0.44, Module 1.11.3_Responses to IR#43_Clarification for IMM subset discrepancies and hematology parameter analyses
- STN125777/0.49, Module 1.11.3_Responses to IR#49_Subgroup analyses of AESIs
- STN125777/0.52, Module 1.11.3_Responses to IR#46_Postmarketing pregnancy study
- STN125777/0.53, Module 1.11.3_Responses to IR#50_Postmarketing confirmatory study (b) (4) -402
- STN125777/0.64, Module 1.11.3_Responses to IR#50_Postmarketing confirmatory study (b) (4) -402
- STN125777/0.67, Module 1.11.3 & 5.3.5.1_Responses to IR#65_AESIs
- STN125777/0.68, Module 1.11.3_Responses to IR#66_Causality assessment of AESIs
- STN125777/0.78, Module 1.11.3_Responses to IR#74_Clinical datasets
- STN125777/0.81, Module 1.11.3_Responses to IR#78_Hematology data analyses
- STN125777/0.84, Module 5.3.5.4_Protocol (b) (4) -404
- STN125777/0.87, Module 5.3.5.4_Protocol (b) (4) -404
- STN125777/0.90, Module 1.11.4_Responses to CBER comment on prolonged AESI
- STN125777/0.93, Module 1.11.3_Responses to IR#89-Protocol (b) (4) -402
- STN125777/0.94, Module 1.11.3_Responses to IR#91-Protocol (b) (4) -402 and (b) (4) -404
- STN125777/0.95, Module 1.11.3_Responses to IR#92-Hematology data
- STN125777/0.96, Module 1.11.3_Responses to IR#93-Protocol (b) (4) -404
- STN125777/0.97, Module 1.11.3_Responses to IR#87-Labeling

5.3 Table of Studies/Clinical Trials

Table 4. Overview of Clinical Trials That Support the Application

Study ID	Study 101	Study 301	Study 302
NCT ID	NCT03382964	NCT04546724	NCT04786444
Phase	1	3	3
IND Study	Yes	Yes	Yes
Study sites	2 U.S. sites	43 U.S. sites	12 U.S. sites
Study design	Open-label dose escalation study	Double blind, randomized placebo-controlled study	Double blind, randomized lot-to-lot consistency study
Participants planned	120 (low: 30; medium: 30; high: 60)	4,060 (VLA1553: 3045; placebo: 1015)	402 (134 participants in each Lot)
Participants enrolled	120 (low: 31; medium: 30; and high: 59)	4,128 (VLA1553: 3093; placebo: 1035)	409 (Lot 1: 136; Lot 2: 137; and Lot 3: 136)
Age range (years of age)	18-45	18-88	18-45
Median age of participants (years of age)	32.5	45	34
Treatment route	IM, deltoid, Initial dose followed by re-vaccination at Month 6 or Month 12*	IM, deltoid, Single dose	IM, deltoid, Single dose
Treatment dose	Low: 3.2×10^3 $TCID_{50}$ in 0.1 mL Medium: 3.2×10^4 $TCID_{50}$ in 1 mL High: 3.2×10^5 $TCID_{50}$ in 1 mL	1×10^4 $TCID_{50}$ in 0.5 mL placebo in 0.5 mL	1×10^4 $TCID_{50}$ in 0.5 mL Lot 1, Lot 2, or Lot 3

Study ID	Study 101	Study 301	Study 302
Primary endpoint	Safety	Percentage of participants with a seroresponse titer $\mu PRNT_{50}$ ≥150 at 28 days postvaccination	Geometric mean titer of CHIKV-specific neutralizing antibodies at 28 days postvaccination
Follow-up duration	12 or 13 months follow-up after initial dose	6 months	6 months

Source: Adapted from STN125777, VLA1553-301Clinical Study Report, Module 5.2, Tabular Listing of all Clinical Studies; and VLA1553-302 CSR
Notes: Participants in low and medium dose groups in Study 101 also received a high dose of VLA1553 at Month 12, and 50% participants in the high dose group received a second high dose at Month 6 and the other 50% participants received a second high dose at Month 12.
Abbreviations: NCT ID, National Clinical Trials Identifier; IM, intramuscular; $TCID_{50}$, median tissue culture infectious dose; $\mu PRNT_{50}$, 50% plaque reduction in a micro-plaque reduction neutralization test.

5.4 Consultations

No external consults or collaborations were sought.

5.5 Literature Reviewed

Ali, A. A. et al (2022). Maternal and perinatal outcomes during a Chikungunya outbreak in Kassala, eastern Sudan. *Archives of Gynecology and Obstetrics, 305*(4), 855–858. https://doi.org/10.1007/s00404-021-06204-6

Alvarez, M. F. et al (2017). Cardiovascular involvement and manifestations of systemic Chikungunya virus infection: A systematic review. *F1000Research, 6*, 390. https://doi.org/10.12688/f1000research.11078.2

Aspromonte, N. et al (2017). ANMCO/ELAS/SIBioC Consensus Document: biomarkers in heart failure. *European Heart Journal Supplements : Journal of The European Society of Cardiology, 19*(Suppl D), D102–D112. https://doi.org/10.1093/eurheartj/sux027

Bettis, A. A. et al (2022). The global epidemiology of chikungunya from 1999 to 2020: A systematic literature review to inform the development and introduction of vaccines. *PLoS Neglected Tropical Diseases*,*16*(1), e0010069. https://doi.org/10.1371/journal.pntd.0010069

Bonten, M. J. et al (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *The New England Journal of Medicine, 372*(12), 1114–1125. https://doi.org/10.1056/NEJMoa1408544

Burt, F. et al (2014). Chikungunya virus and arthritic disease. *The Lancet. Infectious Diseases, 14*(9), 789–790. https://doi.org/10.1016/S1473-3099(14)70869-2

Bustos Carrillo, F et al. (2019). Epidemiological Evidence for Lineage-Specific Differences in the Risk of Inapparent Chikungunya Virus Infection. *Journal of virology, 93*(4), e01622-18. https://doi.org/10.1128/JVI.01622-18

Centers for Disease Control and Prevention (2022) Chikungunya Virus Chikungunya virus | CDC

Centers for Disease Control and Prevention (2023) Chikungunya Virus Chikungunya in the US | Chikungunya virus | CDC

Clerico, A. et al (2011). Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones. *American journal of physiology. Heart and circulatory physiology, 301*(1), H12–H20. https://doi.org/10.1152/ajpheart.00226.2011

Chakraborty R.K. et al (2023) Systemic Inflammatory Response Syndrome. https://www.ncbi.nlm.nih.gov/books/NBK547669

Cotella, J. I. et al (2021). Chikungunya and the Heart. *Cardiology, 146*(3), 324–334. https://doi.org/10.1159/000514206

Couderc, T. et al (2009). Focus on Chikungunya pathophysiology in human and animal models. *Microbes and infection,11*(14-15), 1197–1205. https://doi.org/10.1016/j.micinf.2009.09.002

de Lima Cavalcanti T.Y.V. et al (2022) A Review on Chikungunya Virus Epidemiology, Pathogenesis and Current Vaccine Development. *Viruses*, *14*(5):969. https://doi.org/10.3390/v14050969

de Oliveira Ribeiro, G. et al (2022). Chikungunya Virus Asian Lineage Infection in the Amazon Region Is Maintained by Asiatic and Caribbean-Introduced Variants. *Viruses, 14*(7), 1445. https://doi.org/10.3390/v14071445

Folegatti, P. M. et al (2021). A single dose of ChAdOx1 Chik vaccine induces neutralizing antibodies against four chikungunya virus lineages in a phase 1 clinical trial. *Nature communications, 12*(1), 4636. https://doi.org/10.1038/s41467-021-24906-y

Gérardin, P. et al (2008). Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the island of La Réunion. *PLoS medicine, 5*(3), e60. https://doi.org/10.1371/journal.pmed.0050060

Goetze, J. P. et al (2020). Cardiac natriuretic peptides. Nature reviews. Cardiology, 17(11), 698–717. https://doi.org/10.1038/s41569-020-0381-0

Goo, L. et al (2016). A Virus-Like Particle Vaccine Elicits Broad Neutralizing Antibody Responses in Humans to All Chikungunya Virus Genotypes. *The Journal of infectious diseases, 214*(10), 1487–1491. https://doi.org/10.1093/infdis/jiw431

Gordon, A. et al (2018). Differences in Transmission and Disease Severity Between 2 Successive Waves of Chikungunya. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 67(*11), 1760–1767. https://doi.org/10.1093/cid/ciy356

Gupta, S. et al (2019). Short-term pregnancy outcomes in patients chikungunya infection: An observational study. *Journal of family medicine and primary care, 8*(3), 985–987. https://doi.org/10.4103/jfmpc.jfmpc_274_18

Hawman, D. W. et al (2013). Chronic joint disease caused by persistent Chikungunya virus infection is controlled by the adaptive immune response. *Journal of Virology, 87*(24), 13878–13888. https://doi.org/10.1128/JVI.02666-13

Khongwichit, S. et al (2021). Chikungunya virus infection: molecular biology, clinical characteristics, and epidemiology in Asian countries. *Journal of Biomedical Science, 28*(1), 84. https://doi.org/10.1186/s12929-021-00778-8

Kumar, R. et al (2021). Chikungunya and arthritis: An overview. *Travel Medicine and Infectious Disease, 44*, 102168. https://doi.org/10.1016/j.tmaid.2021.102168

Lang, K. et al (2012). Trends in self-reported spontaneous abortions: 1970-2000. *Demography, 49*(3), 989–1009. https://doi.org/10.1007/s13524-012-0113-0

Langsjoen, R. M. et al (2016). Molecular Virologic and Clinical Characteristics of a Chikungunya Fever Outbreak in La Romana, Dominican Republic, 2014. *PLoS Neglected Tropical Diseases, 10*(12), e0005189. https://doi.org/10.1371/journal.pntd.0005189

Langsjoen, R. M. et al (2018). Chikungunya Virus Strains Show Lineage-Specific Variations in Virulence and Cross-Protective Ability in Murine and Nonhuman Primate Models. *mBio, 9*(2), e02449-17. https://doi.org/10.1128/mBio.02449-17

Magnus, M. C. et al (2019). Role of maternal age and pregnancy history in risk of miscarriage: prospective register-based study. *BMJ (Clinical research ed.), 364*, l869. https://doi.org/10.1136/bmj.l869

McLaughlin, J. M. et al (2018). Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 67*(10), 1498–1506. https://doi.org/10.1093/cid/ciy312

Pal, P. et al (2014). Chikungunya viruses that escape monoclonal antibody therapy are clinically attenuated, stable, and not purified in mosquitoes. *Journal of Virology, 88*(15), 8213–8226. https://doi.org/10.1128/JVI.01032-14

Ramakrishnan, V. et al (2020). Natriuretic Peptides, Inflammation, and Sounding the Alarm. *Circulation. Heart failure, 13*(7), e007208. https://doi.org/10.1161/CIRCHEARTFAILURE.120.007208

Rossen, L. M. et al (2018). Trends in Risk of Pregnancy Loss Among US Women, 1990-2011. *Paediatric and Perinatal Epidemiology, 32*(1), 19–29. https://doi.org/10.1111/ppe.12417

Rossi, S. L. et al (2019). Immunogenicity and Efficacy of a Measles Virus-Vectored Chikungunya Vaccine in Nonhuman Primates. *The Journal of Infectious Diseases, 220(*5), 735–742. https://doi.org/10.1093/infdis/jiz202

Simon, F. et al (2015). Chikungunya Virus Infections. *The New England Journal of Medicine, 373*(1), 93–94. https://doi.org/10.1056/NEJMc1505501

Sissoko, D. et al (2009). Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. PLoS neglected tropical diseases, 3(3), e389. https://doi.org/10.1371/journal.pntd.0000389

Song, W. et al (2015). Atrial natriuretic peptide in cardiovascular biology and disease (NPPA). *Gene, 569*(1), 1–6. https://doi.org/10.1016/j.gene.2015.06.029

Suhrbier, A. et al (2012). Arthritogenic alphaviruses-an overview. *Nature Reviews. Rheumatology*, 8(7), 420–429. https://doi.org/10.1038/nrrheum.2012.64

Teo, T. et al (2015) Caribbean and La Réunion Chikungunya Virus Isolates Differ in Their Capacity To Induce Proinflammatory Th1 and NK Cell Responses and Acute Joint Pathology. *Virol 89* (15) 7955–7969 https://doi.org/10.1128/JVI.00909-15

Traverse, E. M. et al (2021). Cardiomyopathy and Death Following Chikungunya Infection: An Increasingly Common Outcome. *Tropical Medicine and Infectious Disease, 6*(3), 108. https://doi.org/10.3390/tropicalmed6030108

Tsetsarkin, K. A. et al (2007). A single mutation in chikungunya virus affects vector specificity and epidemic potential. *PLoS pathogens*, *3*(12), e201. https://doi.org/10.1371/journal.ppat.0030201

Vairo, F. et al (2019). Chikungunya: Epidemiology, Pathogenesis, Clinical Features, Management, and Prevention. *Infectious Disease Clinics of North America, 33*(4), 1003–1025. https://doi.org/10.1016/j.idc.2019.08.006

Yasir M. et al (2023) Syndrome of Inappropriate Antidiuretic Hormone Secretion. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK507777/

Yoon, I. K et al (2015). High rate of subclinical chikungunya virus infection and association of neutralizing antibody with protection in a prospective cohort in the Philippines. *PLoS Neglected Tropical Diseases, 9*(5), e0003764. https://doi.org/10.1371/journal.pntd.0003764

Yoon, I. K. et al (2020). Pre-existing chikungunya virus neutralizing antibodies correlate with risk of symptomatic infection and subclinical seroconversion in a Philippine cohort. *International Journal of Infectious Diseases: IJID : Official Publication of the International Society for Infectious Diseases, 95*, 167–173. https://doi.org/10.1016/j.ijid.2020.03.073

Zauche, L. H.et al (2021). Receipt of mRNA COVID-19 vaccines preconception and during pregnancy and risk of self-reported spontaneous abortions, CDC v-safe COVID-19 Vaccine Pregnancy Registry 2020-21. *Research Square*, rs.3.rs-798175. https://doi.org/10.21203/rs.3.rs-798175/v1

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (Study VLA1553-301)

NCT04546724
"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 older."

6.1.1 Objectives

Primary Objective
To evaluate the immunogenicity and safety of the final dose of the live-attenuated CHIKV vaccine (VLA1553) 28 days following vaccination in a population of adults ≥18 years of age after a single immunization.

Secondary Objective
To assess the immunogenicity and safety of the final dose of VLA1553 up to 180 days following vaccination in a population of adults ≥18 years of age after a single immunization.

6.1.2 Design Overview

Study 301 was a prospective, randomized, double-blind, multicenter, pivotal clinical study evaluating the final dose of VLA1553 (1x10E4 median tissue culture infectious dose [$TCID_{50}$] per 0.5 mL) in comparison to a placebo control (phosphate buffered saline [PBS], 0.5 mL) randomized at a 3:1 ratio. Participants were followed for safety, immunogenicity, and antibody persistence for 6 months.

6.1.3 Population

Individuals were eligible to be included if they were ≥18 years of age on the day of screening and generally healthy. Individuals of childbearing potential were eligible to participate if they had been using contraception during the month before screening, had a negative serum or urine pregnancy test, and agreed to use adequate contraception for the first 3 months postvaccination.

Individuals were not eligible for enrollment if they had CHIKV infection in the past, including suspected CHIKV infection; were taking medication or other treatment for unresolved symptoms attributed to a previous CHIKV infection; or had participated in a clinical study involving an investigational CHIKV vaccine. Individuals were also excluded for any of the following: acute infection at screening, positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV), immune-mediated or clinically relevant arthritis/arthralgia, and history of malignancy in the past 5 years.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Participants received one dose of VLA1553 (CHIKV vaccine) as an intramuscular (IM) vaccination in the deltoid region of the arm on study Day 1.

CHIKV Vaccine
Each participant randomized to receive CHIKV vaccine received an IM shot from a 0.5mL prefilled syringe containing VLA1553 1 x 10^4 $TCID_{50}$. Batch numbers refer to a single batch used throughout the study: (b) (4) , 2005040029, 2006300061 (packed), 0030620 (CI. no.).

Placebo
Each participant randomized to receive placebo received a 0.5 mL IM shot of phosphate buffered saline (PBS) in a liquid formulation.

6.1.5 Directions for Use

VLA1553 was available as a vaccine kit containing one single-use (b) (4) vial with the lyophilized vaccine powder and one prefilled syringe of 0.5 mL sterile water for reconstitution to a suspension of targeted 1 x 10^4 $TCID_{50}$ per 0.5 mL injectable dose. The full volume contained in the prefilled syringe was administered.

VLA1553 or placebo was administered intramuscularly into the deltoid muscle as a single shot on Day 1.

6.1.6 Sites and Centers

The study was conducted at 43 investigational sites in the U.S.

6.1.7 Surveillance/Monitoring

Solicited adverse reactions, unsolicited AEs, AESIs, medically attended AEs, AEs leading to withdrawal from the study, and SAEs were assessed. The following AEs were documented and monitored:

Solicited Systemic and Injection-Site Adverse Reactions
During the first 10 days postvaccination, participants reported any solicited adverse reactions in the participant eDiary and were recorded on the AE page of the eCRF.

Solicited systemic reactions included arthralgia, fever, fatigue, headache, nausea, rash, and vomiting. Injection site (IS) reactions included IS pain, tenderness, erythema/redness, induration, and swelling. Participants were provided with a measuring device to measure the size of any IS reaction that developed postvaccination. The participant was instructed on how to measure any such reaction over a period of 10 consecutive days postvaccination along the longest diameter of the reaction area and record this measurement in the participant eDiary.

Unsolicited AEs
Participants were provided with an eMemory Aid to collect unsolicited AEs occurring until the end of study (Visit 5). Additionally, the investigator inquired about AEs during study visits. Clinically relevant laboratory parameter changes constituted unsolicited AEs, unless they were considered a symptom of an underlying AE or part of a syndrome that was reported as AE (e.g., the presence of blood cells in urine in a person diagnosed with urinary tract infection). In addition, symptoms noted during the symptom-driven physical examination (unless already covered by an AE) constituted AEs. All unsolicited AEs needed to be documented in the respective AE section of the eCRF during the applicable study visit (Visits 1 to 5 or unscheduled visit(s)).

AESIs
Participants were monitored for signs and symptoms suggestive of an acute stage of CHIKV-associated events. The following cluster of symptoms suggestive of CHIKV infection with or without remissions or exacerbations were assessed in the study as AESIs and necessitated presentation for an unscheduled visit:

1. Fever (≥38.0°C [100.4°F] measured orally)

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] and edema of the face and extremities), polyadenopathies
3. Onset of symptoms 2 to 21 days postvaccination
4. Duration of event ≥3 days

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

Reviewer comment: *In review of the BLA, we considered the above protocol definition of AESI as inadequate to identify all potential AESIs and asked the Applicant to revise the AESI definition and analyze the data based on the revised AESI definition. Please refer to Section 6.1.12.5 for the revised AESI definition and the rationale for the revision.*

An independent Data Safety Monitoring Board (DSMB) met to review accumulating safety data (SAEs, AESIs, and Grade 3 solicited AEs) on a regular basis until all participants received the vaccination on Day 1 and until all participants completed at least Visit 2. In addition, the DSMB periodically reviewed accruing safety information throughout the study, as applicable.

6.1.8 Endpoints and Criteria for Study Success

6.1.8.1 Primary Endpoint

The primary endpoint was the percentage of participants with seroresponse, defined as a CHIKV-specific neutralizing antibody titer ≥150 in $\mu PRNT_{50}$ 28 days postvaccination.

6.1.8.2 Main Secondary Endpoints

The immunogenicity and safety measures considered as secondary endpoints are as follows:

Immunogenicity Endpoints

1. Immune response as measured by CHIKV-specific neutralizing antibody titers on Day 8, Day 29, Day 85 and at Day 180 postvaccination as determined by $\mu PRNT_{50}$ assay.
2. Percentage of participants with seroresponse (defined as $\mu PRNT_{50}$ ≥150 for baseline negative participants) on Day 8, Day 85 and at Day 180 postvaccination as determined by $\mu PRNT_{50}$ assay.

Safety Endpoints

1. Frequency and severity of unsolicited AEs within 28 days postvaccination.
2. Frequency and severity of solicited IS AEs and systemic AEs within 10 days postvaccination.
3. Frequency, severity, and relatedness of any AE during the entire study period.
4. Frequency and relatedness of any SAE during the entire study period.
5. Frequency and relatedness of any AESI within 2 to 21 days postvaccination.

6.1.9 Statistical Considerations & Statistical Analysis Plan

6.1.9.1 Study Hypotheses and Analyses of Primary Endpoint

The primary immunogenicity endpoint was defined as the percentage of participants in the PP population with a CHIKV antibody seroresponse level (defined as $\mu PRNT_{50}$ ≥150 for baseline negative participants) 28 days postvaccination.

A hypothesis test was defined for the primary immunogenicity analysis using a one-sided significance level of 2.5%. There was no adjustment for multiplicity for any immunogenicity endpoints. The null-hypothesis H0 was LB of 95% CI of seroresponse rate ≤70%, and the alternative H1 was LB of 95% CI of seroresponse rate >70%.

The primary immunogenicity analysis, seroresponse rate, was conducted using an exact binomial test with a one-sided significance level of 2.5% was applied and exact (Clopper-Pearson) two-sided 95% CIs were calculated.

Reviewer comment: *In our responses to the Applicant's pre-BLA meeting questions, we requested that the Applicant use the term "seroresponse", instead of "seroprotection", to define the surrogate endpoint that is reasonably likely to predict clinical benefit to avoid potential misconception because a protective neutralizing antibody titer against CHIKV has not been established. However, the Applicant still used the term "seroprotection" in the application. Throughout this review, the term seroresponse is used and defined as a* $\mu PRNT_{50}$ *≥150.*

6.1.9.2 Sample Size Calculation

The proposed sample size of approximately 3,000 VLA1553 vaccinated participants would 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 would 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 percentage of participants with a seroresponse level (defined as $\mu PRNT_{50}$ ≥150 for baseline negative participants) at Day 29. Assuming 80% of participants vaccinated with VLA1553 achieved an $\mu PRNT_{50}$ ≥150, 200 VLA1553-vaccinated participants would thus be necessary for a statistical power of 90%. With an expected drop-out/major protocol deviations rate of approximately 10%, 225 participants vaccinated with VLA1553 would need to be allocated to the immunogenicity subset.

To account for placebo participants, to achieve a meaningful number of participants in both age strata, and to enroll sufficient numbers of participants for a long-term follow-up in a potential subsequent trial, the first 500 participants enrolled and randomized to the study from all 12 study sites were designated as the immunogenicity subset.

6.1.9.3 Methods of Handling Missing Data

All statistical analyses were generally based on observed values, missing values were not imputed. Any AE with missing severity was classified as severe. AEs with missing causality assessment were considered related unless further specified.

6.1.9.4 Interim Analysis

No interim analysis was planned or conducted.

6.1.9.5 Safety Analyses

All AEs including solicited adverse reactions, unsolicited AEs, SAEs and AESIs were analyzed on the Safety population.

The number and percentage of participants, plus number of events in each category were presented.

Summaries of AEs categorized by System Organ Class (SOC) and Preferred Term (PT) coded according to the Medical Dictionary for Regulatory Activities dictionary (MedDRA) were produced. Within these summaries, AE were counted by participant but not by event and participants were only counted once within each SOC or PT.

Where AEs presented by severity (mild, moderate, severe), SOC and PT, participants with multiple events within a particular body system or PT were counted once under the category of their most severe event within that SOC or PT.

In summaries of AEs which were categorized by relationship to investigational medicinal product (IMP), SOC and PT, AEs with a causality reported as probable or possible were considered related to the IMP. Participants with multiple events within a particular SOC or PT were counted under the category of their most drug-related event within that SOC or PT.

Changes in laboratory values from study entry were analyzed descriptively for clinical chemistry, hematology, coagulation, and urinalysis. The rates of participants with laboratory assessments with maximum postbaseline grade of Grade 0 vs. 1 through 4 were calculated. Shift tables of laboratory results by grade were presented for the maximum postbaseline grade.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Participants enrolled and analyzed are presented in the table below.

Table 5. Analysis Sets, Study 301

Analysis Set	VLA1553	Placebo	Total
Participants screened	-	-	6100
Randomized population (n)	3093	1035	4128
Vaccinated participants [n (%)[a]]	3083 (99.7)	1034 (99.9)	4177 (99.7)
Randomized but not vaccinated participants [n (%)[a]]	10 (0.3)	1 (0.1)	11 (0.3)
Immunogenicity Subset [n (%)[a]]	375 (12.1)	126 (12.2)	501 (12.1)
Vaccinated participants in Immunogenicity Subset [n (%)[a]]	371 (12.0)	126 (12.2)	497 (12.0)
Safety population (n[b])	3082	1033	4115
Immunogenicity population (IMM) [n (%)[a]]	344 (11.1)	118 (11.4)	462 (11.2)
Per-Protocol population [n (%)[a]]	266 (8.6)	96 (9.3)	362 (8.8)
Immunogenicity Elderly population (eIMM) [n (%)[a]]	376 (12.2)	127 (12.3)	503 (12.2)
Sensitivity Per-Protocol population (sPP) [n (%)[a]]	275 (8.9)	99 (9.6)	374 (9.1)
Sensitivity Per Protocol 2 Population (sPP2) [n (%)[a]]	267 (8.6)	96 (9.3)	363 (8.8)

Source: Adapted from Table 17 (page 94), and Table 14.1.1.1 (page. 53), VLA1553-301 CSR
Notes: All vaccinated participants were included in the safety population except for one participant who was vaccinated twice and was thus excluded from the Safety population due to lack of Good Clinical Practices (GCP) compliance
a. Percentage of all randomized participants
b. Percentages were not included because participants were grouped according to treatment actually received and not randomized treatment

Table 6. Analysis Populations

Analysis Population	Definition
Randomized	• All enrolled and randomized participants in the study. • Used for sensitivity analyses of the demographic and baseline characteristic data.
Safety	• All participants that entered the study and received one vaccination. • This population was the primary analysis set for all safety endpoints.
Immunogenicity subset	• All participants that were initially enrolled into the immunogenicity evaluation group, regardless of any other factors.
Non-immunogenicity subset	• All participants that were initially enrolled and randomized into the study and were not in the immunogenicity subset.
Immunogenicity (IMM)[a]	• All randomized and vaccinated participants of the immunogenicity subset who were CHIKV seronegative at baseline (defined as $\mu PRNT_{50}$ <20) and had at least one evaluable post-baseline titer measurement postvaccination. • This population was used for sensitivity analyses of the immunogenicity endpoints.
Elderly Immunogenicity (eIMM)[a]	• All randomized and vaccinated participants of the IMM subset, who received a vaccination, were CHIKV seronegative at baseline, and had a non-missing post-baseline immunogenicity sample, complemented by the randomly selected elderly participants (Stratum B) of the safety analysis population to achieve 154 participants. • This population was used for sensitivity analyses of the immunogenicity endpoints.
Per-Protocol (PP)[a]	• All IMM population participants who had no major protocol deviations that could impact the immune response. • The PP population was the primary analysis set for all immunogenicity analyses.
Sensitivity Per-Protocol (sPP)[a]	• All randomized and vaccinated participants of the IMM subset who were CHIKV seronegative at baseline (defined as $\mu PRNT_{50}$ ≤40), had at least one evaluable post-baseline titer measurement postvaccination, and did not have any exclusionary protocol deviations as described in the protocol. • This population was used for the additional sensitivity analyses of immunogenicity data based on the updated sensitivity threshold for baseline serostatus using the cut-off of $\mu PRNT_{50}$ ≤40.
Sensitivity Per-Protocol 2 (sPP2)	• The sPP2 included all randomized and vaccinated participants of the IMM subset who were CHIKV seronegative at baseline (defined as $\mu PRNT_{50}$ <20), had at least one evaluable post-baseline titer measurement postvaccination, did not have any exclusionary protocol deviations as described in the protocol, and had visit windows as described in the statistical analysis plan. • This population was used for the additional sensitivity analyses of immunogenicity data based on visit windowing of immunogenicity results.

a. Participants were analyzed according to the study group they had been randomized to, rather than by the actual treatment they received.

6.1.10.1.1 Demographics

As shown in Table 7, baseline demographics between the VLA1553 and placebo groups were generally balanced. For both groups, slightly more female participants (around 55%) than male participants participated in the study; the majority of participants were White (around 80%). Median age of the participants was 45.0 years, and a total of 463 elderly participants (≥65

years) were enrolled in the study. Baseline demographics between the VLA1553 and placebo groups for the immunogenicity subset were similar.

Table 7. Baseline Demographic Characteristics, Study 301

Characteristic	VLA1553 N=3082	Placebo N=1033
Age (Years)	-	-
Mean (SD)	45.1 (15.4)	45.0 (15.6)
Median	45.0	45.0
Range	18-88	18-94
Age Band, n (%)	-	-
18-64 years	2736 (88.8)	916 (88.7)
≥65 years	346 (11.2)	117 (11.3)
Sex, n (%)	-	-
Female	1682 (54.6)	569 (55.1)
Male	1400 (45.4)	464 (44.9)
Race, n (%)	-	-
American Indian or Alaskan Native	27 (0.9)	5 (0.5)
Asian	51 (1.7)	17 (1.6)
Black or African American	451 (14.6)	122 (11.8)
Native Hawaiian/Pacific Islander	13 (0.4)	5 (0.5)
White	2456 (79.7)	853 (82.6)
Other	84 (2.7)	31 (3.0)
Ethnicity, n (%)	-	-
Hispanic or Latino	545 (17.7)	177 (17.1)
Non-Hispanic/Latino	2498 (81.1)	840 (81.3)
Not Reported	34 (1.1)	14 (1.4)
Unknown	5 (0.2)	2 (0.2)

Source: Adapted from Tables 13 & 14 of VLA1553-301 CSR (page 88-89) under Module 5.3.5.1, STN125777/0.3.
Abbreviations: N=total number of participants in the group, n=number of participants in the corresponding category

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

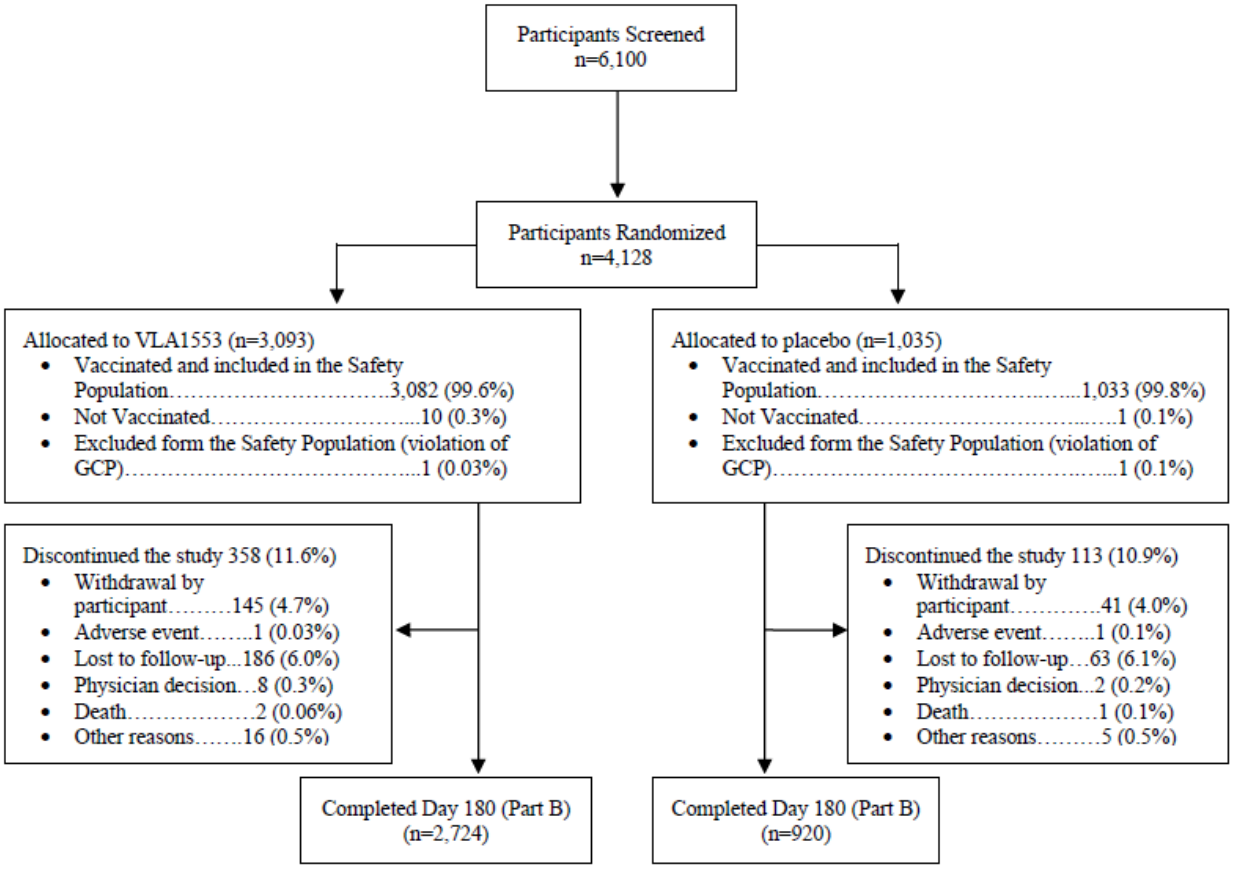
The percentage of participants with any medical history was similar between the two groups, including medical history of arthralgia (VLA1553, 3.3%; placebo, 3.6%), myalgia (VLA1553, 0.9%; placebo, 0.8%) and fibromyalgia (VLA1553, 0.8%; placebo, 0.9%).

Most participants, 76.4% (2354/3082) in the VLA1553 group and 76.5% (790/1033) in the placebo group, received concomitant medications. The most common concomitant medications were vaccines (25.5% in VLA1553 and 27.4% in placebo) and almost all the concomitant vaccines were COVID-19 vaccines. Similar percentages of participants in VLA1553 (1.7%) and placebo (1.6%) groups received concomitant systemic steroids. In addition, five participants, all in VLA1553 group, received concomitant denosumab that has an increased risk of infections due to its effects on the immune system.

6.1.10.1.3 Subject Disposition

The disposition of participants is provided in Figure 1.

Figure 1. Disposition of Participants, Study 301



Source: Duplicated from Figure s (page 85), VLA1553-301 CSR, Module 5.3.5.1, STN125777/0.3.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary immunogenicity endpoint of CHIKV-specific neutralizing antibody as determined by $\mu PRNT_{50}$ at 28 days postvaccination (Day 29) was evaluated on the PP population. All participants in the PP population had a $\mu PRNT_{50}$ titer <20 at baseline. At Day 29, 98.9% (263/266) participants in the VLA1553 group had a CHIKV antibody level $\mu PRNT_{50}$ ≥150, while no participants in the placebo group had a CHIKV antibody titer ≥150 (Table 8). The LB of the 95% CI of seroresponse rate was 96.7%, which was above the pre-specified success criterion of LB of 95% CI >70%; therefore, the study success criterion was met.

Table 8. Seroresponse Rate for CHIKV-Specific Neutralizing Antibodies on Day 29, Study 301

Populations	VLA1553	Placebo
PP, N	266	96
Seroresponse rate[a] % (95% CI)	98.9 (96.7, 99.8)	0 (0.0, 3.8)
sPP, N	275	99
Seroresponse rate[a] % (95% CI)	98.9 (96.8, 99.8)	0 (0.0, 3.7)
sPP2 N	267	96
Seroresponse rate[a] % (95% CI)	98.9 (96.8, 99.8)	0 (0.0, 3.8)

Source: Adapted from Tables 18, 19 and 20 of VLA1553-301 CSR (page 97, 99 and 100, respectively) under Module 5.3.5.1, STN125777/0.3.
Notes: a. Seroresponse rate was defined as a percentage of participants with an anti-CHIKV neutralizing antibody titer≥ 150.
Abbreviations: N, total number of participants in the analysis population; PP, Per-Protocol population; sPP, sensitivity Per-Protocol population, sPP2, sensitivity Per-Protocol 2 population

As shown in Table 8 (above), the Applicant also conducted two sensitivity analyses to investigate if the different threshold for baseline serostatus or visit window had an impact on the overall immunogenicity outcome.

In the sensitivity Per-Protocol population (sPP), CHIKV seronegativity at baseline was defined as anti-CHIKV neutralizing antibody $\mu PRNT_{50}$ titer ≤40 instead of <20 (definition used for the PP population). The sensitivity Per-Protocol 2 population (sPP2) included all randomized and vaccinated participants of the immunogenicity subset who were CHIKV seronegative at baseline ($\mu PRNT_{50}$ titer <20) who had data available from a visit at Day 28 within the +/- 8 day visit window as described in the protocol, even if the visit label was not "Visit 3", as required for inclusion in the PP population. As shown in Table 8 , neither the baseline serostatus cut-off level nor use of alternative visit label had an impact on the overall immunogenicity outcome.

Reviewer comment: *The sensitivity analysis was conducted in sPP because 22 participants (16 in the VLA1553 group and six in the placebo group) had an anti-CHIKV titer at baseline of ≥20, the cut-off value for CHIKV seropositivity. Of these 22 participants, seven had baseline $\mu PRNT_{50}$ >40 (four in the VLA1553 group and three in the placebo group), and 15 had baseline $\mu PRNT_{50}$ of ≥20 and ≤40 (12 in the VLA1553 group and three in the placebo group). The immunogenicity analyses of the seven participants with a baseline titer >40 is presented in Section 6.1.11.2.*

Results obtained in the immunogenicity (IMM) population and the elderly immunogenicity (eIMM) population were similar. The seroresponse rates at Day 29 for IMM and eIMM populations were 98.8% (95% CI: 96.5, 99.8) and 99.0% (95% CI: 94.8, 100.0) (Data source: VLA1553-301, Clinical Study Report Table 14.2.1.3).

6.1.11.2 Analyses of Secondary Endpoints

Immune Response Kinetics of VLA1553
The summary of immune responses as expressed in GMTs and seroresponse rates in the PP population at various time points following vaccination is presented in Table 9.

At Day 1, none of the participants in the VLA1553 or placebo groups had a detectable anti-CHIKV neutralizing antibody titer. At Day 8, a few participants had an anti-CHIKV neutralizing antibody titer ≥150, with a GMT of 13.6 in the vaccination group. Anti-CHIKV neutralizing antibody titers peaked at Day 29 with a GMT of 3361.6, and gradually decreased to a GMT of 1083.6 and 752.1 at Day 85 and Day 180 (6 months), respectively. No participant in the placebo group had a detectable anti-CHIKV neutralizing antibody titer at any visit throughout the study period.

Although anti-CHIKV neutralizing antibody titers decreased significantly from Day 29 to Day 180, the percentage of participants with a seroresponse titer (defined as anti-CHIKV neutralizing antibody titer ≥150) remained almost at the same level from Day 29 (98.9%) to Day 180 (96.3%) in the VLA1553 group. None of the participants in the placebo group demonstrated a seroresponse.

Table 9. Immune Response Kinetics Following Vaccination with VLA1553, Per-Protocol Population, Study 301

Time Point	n	VLA1553 N=266	n	Placebo N=96
GMT (95% CI)	-	-	-	-
Day 1	266	10.0 (10.0, 10.0)	96	10.0 (10.0, 10.0)
Day 8	251	13.6 (12.4, 15.0)	93	10.2 (9.9, 10.4)
Day 29	266	3361.6 (2993.8, 3774.5)	96	10.1 (9.9, 10.3)
Day 85	246	1083.6 (968.3, 1212.6)	91	10.2 (9.9, 10.4)
Day 180	242	752.1 (665.9, 849.5)	91	10.0 (10.0, 10.0)
Seroresponse rate[a] % (95% CI)	-	-	-	-
Day 1	266	0 (0, 0)	96	0 (0, 0)]
Day 8	251	1.6 (0.4, 4.0)	93	0 (0.0, 3.9)
Day 29	266	98.9 (96.7, 99.8)	96	0 (0.0, 3.8)
Day 85	246	98.0 (95.3, 99.3)	91	0 (0.0, 4.0)
Day 180	242	96.3 (93.1, 98.3)	91	0 (0.0, 4.0)

Source: Adapted from Table 14.2.2.1 (pages 363-371, GMTs) and Tables 14.2.1.5 (pages 321-325, Seroresponse rates), Appendix 16.1.9, VLA1553-301, Module 5.3.5.1, STN125777/0.3.
Notes: a seroresponse rate was defined as a percentage of participants with an anti-CHIKV neutralizing antibody titer≥ 150.
Abbreviations: N, total number of participants in the group; n, number of participants in the analysis population; GMT, geometric mean titer; CI, confidence interval

The Applicant also conducted sensitivity analyses for the above secondary endpoints on the sPP and sPP2 populations. The results from the sensitivity analyses on the sPP and sPP2 populations were comparable to those on the PP population, indicating that neither the baseline serostatus cut-off level nor alternative visit windowing had an impact on the immunogenicity endpoints (data not shown).

Anti-CHIKV Neutralizing Antibody Titer Changes for Participants with a Baseline Anti-CHIKV Titer >40

Although participants with suspected CHIKV infection were excluded from the study, it was still possible to enroll participants with unknown or unidentified CHIKV infection. Therefore, baseline blood samples were collected from all participants for potential retrospective investigation of pre-existing antibodies, including, but not limited to, other alphaviruses (i.e., Mayaro), dengue, and Zika.

In Study 301, seven participants had a baseline antibody titer >40. These seven participants might have been infected with CHIKV prior to enrollment into this study. The anti-CHIKV neutralizing antibody titers at various time points during the study among these seven participants were analyzed. As shown in Table 10, the baseline anti-CHIK neutralizing antibody GMT in the VLA1553 group was 501.1, and the GMT increased more than 4-fold to 2754.5 at Day 29; the GMTs remained about 2-fold above the baseline value through Day 180. In contrast, anti-CHIKV neutralizing antibody titers in the placebo group remained at the same level from baseline throughout the study period.

Table 10. Anti-CHIKV Neutralizing Antibody Titers in Participants With a Baseline Titer >40, Safety Population, Study 301

Time Point	VLA1553 N=4	Placebo N=3
GMT % (95% CI) [n]	-	-
Day 1	501.1 (23.6, 10654.4) [4]	955.4 (5.1, 177568.2) [3]
Day 8	531.4 (22.1, 12778.2) [4]	1055.1 (5.7, 196904.8) [3]
Day 29	2754.5 (1293.0, 5868.0) [4]	881.5 (38.0, 20447.8) [3]
Day 85	1408.6 (520.1, 3814.5) [4]	787.3 (22.8, 27151.2) [3]
Day 180	1166.6 (169.0, 8053.6) [4]	395.2 (8.8, 17689.4) [2]

Source: Adapted from Table 14.2.5.6 (pages 426-431), Appendix 16.1.9, VLA1553-301, Module 5.3.5.1, STN125777/0.3.
Abbreviations: N, total number of participants in the group; n, number of participants in the analysis population
GMT, geometric mean titer

Reviewer comment: *Based on aggregate analyses of the four participants with a baseline titer of anti-CHIKV >40, it appears that VLA1553 is immunogenic among participants with pre-existing anti-CHIKV antibodies. However, two participants with high anti-CHIKV titer at baseline titers of 3186 and 2166, respectively) had an anti-CHIKV titer at Day 29 (1493 and 2597, respectively) that was comparable or decreased from baseline. The remaining two participants with lower baseline anti-CHIKV GMTs (GMT of 105 for Participant VLA1553-301-*(b) (6) *and GMT of 87 for Participant VLA1553-301*(b) (6) *had anti-CHIKV GMTs that increased at least 30-fold at Day 29. These results are consistent with the findings in Study 101, which showed that re-vaccination at either 6 months or 12 months after the first vaccination had no effect on anti-CHIKV titers compared with the titer prior to re-vaccination. The clinical significance of these findings is unknown. None of the four participants experienced an SAE, severe AE, or an AESI.*

6.1.11.3 Subpopulation Analyses

Subgroup analyses of VLA1553 vaccine effectiveness in terms of seroresponse rate and GMT in the PP set at postvaccination Day 28 by age, sex, race, and ethnicity in the pivotal study are presented in Table 11. No statistically significant difference in either seroresponse rates or GMT was noted among the subgroups. However, in subgroups by race, only a few participants were Asian, American Indian/Alaska Native, or Native Hawaiian/other Pacific Islander, which is a limitation of the study. Therefore, even though there appeared to be no significant difference in seroresponse rates or GMTs among the racial subgroups, differences in antibody responses among these subgroups cannot be ascertained based on the available data.

Table 11. Anti-Chikungunya Specific Neutralizing Antibody Response Rate, Per Protocol Analysis Set, Study 301

Subgroup	N	Seroresponse Rate % (95% CI)	GMT (95% CI)
Age (years)	-	-	-
18 to 64	207	98.6 (95.8, 99.7)	3273.7 (2860.9, 3746.0)
≥65	59	100 (93.9, 100.0)	3688.8 (2938.9, 4630.1)
Sex	-	-	-
Female	154	98.1 (94.4, 99.6)	3304.2 (2784.8, 3920.4)
Male	112	100 (96.8, 100.0)	3442.1 (2974.9, 3982.7)

Subgroup	N	Seroresponse Rate % (95% CI)	GMT (95% CI)
Race	-	-	-
White	212	99.5 (97.4, 100.0)	3342.1 (2963.9, 3768.6)
Black or African American	41	95.1 (83.5, 99.4)	3127.4 (2036.5, 4802.6)
Asian	2	100 (15.8, 100.0)	3079.6 (23.9, 396812)
American Indian or Alaska Native	2	100 (15.8, 100.0)	7952.7 (64.0, 988526)
Native Hawaiian or other Pacific Islander	1	100 (2.5, 100.0)	3999.0 (NC, NC)
Other	8	100 (63.1, 100.0)	4576.5 (3309.4, 6328.7)
Ethnicity	-	-	-
Hispanic or Latino	21	100 (83.9, 100.0)	4212.2 (3256.2, 5449.1)
Non-Hispanic or Latino	241	98.8 (96.4, 99.7)	3320.2 (2931.3, 3760.8)

Source: Adapted from Table 1 (page 5), Module 1.11.3 IR Response, STN125777/0.10.
Notes: Seroresponse of CHIKV-specific neutralizing antibody titer is defined as $\mu PRNT_{50}$ ≥150.
Abbreviations: N, participants in each subgroup with non-missing neutralizing antibody titer result at Day 29; n, number of participants with seroresponse; NC, non-calculable; GMT, geometric mean titer; CI, confidence interval.

6.1.11.4 Dropouts and/or Discontinuations

The overall dropout rate for this study was around 10%, similar to other vaccine studies. The major reasons for discontinuations were due to withdrawal by participants and lost-to-follow-up. Based on the timing of the dropouts and discontinuations and adequacy of the immunogenicity population to meet the statistical success criterion, it is unlikely that dropouts and discontinuations had an impact on the study conclusions. Assuming all dropouts showed no seroresponse, the LB of the 95% CI of seroresponse would be still >70%,

6.1.11.5 Exploratory and Post Hoc Analyses

Impact of Pre-Existing Antibodies to Alphaviruses or Flaviviruses on Anti-CHIKV Response to VLA1553

Post hoc analyses were conducted to assess whether pre-existing antibodies to alphaviruses or flaviviruses at baseline impact antibody response to VLA1553. The results showed that participants with pre-existing antibodies to flaviviruses, either dengue or Zika, tended to have a higher anti-CHIKV neutralizing antibody titers compared with the corresponding participants without the pre-existing antibodies (data not shown). However, this phenomenon was observed in Study 302 but not in Study 301. The pre-existing anti-dengue or anti-Zika titers were similar between Study 301 and Study 302.

In contrast, participants with pre-existing anti-CHIKV antibodies tended to have lower anti-CHIKV neutralizing antibody titer following vaccination with VLA1553 compared with participants without pre-existing anti-CHIKV antibodies. Interestingly, this phenomenon was also observed only in participants in Study 302 (Table 12). Pre-existing antibodies to the other alphavirus, Mayaro, did not appear to impact antibody response to VLA1553 (data not shown). Since the pre-existing anti-CHIKV titers in Study 302 were numerically higher than in Study 301, it is

unknown whether the magnitude of pre-existing anti-CHIKV titers played a role in this observation.

Table 12. Impact of Pre-Existing Anti-CHIKV Antibodies (Abs) at Baseline on Antibody Response to VLA1553

Anti-CHIKV Abs Demographic	Anti-CHIKV Abs at Day 1 GMT (95% CI)	Anti-CHIKV Abs at Day 29 GMT (95% CI)
Study 301	-	-
Participants without pre-existing anti-CHIKV Abs (N=351)	10.0 (10.0, 10.0)	3115.9 (2817.6, 3445.8)
Participants with pre-existing anti-CHIKV Abs (N=15)	47.7 (19.9, 114.7)	2901.3 (2171.7, 3875.9)
Study 302	-	-
Participants without pre-existing anti-CHIKV Abs (N=334)	10.0 (10.0, 10.0)	2591.8 (2314.1, 2902.8)
Participants with pre-existing anti-CHIKV Abs (N=12)	98.8 (34.9, 279.7)	1171.0 (380.7, 3601.7)
Combined Studies 301 and 302	-	-
Participants without pre-existing anti-CHIKV Abs (N=667)	10.0 (10.0, 10.0)	2834.3 (2626.4, 3058.7)
Participants with pre-existing anti-CHIKV Abs (N=27)	67.0 (35.1, 127.9)	1903.9 (1117.1, 3244.8)

Source : Table 4 (page 10), Module 1.11.3_IR response, STN125777/0.19
Abbreviations: CHIKV, chikungunya virus; GMT, geometric mean titer; CI, confidence interval

Reviewer comment: *Due to the limited sample size and lack of vaccine efficacy data, the clinical significance of pre-existing antibodies to alphaviruses or flaviviruses is unknown.*

6.1.12 Safety Analyses

6.1.12.1 Methods

All enrolled participants who received at least one vaccination were included in the safety analysis. Safety tabulations included both solicited adverse reactions and unsolicited AEs. The number and percentage of participants, plus number of events in each category were presented.

Summary of AEs were presented and categorized by SOC and PT coded according to MedDRA and by severity (mild, moderate, severe) and relatedness if applicable. AEs with a causality reported as probable or possible were considered related to the IMP.

AEs were coded using MedDRA version 24.1.

6.1.12.2 Overview of Adverse Events

An overview of all AEs during the clinical trial in the safety population is presented in Table 13.

The occurrence of at least one AE (solicited and/or unsolicited) was reported by a higher percentage of participants in the VLA1553 group compared with the placebo group (62.5% versus 44.8%). Most AEs were mild or moderate; however, 3.4% (104/3,082) of participants experienced severe (Grade 3) AEs following vaccination with VLA1553 compared to 1.4% (14/1,033) of participants in the placebo group.

SAEs were reported in 46/3,082 (1.5%) and 8/1,033 (0.8%) participants in the VLA1553 and placebo groups, respectively. AESIs were reported in 361/3,082 (11.7%) and 6/1,033 (0.6%) participants in the VLA1553 and placebo groups, respectively.

Table 13. Adverse Events, Safety Population, Study 301

Category	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
At least one AE	1926 (62.5)	463 (44.8)
AE ≥Grade 3	104 (3.3)	14 (1.4)
Any solicited reaction	1628 (52.8)	331 (32.0)
Any solicited local reaction	463 (15.0)	115 (11.1)
Any solicited systemic reaction	1547 (50.2)	278 (26.9)
Any unsolicited AE	933 (30.3)	248 (24.0)
Any MAAE	386 (12.5)	110 (11.4)
SAE	46 (1.5)	8 (0.8)
AESI	361 (11.7)	6 (0.6)
AE leading to withdrawal	3 (0.1)	2 (0.2)
Death	2 (0.1)	1 (0.1)

Source: Adapted from Table 14.3.2.1.1 (pages 481-490) and Table 14.1.13.1 (page 56), Appendix, Module 16.1.9, VLA1553-301 CSR, STN1256777/0.3, Module 5.3.5.1, and Table 2 (page 7), Module 1.11.3 IR responses, STN125777/0.43.
Abbreviations: N, total number of participants in the group; n, number of participants with adverse events; AE, adverse event; SAE, serious adverse event; AESI, adverse event of special interest; MAAE, medically-attended adverse event

Reviewer comment: *Some AESIs were not included in the Applicant's analysis because the symptoms of these AESIs did not cluster and occur simultaneously. CBER requested the Applicant include in their analysis all AESIs with onset within 30 days postvaccination, regardless of whether the symptoms occurred at the same time. The incidence of AESIs presented in the above table reflects the results of the requested analysis. Please refer to Section 6.1.12.5 for details.*

Solicited Adverse Events
Solicited IS reactions and systemic reactions during a 10-day postvaccination period are summarized in Table 14 and Table 15, respectively.

Solicited IS reactions were more frequent in the VLA1553 group (15.0%) than the placebo group (11.1%); however, a majority of IS reactions in both groups were mild (>90%) or moderate (<5%) (Table 14). A severe solicited IS reaction was reported by only one participant (Participant (b) (6) in the VLA1553 group, who experienced pain lasting for 7 days.

Table 14 Solicited Injection Site Reactions Within 10 Days Postvaccination, Safety Population, Study 301

Adverse Reaction	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
Any Injection-Site Reactions	463 (15.0)	115 (11.1)
Severe Reactions	1 (0.0)	0 (0.0)
Pain/Tenderness	328 (10.6)	84 (8.1)
Erythema/Redness	46 (1.5)	15 (1.5)
Swelling	21 (0.7)	8 (0.8)
Induration	44 (1.4)	8 (0.8)

Source: Adapted from Table 32 (p133) and Table 36 (page 143), VLA1553-301 CSR, Module 5.3.5.1, STN125777/0.3.
Abbreviations: N, total number of participants in the group; n, number of participants with the corresponding events.

As shown in Table 15, percentage of participants reporting any solicited systemic reaction were higher in the VLA1553 group (52.8%) than in the placebo group (32.0%). Overall, most solicited systemic reactions were mild or moderate.

The percentage of participants with severe systemic reactions in the VLA1553 group (2.1%) was also higher than in the placebo group (0.1%). The most frequently reported severe systemic reaction following vaccination with VLA1553 was fever [44/3,082 (1.4%)], followed by arthralgia [9/3,082, (0.3%)], and myalgia [8/3,082 (0.3%)].

Table 15. Solicited Systemic Adverse Reactions Within 10 Days Postvaccination, Safety Population, Study 301

Adverse Reaction	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
Any systemic reaction	1628 (52.8)	331 (32.0)
Severe reactions	64 (2.1)	1 (0.1)
Any headache	969 (31.4)	151 (14.6)
Severe headache	3 (0.1)	1 (0.1)
Fatigue	879 (28.5)	130 (12.6)
Severe fatigue	5 (0.2)	0 (0.0)
Myalgia	735 (23.8)	76 (7.4)
Severe myalgia	8 (0.3)	0 (0.0)
Arthralgia	520 (16.9)	50 (4.8)
Severe arthralgia	9 (0.3)	0 (0.0)
Fever	414 (13.4)	8 (0.8)
Severe fever	44 (1.4)	0 (0.0)
Nausea	345 (11.2)	58 (5.6)
Severe nausea	0 (0.0)	0 1 (0.1)
Rash	70 (2.3)	5 (0.5)
Severe rash	0 (0.0)	0 (0.0)
Vomiting	58 (1.9)	10 (1.0)
Severe vomiting	0 (0.0)	1 (0.1)

Source: Adapted from Table 32 (p133), Table 33 (page 139) and Table 34 (page 141), VLA1553-301 CSR, Module 5.3.5.1, STN125777/0.3
Abbreviations: N, total number of participants in the group; n, number of participants with the corresponding events

Reviewer comment: *A significant number of eDiary cards had missing information. This reviewer requested that the digital health technology reviewer, Dr. Hussein Ezzeldin (Office of Biostatistics and Pharmacovigilance, OBPV), conduct an in-depth analysis of missing data. After multiple IRs to the Applicant, Dr. Ezzeldin concluded that the missing data in the VLA1553 and placebo groups appeared to be at random and no modification of data presented by the Applicant is necessary. Please refer to Dr. Ezzeldin's review for details.*

Concomitant use of anti-inflammatory/anti-rheumatic products and analgesics in the VLA1553 and placebo groups were comparable prior to vaccination (at baseline): anti-inflammatory/anti-rheumatic products—0.5% in VLA1553 and 0.9% in placebo, and analgesics—0.4% in VLA1553 and 0.2% in placebo.

Numerically more participants in the safety population received anti-inflammatory and anti-rheumatic products in the VLA1553 group (24.3%) compared to placebo group (15.4%) postvaccination. Similarly, more participants received analgesics in the VLA1553 group (23.9%) compared to placebo group (16.3%).

Reviewer comment: *Although concomitant use and anti-inflammatory/anti-rheumatic products and analgesics in the VLA1553 and placebo groups were comparable prior to vaccination, there was a higher percentage of participants with concomitant anti-inflammatory products/analgesics in the VLA1553 group compared with the placebo group postvaccination. This correlates with the higher incidence of myalgia and arthralgia postvaccination in the VLA1553 group (VLA1553, 23.8% vs. placebo, 7.4% for myalgia, and VLA1553 16.9% vs. placebo, 4.8 % for arthralgia).*

Unsolicited Adverse Events
Unsolicited AEs were collected via eMemory card. Table 16 summarizes unsolicited AEs occurring in ≥1% of participants during the 28 day postvaccination period by SOC and PT. Differences in event rates of >1% were observed between the VLA1553 and placebo groups for neutropenia (6.7% in VLA1553 vs. 0.8% in placebo), leukopenia (3.8% in VLA1553 vs. 0% in placebo), diarrhea (1.4% in VLA1553 vs. 0.4% in placebo), and chills (1.8% in VLA1553 vs. 0.2% in placebo).

Reviewer comment: *The eMemory aid was reviewed by the Digital Health Technical reviewer; no significant issue was identified.*

One participant (Participant (b) (6) experienced an event of prolonged right hand joint polyarthritis, which was considered not related to VLA1553 by the investigator and the Applicant.

Reviewer comment: *This case (Participant (b) (6) was unblinded at the participant's request. In the CSR of VLA1553-301 (page 47), the case was described as "bilateral hand polyarthritis, right hand greater than left, shortly after receiving study vaccine". However, the DSMB meeting indicated that the symptoms were not typical for CHIK and probably related to another cause (e.g., cold weather) and the rheumatologist also stated that the symptoms were not related to VLA1553 without providing the rationale for such a causality assessment. An IR was conveyed to the Applicant on 17 July 2023 asking for the narrative of the case and the Applicant's causality assessment.*

The Applicant submitted its response to the IR to STN125777/0.68. The case, including the Applicant's causality assessment, is summarized below:

- Participant (b) (6): A 60-year-old White female with a medical history of cervical spinal stenosis and irritable bowel syndrome (IBS) experienced moderate arthralgia and mild myalgia starting on the day following VLA1553 vaccination. Myalgia resolved one day later; however, the hand joint pain persisted. Five days postvaccination, she visited the study site for an evaluation of the arthralgia and was diagnosed with synovitis in third and fourth metacarpophalangeal joints (MCP3 and MCP4) in right hand. The investigator considered the synovitis not related to VLA1553, without providing a rationale for the causality assessment.

  At three months postvaccination, she visited a rheumatologist for pain, swelling and stiffness in right MCP3 and MCP4. She was treated with prednisone for a month starting at 20 mg and tapering down by 5 mg each week, but after four weeks, the pain and swelling in the MCP3 and MCP4 of the right hand returned. She received a steroid injection for the right middle finger with improvement for four weeks in the third and fourth fingers of the right hand, but the pain and swelling recurred. The treating physician performed surgery on the middle finger at five months postvaccination. The participant returned to the clinic six months postvaccination complaining of recurrence of pain,

stiffness and swelling in the right MCP3 joint and was treated with hydroxychloroquine. However, she discontinued the medicine because she could not tolerate its side effects. In her last clinical visit at eight months postvaccination, she presented with inflammatory polyarthropathy in the right MCP3 and MCP4. Physical exam was not remarkable except for tender and swollen joints in MCP3 and MCP4 of the right hand. The event of arthralgia was ongoing at the end of study.

The participant tested negative for CHIK, Dengue, Mayaro and Zika Virus Antibodies at Visit 1 (Day of vaccination) and was not tested for CHIKV viremia following vaccination with VLA1553.

The Applicant considered the case not related to VLA1553 for the following reasons:

a) The time frame for symptom onset was not typical for CHIK. The Applicant argued that the incubation period was typically 3-7 days following natural CHIKV infection although the Applicant acknowledged that the range of incubation period was 1-12 days.
b) The participant did not have fever, which is typically associated with CHIKV infection.
c) The participant had a history IBD and patient with IBD may be at an increased risk of developing joint pain or arthritis.

In its response to the IR, the Applicant also clarified that neither the events reported by the investigator in the eCRF nor the report from the rheumatologist indicated that the participant developed bilateral hand polyarthritis, and, as such, the case was incorrectly described in the CSR of VLA1553-301.

Reviewer Comment: *This reviewer does not agree with the causality assessment of the chronic polyarthritis by the investigator, DSMB, and the Applicant, and considers the chronic polyarthritis was at least possibly related to VLA1553 for the following reasons:*

a) The events are closely temporally associated with vaccination
b) The onset of symptoms was within the range of the incubation period following natural CHIKV infection. Arthralgia was reported by other participants in this study, with an onset on the vaccination day.
c) Although CHIKV infection is typically associated with a fever, not all people infected with CHIKV manifest fever.
d) It is biologically plausible. Vaccine viremia was associated with arthralgia in many other participants, including prolonged arthralgia in two participants in this study as well as two other studies in the vaccine development program.
e) No alternative etiology for the polyarthritis was provided. This reviewer agrees that a patient with IBD may be at an increased risk of developing joint pain or arthritis; however, relatedness of VLA1553 cannot be excluded.

During the 28 days postvaccination, unsolicited AEs were reported by a higher percentage of participants in the VLA1553 group [671/3,082 (21.8%)] than in the placebo group [137/1,033 (13.3%). Overall, most unsolicited AEs were mild or moderate, and 0.6% participants in both VLA1553 group [18/3,082 (0.6%)] and placebo group [6/1,033 (0.6%)] experienced at least one severe unsolicited AE. The most common severe unsolicited AE was neutropenia [11/372 (3.0%) in VLA1553 group, none in placebo group]. The Applicant considered chills, diarrhea, back pain, and lymphadenopathy (0.9% in VLA1553 group and 0% in the placebo group, not shown in Table 16) to be likely related to the vaccine.

Table 16. Unsolicited Adverse Events with a Frequency ≥1% in at Least One Study Group, by System Organ Class and Preferred Term, During the 28 Days Postvaccination, Safety Population, Study 301

Unsolicited Adverse Events	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
Any unsolicited adverse event	671 (21.8)	137 (13.3)
Blood and lymphatic system disorders	84 (2.7)	7 (0.7)
Neutropenia[a]	34 (9.1)	1 (0.8)
Leukopenia[a]	18 (4.8)	0 (0.0)
Gastrointestinal disorders	91 (3.0)	15 (1.5)
Diarrhea	43 (1.4)	4 (0.4)
General disorders and administration site conditions	108 (3.5)	16 (1.5)
Chills	57 (1.8)	2 (0.2)
Infections and infestations[b]	116 (3.8)	27 (2.6)
Injury, poisoning and procedural complications[b]	43 (1.4)	10 (1.0)
Musculoskeletal and connective tissue disorders	125 (4.1)	37 (3.6)
Back pain	35 (1.1)	6 (0.6)
Nervous system disorders	77 (2.5)	20 (1.9)
Headache	27 (0.9)	12 (1.2)
Respiratory, thoracic, and mediastinal disorders[b]	58 (1.9)	8 (0.8)
Skin and subcutaneous tissue disorders[b]	39 (1.3)	11 (1.1)

Source: Adapted from Table 14.3.3.3.1 (pages 1-38), VLA1553-301 CSR, Module 1.11.3, STN125777/0.95; and Table 1 (page 7), Module 1.11.3_IR Response, STN125777/0.44
a Safety laboratory samples were only taken from the IMM subset (i.e., the total number of participants in this subset was 497 with 372 participants in VLA1553 group and 125 in placebo group
b No preferred term with an incidence of ≥1% under this system organ class
Abbreviations: N, number of participants in the group; n, number of participants with an indicated event

Reviewer comment: *Hematology parameters were assessed in the immunogenicity subset only at specified time points as described in the protocol. Neutropenia and leukopenia were also reported by investigators as unsolicited AEs in the safety population. As a result, the frequency of neutropenia and leukopenia were different from those reported in Section 6.1.12.6. Note the definition of neutropenia varied depending on the analysis population. In the immunogenicity subset, neutropenia was defined by FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. In the safety population, neutropenia was reported if the participant had an abnormal and clinically relevant decrease in neutrophil counts, as judged by the investigator.*

Similarly, during the 180 days postvaccination, unsolicited AEs were more frequently reported in the VLA1553 group [933/3,082 (30.3%)] than in the placebo group [248/1,033 ([24.0%)]. Most unsolicited AEs were mild or moderate, and 1.4% participants in VLA1533 group (43/3,082) and 1.3% participants (13/1,033) experienced at least one severe unsolicited AE (data not shown).

Medically Attended Adverse Events
Overall, 12.5% (386/3082) of VLA1553 recipients and 11.4% (118/1033) of placebo recipients experienced at least one medically attended AE (MAAE) during the study. The most common MAAEs were headache (1.0% in the VLA1553 group and 0.3% in the placebo group), COVID-19 (0.8% in each group), arthralgia (0.6% VLA1553, 0.7% placebo group), urinary tract infection (0.6% VLA1553 group, 0.5% placebo group), myalgia (0.6% VLA1553 group, 0.2% placebo group), and pyrexia (0.6% VLA1553 group, 0.3% placebo group).

Most MAAEs were mild or moderate, and 1.2% participants in each treatment group experienced at least one MAAE that was severe. The most common severe MAAE was pyrexia, occurring in 4/3,082 (0.1%) participants in the VLA1553 group and none in the placebo group.

6.1.12.3 Deaths

Three participants died during the study, two [2/3,082 (0.1%)] in the VLA1553 group and one [1/1,033 (0.1%)] in the placebo group. Narratives for these 3 participants are summarized below:

- Participant (b) (6): A 52-year-old White male with a body mass index (BMI) of 40.0 kg/m^2 experienced severe coronary artery disease on Day (b) (6) postvaccination with VLA1553 and died on the same day. Relevant medical history included hypertension (since 2011) and hypercholesterolemia (since 2000). He had been treated with metoprolol (since 2014), amlodipine besylate (since 2018), losartan (since 2020) and atorvastatin (since 2017) for hypertension and hypercholesterolemia. The event was assessed by the investigator and the Applicant as not related to vaccination.

- Participant (b) (6): A 57-year-old White female experienced severe COVID-19 on Day 165 postvaccination with VLA1553. She was subsequently hospitalized and died on Day (b) (6). No treatment was reported for this event. The event was assessed by the investigator and the Applicant as not related to vaccination.

- Participant (b) (6): A 63-year-old White male experienced severe mental status changes (altered mental state) on Day 151 after he received the placebo and died on Day (b) (6). No clear cause for the event was found despite extensive testing; 4 days after hospitalization the participant experienced a respiratory arrest and never recovered. At Day (b) (6), the participant was diagnosed with severe cerebral dysfunction and brain death. No treatment was reported for this event. The event was assessed by the investigator and the Applicant as not related to vaccination.

Reviewer comment: *This reviewer has reviewed the narratives and CRFs and concurs with the Applicant that the deaths reported in this study were unlikely related to the study vaccine.*

6.1.12.4 Nonfatal Serious Adverse Events

Overall, 83 non-fatal SAEs were experienced in 54/4,115 (1.3%) participants during the study, 1.5% (46/3,082) of participants in the VLA1553 group and 0.8% (8/1,033) of participants in the placebo group. The most frequent SAEs were in the SOCs *Infections and infestations* [0.3% participants each in the VLA1553 group (9/3,082) and in the placebo group (3/1,033)], followed by *Injury and poisoning* [0.3% in the VLA1553 group (8/3,082), and 0.1% in the placebo group (1/1,033)], *Psychiatric disorder* [0.2% each in the VLA1553 (7/3,082) and placebo (2/1,033) groups], and *Cardiac disorder* [0.2% in the VLA1553 group (5/3,082) and none in the placebo group]. All 5 events of *Cardiac disorder* were reported among participants ≥65 years of age in the VLA1553 group.

Non-fatal SAEs by SOC and PT are provided in Table 17.

Table 17. Non-Fatal Serious Adverse Events, by System Organ Class and Preferred Term, Postvaccination, Safety Population, Study 301

Non-Fatal Serious Adverse Events	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
Any unsolicited adverse event	46 (1.5)	8 (0.8)
Cardiac disorders	5 (0.2)	0
Atrial fibrillation	2 (0.1)	0
Cardiac arrest	1 (0.0)	0
Cardiomyopathy	1 (0.0)	0
Coronary artery disease	1 (0.0)	0
Endocrine disorders	1 (0.0)	0
Inappropriate antidiuretic hormone	1 (0.0)	0
Gastrointestinal disorders	3 (0.1)	1 (0.1)
Abdominal pain	1 (0.0)	0
Cannabinoid hyperemesis syndrome	1 (0.0)	0
Colitis	1 (0.0)	0
Gastrointestinal hemorrhage	0	1 (0.1)
Nausea	1 (0.0)	0
Small intestinal obstruction	1 (0.0)	0
Vomiting	1 (0.0)	0
General Disorders and Administration Site Conditions	1 (0.0)	0
Non-cardiac chest pain	1 (0.0)	0
Hepatobiliary disorders	1 (0.0)	0
Cholecystitis	1 (0.0)	0
Immune system disorders	1 (0.0)	0
Anaphylactic reaction	1 (0.0)	0
Infections and Infestations	9 (0.3)	3 (0.3)
Pneumonia	2 (0.1)	1 (01)
COVID-19	1 (0.0)	1 (0.1)
Appendicitis	1 (0.0)	0
Arthritis bacterial	1 (0.0)	0
COVID-19 pneumonia	1 (0.0)	0
Complicated appendicitis	1 (0.0)	0
Diverticulitis	1 (0.0)	0
Kidney infection	0	1 (0.1)
Pyelonephritis	1 (0.0)	0
Injury, Poisoning and Procedural complications	8 (0.3)	1 (0.1)
Ankle fracture	2 (0.1)	0
Road traffic accident	2 (0.1)	0
Tibia fracture	2 (0.1)	0
Alcohol poisoning	1 (0.0)	0
Fall	1 (0.0)	0
Fibula fracture	1 (0.0)	0
Hip fracture	0	1 (0.1)
Post procedural hematoma	1 (0.0)	0
Procedural pain	1 (0.0)	0
Splenic rupture	1 (0.0)	0
Tendon rupture	1 (0.0)	0
Traumatic liver injury	1 (0.0)	0
Investigations	1 (0.0)	0
SARS-CoV-2 test positive	1 (0.0)	0
Metabolism and Nutrition Disorders	1 (0.0)	0
Hypokalemia	1 (0.0)	0

Non-Fatal Serious Adverse Events	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
Musculoskeletal and Connective Tissue Disorders	2 (0.1)	0
Lumbar spinal stenosis	1 (0.0)	0
Myalgia	1 (0.0)	0
Neoplasms: benign, malignant, and unspecified (incl cysts and polyps)	3 (0.1)	0
Chronic lymphocytic leukemia	1 (0.0)	0
Non-small cell lung cancer, recurrent	1 (0.0)	0
Papillary thyroid cancer	1 (0.0)	0
Nervous system disorders	4 (0.1)	1 (0.1)
Cerebellar hemorrhage	0	1 (0.1)
Guillain-Barre syndrome	1 (0.0)	0
Neuropathy peripheral	1 (0.0)	0
Syncope	1 (0.0)	0
Transient ischemic attack	1 (0.0)	0
Pregnancy, puerperium, and perinatal conditions	3 (0.1)	0
Abortion spontaneous	2 (0.1)	0
Fetal death	1 (0.0)	0
Psychiatric disorders	7 (0.2)	2 (0.2)
Suicidal ideation	3 (0.1)	1 (0.1)
Depression	3 (0.1)	0
Anxiety	0	1 (0.1)
Anxiety disorder	1 (0.0)	0
Depression suicidal	1 (0.0)	0
Mental status changes	0	1 (0.1)
Renal and urinary disorders	2 (0.1)	0
Acute kidney injury	1 (0.0)	0
Hydronephrosis	1 (0.0)	0
Nephrolithiasis	1 (0.0)	0
Reproductive system and breast disorders	1 (0.0)	0
Prostatomegaly	1 (0.0)	0
Respiratory, thoracic, and mediastinal disorders	2 (0.1)	0
Pulmonary embolism	1 (0.0)	0
Acute respiratory failure	1 (0.0)	0
Hypoxia	1 (0.0)	0
Skin and subcutaneous tissue disorders	1 (0.0)	0
Skin ulcer	1 (0.0)	0
Vascular disorders	1 (0.0)	0
Hypotension	1 (0.0)	0

Source: Adapted from 44 (page 162-163), VLA1553-301 CSR, Module 5.3.5.1, STN125777/0.3.
Notes: N, number of participants in the group; n, number of participants with an indicated event.

Reviewer comment: *A numeric imbalance in SAEs exists between the VLA1553 group (1.5%) and the placebo group (0.8%). As discussed below, two SAEs were considered related to vaccination. Additional details about imbalances in the MedDRA SOCs of Cardiac disorders; Injury, Poisoning and Procedural Complications; and Pregnancy, puerperium, and perinatal conditions are provided below:*

- *Five cases of cardiac events were reported among VLA1553 recipients and none among placebo recipients. This reviewer has assessed all these five cases and is inclined to agree with the Applicant that three (Participants* (b) (6) *of the five cases were unlikely related to VLA1553.*

However, NHP studies showed that the vaccine virus RNA persisted in some tissues for at least 90 days postvaccination, and persistence of CHIKV RNA in tissues is believed to contribute to chronic CHIK. Based on the information provided by the Applicant, it is unknown whether vaccination with VLA1553 exacerbated or triggered the pre-existing medical conditions for the events experienced by Participants (b) (6) .

- *Participant* (b) (6) *had a history of hypercholesterolemia and hypertension. He experienced coronary artery disease and died on the same day at Day 119 postvaccination.*
- *Participant* (b) (6) *was infected with SARS-CoV-2 and experienced Grade 3 acute respiratory failure, pulmonary embolism, and cardiomyopathy at Day 162 postvaccination. The event of cardiomyopathy was related to COVID-19.*
- *Participant* (b) (6) *had a history of atrial fibrillation for 15 years before enrollment. He experienced five episodes of atrial fibrillation at postvaccination Days 111, 117, 132, 153 and 164 respectively. The report did not provide the information regarding frequency of atrial fibrillation episode prior to enrollment. It is unknown whether VLA1553 exacerbated the atrial fibrillation.*
- *Participant* (b) (6) *had a history of hyperlipidemia and hypertension and experienced cardiac arrest at postvaccination Day 32. Although the medical condition could be the etiology of the cardiac arrest, it is unknown whether VLA1553 triggered the cardiac arrest due to the close temporal association between vaccination and the onset of the event. This reviewer considers this case possibly related to the vaccine.*
- *Participant* (b) (6) *experienced myalgia, fever, atrial fibrillation and hypovolemic hyponatremia starting from Day 3 postvaccination. This reviewer considers the events likely related to VLA1553. Please refer to the narratives of this case for detail below.*

- *Eight events in SOC Injury, Poisoning and Procedural Complications in VLA1553 (0.3%) and 1 event in the same SOC in the placebo group (0.1%). This reviewer agrees that all these events were unlikely related to VLA1553.*
- *Two cases of spontaneous abortion and one case of fetal death were reported in VLA1553 group, and none in the placebo group. Please refer to Section 9.1.1 for a discussion of these events.*

We acknowledge that numerical imbalances in adverse events between VLA1553 and placebo, particularly with low frequency events, may be a result of the trial design where a 3:1 randomization ratio was used.

Since Guillain-Barre syndrome (GBS) and allergic reactions are potential adverse reactions associated with vaccination, the narratives of the GBS and allergic reaction reported in the study are described below.

- Participant (b) (6) experienced a Grade 3 GBS resulting in hospitalization at Day 70 post-VLA1553 vaccination. The participant was diagnosed with GBS and COVID-19 during hospitalization. The event of GBS was recovered after 5 days of hospitalization and the Applicant considered the event was related to COVID-19 and unlikely related to VLA1553. This reviewer agrees with the Applicant's causality assessment.
- Participant (b) (6) who had a history of allergies to lactose, seasonal pollen, shellfish, Compazine, and morphine, experienced Grade 3 anaphylactic reaction and was hospitalized at Day 33 post-VLA1553 vaccination. The event occurred after ingestion of peanuts and was recovered after treatment with intramuscular injection of epinephrine, oral diphenhydramine, and other medicines. The Applicant considered the anaphylactic

reaction not related to VLA1553. This reviewer agrees with the Applicant's causality assessment.

Two SAEs reported in the VLA1553 group were considered related to the vaccination by the Applicant. The two cases are summarized below:

- Participant (b) (6): A 58-year-old White female with past medical history notable for fibromyalgia, hypertension, and migraines was hospitalized due to Grade 3 myalgia on postvaccination Day 3.

  One day after VLA1553 vaccination, she experienced photophobia, severe body aches (myalgia) and a mild headache. The myalgia was reported by the participant as 9 out of 10 on the pain scale. However, the investigator graded the severity of myalgia as mild. On postvaccination Day 3 the participant presented to the emergency department with headache and body aches and was admitted to the hospital. At presentation, vital signs included a heart rate of 99 beats/minute and respiratory rate of 20 breaths/min. Because of the tachycardia and tachypnea, the differential diagnosis included possible sepsis syndrome/systemic inflammatory response syndrome. Computed tomography (CT) scan of the head without contrast showed no acute abnormality, chest X-ray showed no abnormality, and lab work showed normal procalcitonin, normal creatine phosphokinase, mildly elevated C-reactive protein (CRP), and elevated D-dimer. Blood culture showed no bacterial growth and tests for COVID-19 were negative two times. The participant was treated with intravenous hydromorphone (0.5 mg prn); oral acetylsalicylic acid/caffeine/paracetamol (2 tablet prn); oral cyclobenzaprine (10 mg prn); and oral oxycodone (5 mg prn) for the event.

  Headache was considered resolved 5 days after its onset, and the participant was discharged after 5 days of hospitalization with a diagnosis of systemic inflammatory response syndrome (SIRS) due to suspected viral syndrome vs. adverse vaccine reaction.

  The event of myalgia resolved 30 days after its onset and was considered probably related to VLA1553. However, neither the investigator nor the Applicant considered SIRS an accurate diagnosis due to lack of respective symptoms. The investigator confirmed that the participant had no acute encephalopathy or arterial hypotension/shock or thrombocytopenia or arterial hypoxemia or renal dysfunction or metabolic acidosis to support the diagnosis of SIRS. Furthermore, the participant was alert, in a stable state, and with no mention of any intensive care need, as would be the case for systemic inflammatory response syndrome.

Reviewer comment: *The participant felt her myalgia was 9 out 10. However, the investigator considered the myalgia as mild. This reviewer considered the myalgia experienced by the participant severe (Grade 3) because she was hospitalized due to complaints of body aches (myalgia). This reviewer agrees that the events were vaccine related.*

Regarding the diagnosis of SIRS, this reviewer agrees that the participant's symptoms did not appear to support the diagnosis of SIRS. SIRS is defined by the satisfaction of any two of the four criteria below (Chakraborty, 2023):

- *Body temperature over 38ºC or under 36ºC.*
- *Heart rate greater than 90 beats/minute*

- *Respiratory rate greater than 20 breaths/minute or partial pressure of CO_2 less than 32 mmHg*
- *Leukocyte count greater than 12000 or less than 4000 /microliters or over 10% immature forms or bands.*

The participant's symptoms did not meet at least two of the criteria above.

- Participant (b) (6): A 66-year-old White male was hospitalized due to severe atrial fibrillation on Day 11. Relevant medical history included hypertension since 2008.

  The participant experienced Grade 2 diffuse myalgia on Day 4, and Grade 1 nausea and Grade 3 pyrexia on Day 6. He experienced one to three spikes of fever per day and his highest temperature was 39.6ºC on Day 11.

  On Day 10, he also experienced mild diarrhea without abdominal pain or blood in stool. On Day 11, he was unable to manage the myalgia and fever despite using ibuprofen, naproxen and self-hydration. Therefore, he went to emergency room and was hospitalized the same day due to rapid atrial fibrillation. ECG showed heart rate of 170 beats/minute with no ST-T wave changes or no ectopy. Body temperature was 38.2ºC, respiratory rate 19 breath/min, and blood pressure 128/99 mm Hg. Laboratory results were: serum sodium of 114 mmol/l (reference range: 135-148), CRP 30.9 mg/L (≤ 4.9), brain natriuretic peptide (BNP) 2618 pg/mL (≤ 124), troponin T 16 ng/L (reference range ≤ 11), hematocrit (HCT) 37.8 % (40-53), bilirubin 1.7 mg/dL (0.2-1.3), albumin 3.2 g/dL (3.4-4.9), calcium 7.8 mg/dL (8.8-10.4), lactic acid 1.6 mmol/L, chloride 84 mmol/L (95-108), and red cell distribution width standard deviation (RDW-SD) 36 fl (38-49). He was diagnosed with severe hyponatremia. The investigator stated that "the diarrhea was very mild and therefore was not likely to have contributions to later serious adverse event" (i.e., hypovolemic hyponatremia).

  He was found to have severe atrial fibrillation and severe hyponatremia and was diagnosed with syndrome of inappropriate antidiuretic hormone secretion (SIADH) by a nephrologist. No other cause for SIADH was identified or mentioned by the treating physicians. The event was assessed by the investigator as probably related to vaccination due to prolonged fever/symptoms postvaccination. The event of SIADH was resolved on Day 24.

  The event of atrial fibrillation was resolved on Day 12 and was assessed as unlikely related to vaccination. The Applicant questioned the diagnosis of SIADH but agreed that hypovolemic hyponatremia was present. However, based on the available information provided by the investigator, diagnostic parameters to confirm the diagnosis of SIADH and to provide a reliable differential diagnosis versus hypovolemic hyponatremia were missing. Thus, the DSMB recommended to follow up the participant by analyzing the missing laboratory parameters in order to re-evaluate the diagnosis of SIADH, and results obtained about 9 months postvaccination indicated a reversible cause of hyponatremia. Retrospectively, SIADH could not be completely ruled out, although hypovolemic hyponatremia was much more likely.

  Reviewer comment: *This reviewer agrees with the Applicant that the events of myalgia, nausea and fever were related to VLA1553. However, this reviewer disagrees with the Applicant that the atrial fibrillation was not related to VLA1553 for the following reasons:*
  - *The participant had no alternative etiology of the atrial fibrillation.*

- *The participant had high viremia (649,944 genome copy equivalent (GCE)/ml, Page 35775 of Listing 16.2.13, Appendix 16.2.8, Module 5.3.51, STN125777/0.3) at Day 8.*
- *The participant had increased troponin, as a result of cardiac inflammation likely caused by the vaccine virus.*
- *There was a close temporal association of atrial fibrillation with the vaccination.*

Taken together this reviewer considers the atrial fibrillation is probably related to VLA1553.

SIADH does not appear to be an appropriate diagnosis of the participant's medical condition because SIADH is characterized by impaired water excretion leading to hyponatremia with hypervolemia or euvolemia (Yasir, 2023) while the participant had hypovolemia. Based on the available data, this reviewer considers that the hypovolemic hyponatremia was likely due to the increased BNP, which is known to promote natriuresis and diuresis (Song, 2015). The increased secretion of BNP was likely caused by the cardiac dysfunction and myocardial stretch due to the atrial fibrillation and/or by cardiac inflammation potentially caused by the vaccine viremia (Aspromonte, 2017; Clerico, 2011).

In addition, VLA1553 is a live-attenuated CHIKV vaccine and CHIKV infection has been reported to be associated with cardiac disorders including atrial fibrillation (Cotella, 2021; Traverse 2021).Taken together, it is reasonable to conclude that the event of atrial fibrillation was related to VLA1553 and represents an event of CHIK-like illness.

On April 14, 2023, an IR was sent to the Applicant asking why the Applicant considered the event of SIADH related to VLA1553 but atrial fibrillation was not related to VLA1553. The Applicant responded (STN125777/0.31) that the event of atrial fibrillation was related to an electrolyte imbalance caused by diarrhea and fever (sweating) and also cyclobenzaprine but was unlikely related to VLA1553. This reviewer does not agree with the Applicant's assessment for the following reasons:

1. The investigator clearly stated that "the diarrhea was very mild and therefore was not likely to have contributions to later serious adverse event". In addition, the diarrhea occurred just one day before the participant was hospitalized due to atrial fibrillation and lasted for only one day. Therefore, diarrhea can be excluded as a cause for electrolyte imbalance or hypovolemic hyponatremia.
2. The Applicant believed the electrolyte imbalance was caused by fever (sweating) related to VLA1553. Therefore, the event of atrial fibrillation should also be related to VLA1553.
3. Based on the information provided, it is uncertain if it was the electrolyte imbalance that caused atrial fibrillation or the increased BNP that caused hypovolemic hyponatremia because atrial fibrillation/increased BNP and hypovolemic hyponatremia were identified on the same day. Since no reasonable etiology was available to explain such a severe hypovolemic hyponatremia, the increased BNP, either caused by atrial fibrillation and/or vaccine virus-induced inflammation, would be a reasonable and likely explanation for the severe hypovolemic hyponatremia. This reviewer acknowledges the Applicant's argument that troponin was increased slightly and there was unlikely cardiac inflammation. It has been reported that inflammation and proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α stimulated BNP secretion while troponin was unchanged (Ramakrishnan, 2020; Goetze, 2021). Vaccination with VLA1553 can and will cause inflammation and secretion of proinflammatory cytokines.

4. CHIKV infection has been reported to be associated with cardiac disorders, including atrial fibrillation and a high level of BNP (Cotella, 2021; Traverse, 2021)
5. It is known that cyclobenzaprine may cause sinus tachycardia, which is different from atrial fibrillation. Although relatedness of atrial fibrillation to cyclobenzaprine cannot be excluded, the relatedness to VLA1553 cannot be excluded either.
6. It is also known that hypertension is a risk factor for atrial fibrillation. Hypertension alone cannot explain other findings, such as increased BNP and troponin.

In summary, the symptoms and signs presented by this participant were consistent with those of atypic presentation of CHIK following natural CHIKV infection, as reported in literature (Traverse, 2021; Cotella, 2021; Alvarez, 2017)

Reviewer comment: *This reviewer evaluated all other SAEs in addition to those described above and agrees with the Applicant that other SAEs not described above were unlikely related to VLA1553.*

6.1.12.5 Adverse Events of Special Interest (AESIs)

Participants were monitored for signs and symptoms suggestive of an acute stage CHIKV-associated event. The following cluster of symptoms suggestive of CHIKV infection with or without remissions or exacerbations were assessed in the study as AESIs and necessitated presentation for an unscheduled visit:

1. Fever (≥38.0°C [100.4°F] measured orally)
2. Acute (poly)arthralgia/arthritis most frequently in the extremities (wrists, ankles,
    a. 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] and edema of the face and extremities), polyadenopathies
3. Onset of symptoms 2 to 21 days postvaccination
4. Duration of event ≥3 days

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

Reviewer comment: *The AESI definition was provided in Section 17.9 of the protocol. However, following clarifications requested via IR, it became apparent that the Applicant had retrospectively classified only cases with the same onset or overlapping duration of CHIK-like symptoms as AESIs, limiting the number of participants identified as having AESIs to 10 in the VLA1553 group (0.3%) and 1 in the placebo group (0.1%).*

In addition, the incubation period of CHIK ranges from 1 to 12 days. In our review, we noticed 12 participants reported CHIK-like signs and symptoms with onset at 1 day postvaccination. Furthermore, because there is variability in the duration of CHIK-like symptoms in diagnosis of CHIK caused by natural CHIKV infection, limiting the duration of events to ≥ 3 days would exclude some cases of CHIK-like illness. Therefore, CBER requested that the Applicant re-analyze the data evaluating the cluster of CHIK-related symptoms within the first 30 days (to increase sensitivity) postvaccination, irrespective of concurrence or duration. The results presented in the review reflect the analyses according to the Applicant's responses to CBER's IRs to better characterize AESIs as CHIK-like illness, based on the revised definition to capture additional cases as detailed below:

- *Fever (≥38°C / 100.4°F)*
  AND
- *Any one of symptoms described in Section 17.9 of protocols Study 301 and Study 302*
  AND
- *Occurring within 30 days postvaccination, regardless of the order of their onset and duration*

Frequency of CHIK-like Illness and Severe CHIK-like Illness
In total, 367 participants met the revised criteria as defined above: 361 participants (11.7%) in VLA1553 group and 6 participants (0.6%) in the placebo group. Most symptoms were mild or moderate: Severe CHIK-like illness was reported by 48 of 3,082 (1.6%) participants in the VLA1553 group and none of the participants in the placebo group experienced a severe CHIK-like illness. Most events occurred around 3 days postvaccination with a range of onset of 1 to 11 days. The mean duration for all CHIK-like symptoms was 10.1 days with a range of 1 to at least 6 months, and for severe CHIK-like symptoms was 14.1 days with a range of 1 to 171 days.

Frequency of individual CHIK-like symptoms by SOC, PT, and maximum severity are provided in Table 18.

Table 18. Individual CHIK-Like Symptoms by System Organ Class and Preferred Term (≥0.1% Except for Cardiac Disorders), Safety Population, Study 301

CHIK-Like Symptoms	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
General Disorders and Administration Site Conditions	**361 (11.7)**	**6 (0.6)**
Pyrexia	361 (11.7)	6 (0.6)
Severe pyrexia	39 (1.3)	0 (0.0)
Fatigue	264 (8.6)	5 (0.5)
Severe fatigue	2 (0.1)	0 (0.0)
Chills	29 (0.9)	0 (0.0)
Pain	4 (0.1)	0 (0.0)
Oedema peripheral	2 (0.1)	0 (0.0)
Chest pain	0 (0.0)	1 (0.1)
Nervous system disorders	**282 (9.1)**	**5 (0.5)**
Headache	280 (9.1)	5 (0.5)
Dizziness	6 (0.2)	0 (0.0)
Paresthesia	3 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	**249 (8.1)**	**2 (0.2)**
Myalgia	215 (7.0)	1 (0.1)
Severe myalgia	3 (0.1)	0 (0.0)
Arthralgia	159 (5.2)	2 (0.2)
Severe arthralgia	4 (0.1)	0 (0.0)
Back pain	13 (04)	0 (0.0)
Skin and subcutaneous tissue disorders	**25 (0.8)**	**0 (0.0)**
Rash	22 (0.7)	0 (0.0)
Hyperhidrosis	2 (0.1)	0 (0.0)

CHIK-Like Symptoms	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
Blood and Lymphatic System Disorders*	**9 (0.3)**	**0 (0.0)**
Lymphadenopathy	9(0.3)	0 (0.0)
Cardiac disorders	**1 (0.0)**	**0 (0.0)**
Atrial fibrillation	1 (0.0)	0 (0.0)
Severe atrial fibrillation	1(0.0)	0 (0.0)

Source: Adapted from Table 1 (page 3-5), Module 1.11.3, STN125777/0.49; Module 1.2_Cover letter (page 13), STN125777.
Abbreviations: N, number of participants in the group; n, number of participants with an indicated event.
*Hematology parameters were not included in these analyses because they were only assessed in immunogenicity subset.

The frequency of CHIK-like symptoms among participants with CHIK-like illness is presented in Table 19.

Table 19. Frequency of Chikungunya-Like Symptoms Among Participants with Chikungunya-Like Illness (Study 301)

Chikungunya-Like Symptom Chikungunya-Like Symptom (severe)	IXCHIQ (N=361) % (n)
Pyrexia (any)	100 (361)
Pyrexia (severe)	10.8 (39)
Headache (any)	77.6 (280)
Headache (severe)	0.3 (1)
Fatigue (any)	73.1 (264)
Fatigue (severe)	0.6 (2)
Myalgia (any)	59.6 (215)
Myalgia (severe)	0.8 (3)
Arthralgia (any)	44.0 (159)
Arthralgia (severe)	1.4 (5)
Chills (any)a	8.0 (29)
Rash (any)a	6.1 (22)
Back pain (any)	3.6 (13)
Back pain (severe)	0.3 (1)
Lymphadenopathy (any)[a]	2.5 (9)
Dizziness (any) [a]	1.7 (6)
Pain (any) [a]	1.1 (4)
Paresthesia (any) [a]	0.8 (3)
Hyperhidrosis (any) [a]	0.6 (2)
Edema peripheral (any) [a]	0.6 (2)
Asthenia (any)[a]	0.3 (1)
Ataxia (any)[a]	0.3 (1)
Atrial fibrillation (any)	0.3 (1)
Atrial fibrillation (severe)	0.3 (1)
Feeling abnormal (any)[a]	0.3 (1)
Hypoesthesia (any)[a]	0.3 (1)
Influenza like illness (any)[a]	0.3 (1)
Neuropathy peripheral (any)[a]	0.3 (1)
Rash erythematous (any)[a]	0.3 (1)
Syncope (any)[a]	0.3 (1)

Source: Adapted from Table 1 (page 9-10), Module 1.11.4_Response to IR#83 & 87, STN125777/0.90
Notes: a, no severe chikungunya-like symptoms reported.
N, Number of participants with chikungunya-like adverse reactions; n, number of participants with chikungunya-like symptom.

Serious CHIK-like Illness

Two participants were hospitalized due to serious CHIK-like illness, one participant with severe myalgia and the other with serious cardiac disorder atrial fibrillation and hypovolemic hyponatremia (Refer to Section 6.1.12.4 for case summaries).

Prolonged CHIK-like Illness

In response to a CBER IR, the Applicant provided an analysis of all prolonged CHIK-like illness (duration ≥30 days). In total, 14 VLA1553 recipients reported prolonged symptoms (median duration of 94 days, range 30 days to at least 6 months). Prolonged fatigue, headache and myalgia were each reported 3 VLA1553 recipients. Prolonged arthralgia was reported by 5 VLA1553 recipients, including a 46-year-old male who reported severe arthralgia and back pain that lasted for at least 51 days postvaccination, and a 50-year-old female who reported

polyarthralgia and nodular swelling of joints in fingers and foot that lasted for at least 6 months postvaccination.

Day 8 viremia results are available for three participants with prolonged symptoms, all of whom had no viremia or viremia below the limit of detection. The prolonged CHIK-like symptoms were graded as mild to moderate, with the exception of a prolonged case of severe arthralgia reported as follows:

- Participant (b) (6): A 46-year-old White male, experienced Grade 1 back pain and Grade 2 pyrexia (38.3 to 38.7°C) 1 day postvaccination, and Grade 1 arthralgia 3 days postvaccination. The fever resolved by postvaccination Day 5; however, the back pain remained persistent. Physical examination on postvaccination Day 7 showed normal findings, and physical examination about a month later showed no clinically significant findings except for pain in the center of the back. According to the investigator, the participant complained of very severe pain in the center of lower back. He had a negative straight leg raise test, no evidence of sciatica, and no history of back pain. AESI laboratory tests were taken but the results were not received by the site. The participant was advised to take ibuprofen and Tylenol for the back pain and fever, but it is not confirmed that he did in fact treat his symptoms. The participant declined a rheumatology referral. The back pain and arthralgia were resolving at the time of the last study visit, which was on postvaccination Day 51, as the participant discontinued the study thereafter, with a primary reason given as “withdrawal by participant”. The events were considered probably related to VLA1553 by the Applicant.

Hand Stiffness

A hand stiffness test was conducted at each visit, irrespective of participants having any clinical signs or symptoms. An abnormal hand stiffness measurement was not included in the AE domain of the datasets. However, if a new abnormal or worsened abnormal pre-existing condition was detected during a symptom-driven physical examination, the condition was recorded as an adverse event. No major difference in the changes from baseline to Day 8, Day 29, Day 85, or Day 180 observed for hand stiffness between VLA1553 and placebo. There were no major changes in hand stiffness either following vaccination with VLA1553.

Evidence for Causal Relationship

There is a high likelihood that these events of CHIK-like symptoms were related to vaccination, given that the onset of CHIK-like symptoms (ranged 1 to 11 days postvaccination), symptom spectrum and vaccine viremia dynamics were consistent with typical as well as atypic presentation of CHIK caused by natural CHIKV infection. See Section 8.4.8 for details.

Summary of CHIK-like Illness

This causal relationship, in association with severe and serious events, justifies a warning in Section 5 of product labeling for these events. Furthermore, as communicated previously, per the 2011 FDA Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format | FDA , the WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.

In summary, the weight of the available evidence, including the frequency, severity, seriousness, and duration of events of CHIK-like illness, causally linked to VLA1553 by direct evidence of viremia in some cases, warrants a warning statement in the package insert per the 2011 FDA Guidance for Industry mentioned above. The benefit-risk assessment supports restricting use of VLA1553 in individuals who are not at increased risk of exposure to CHIKV.

Reviewer comment: *CHIK-like illness is described as CHIK-like adverse reactions in the package insert (PI).*

6.1.12.6 Clinical Test Results

Safety laboratory samples were only taken from the IMM subset (n=501.)

Hematology Parameters

Decreases in total leukocytes, basophils, eosinophils, lymphocytes, neutrophils, and platelets were observed in a subset of the participants in the VLA1553 group on Day 8 and returned to within normal range on Day 29. A slight increase in erythrocyte sedimentation rate was observed in the VLA1553 group on Day 8 and returned to within normal range on Day 85.

No participant in the placebo group experienced Grade 3 changes in any hematology parameters. In the VLA1553 group, Grade 3 leukocytes decreased, lymphocytes decreased, and platelets decreased were all reported in one participant [1/372 (0.3%)], Grade 3 hemoglobin decreased was reported in three participants [3/372 (0.8%)], and Grade 3 neutrophils decreased was reported in 11 participants [11/372 (3.0%)]. Grade 4 neutrophils decreased was reported in one participant who was Grade 1 at baseline and had a chronic, mild leukopenia/neutropenia.

The Applicant stated that the changes in hematology parameters following vaccination with VLA1553 were considered expected and consistent with a normal physiologic response to a live-attenuated viral vaccine and were unlikely clinically significant.

Reviewer comment: *The Applicant stated that the changes in hematology parameters were unlikely clinically significant; however, it is the opinion of this reviewer that the clinical significance of the changes is unknown based on the available information. The abnormal hematological parameters were not associated with any AEs.*

Chemistry Parameters

In the placebo group (n = 125), the most common shifts in chemistry parameters with any worsening from baseline were hypokalemia (12.8% of participants), hypernatremia (12.0% of participants), alkaline phosphatase increase (10.4% of participants), and hyperkalemia (8.8% of participants). Most of the shifts were Grade 1 or 2. Grade 3 hyponatremia was reported in 1.7% of participants, and Grade 3 hypokalemia, Grade 3 hyperkalemia, and Grade 3 hypernatremia were all reported in 0.8% of participants.

In the VLA1553 group (n = 372), the most common shifts in chemistry parameters with any worsening from baseline were aspartate transaminase (AST) increased (10.8% of participants), alanine aminotransferase (ALT) increase (10.5% of participants), hyperkalemia (9.7% of participants), alkaline phosphatase (ALP) increase (8.6% of participants), hypernatremia (7.8% of participants) and hypokalemia (7.0%) of participants. Most of the shifts were Grade 1 or 2. Grade 3 hypokalemia was reported in 0.8% of participants. Grade 3 hyperkalemia, Grade 3 hyponatremia, and Grade 3 hypernatremia were reported in 0.6% of participants each, and Grade 3 ALT increase, and Grade 3 hypocalcemia were reported in 0.3% of participants each. Grade 4 hyperkalemia was reported in 1.7% of participants. The investigator judged 5 of the 6

events of Grade 4 hyperkalemia not clinically significant and/or due to hemolysis. The sixth participant was referred for further testing and the potassium subsequently dropped.

The increases in ALT and AST in VLA1553 group were on Day 8 and all returned to within normal range on Day 29.

***Reviewer comment**: These transient changes in ALT and AST were considered an expected response to a live-attenuated viral vaccine and were unlikely clinically significant.*

In addition, Grade 4 hypernatremia was reported in 0.8% of participants in the placebo group and in 0.6% of participants in the VLA1553 group. According to the Medical Monitor, all 3 events of Grade 4 hypernatremia were seen at Visit 4 and came from the same site (site 11) at 24-hour interval. The Applicant stated that they might be outliers resulting from collection/processing/lab errors.

***Reviewer comment:** The reasons for hypernatremia, and the clinical significance of the findings even in the placebo group, were unknown, although laboratory errors could not be excluded.*

Viremia
To evaluate a link between vaccine-induced viremia on Day 8 and AE severity, viremia was determined retrospectively upon request by the DSMB for all participants with severe solicited or related severe unsolicited AEs (n= 61) and age- and sex-matched controls (n=129). Vaccine-induced CHIKV viremia was only seen in a minority (12.6%) of tested participants at Day 8 including 22 participants classified as low viremic (<1 X 10^5 GCE/mL) and 2 as high viremic (≥1X 10^5 GCE/mL) and resolved in all participants by Day 29. According to the Applicant, viremic load in general was not related to AE severity, but data interpretation is limited due to the small sample size.

***Reviewer comment:** This reviewer does not agree with the Applicant's conclusion that viral load in general was not related to AE severity since the participants in the analysis were not randomly selected and no viremia was assessed at Day 3, the time point for peak viremia as shown in Study 101. As shown in Study 101 (see the review in Appendix A), viremia was correlated to the frequency and severity of reactogenicity.*

Among the 24 viremic participants at Day 8, 15 participants reported any mild or moderate solicited or related unsolicited AE, and 9 participants reported any severe AE. High viral loads (≥1x10^5 GCE/mL) were seen in 2 of 9 (22.2%) participants with severe AEs (solicited or related unsolicited). Descriptions of the two participants with severe AEs and high levels of vaccine viremia:

1) Participant (b) (6): having hypovolemic hyponatremia and atrial fibrillation(described in Section 6.1.12.4)
2) Participant (b) (6): The participant, a 53-year-old Black male who experienced mild myalgia (Day 2, lasted for 4 days), severe arthralgia and back pain (Day 5, lasted for 5 days) and moderate fever (Day 9, lasted for 2 days) after VLA1553 vaccination. He had a viremia titer >1x10^5 GCE/mL on Day 8. The Applicant considered the events related to VLA1553.

Of note, the CSR of VLA1553-301 (page 172) stated that "All reported AESI cases were non-viremic". However, this reviewer considered both of these participants (Participants (b) (6) to have experienced AESIs. An IR asking for clarification was sent to the Applicant on

April 14, 2023. The Applicant responded to STN125777/0.31 on April 21, 2023, stating that Participant (b) (6) with severe arthralgia and back pain was not classified as an AESI. The Applicant explained that an AESI was defined as the presence of fever and the presence of at least one additional symptom at the same time. In this case, myalgia occurred from 1 to 5 days, arthralgia and back pain from 4 to 9 days, and fever from 9 to 10 days postvaccination. Therefore, the Applicant determined that the case did not meet the definition of AESI.

Reviewer comment: *This reviewer does not agree with the Applicant's explanation that Participant* (b) (6) *severe arthralgia back pain was not classified as an AESI. The Applicant's argument, "per the definition of AESI described in Section 17.9, an AESI was defined as a cluster of symptoms, i.e., the presence of fever (≥ 38.0 °C / 100.4 °F) and the presence of at least one additional symptom at the same time", is not valid for the following reasons: 1) Section 17.9 of the protocol did not explicitly state that the cluster of symptoms had to occur at the same time; 2) All the symptoms experienced by the participant occurred within 2-21 days postvaccination and with overlapping duration; and 3) Although the timing of fever onset was a little odd, not all CHIK patients have fever. This reviewer considers it is appropriate to include the case as an AESI even though the onset of fever occurred after other events. Importantly, the participant still had high level vaccine viremia at Day 8, confirming that the CHIK-like symptoms, myalgia, arthralgia and back pain postvaccination was caused by the vaccine virus, and thus the case should be considered a CHIK-like illness.*

Refer to Section 6.1.12.5 for additional details on AESIs, including IRs sent to the Applicant.

6.1.12.7 Dropouts and/or Discontinuations

Overall, 0.1% (n = 5) participants experienced an AE leading to withdrawal during the study, including three participants in the VLA1553 group and two participants in the placebo group). The AEs were COVID-19, influenza, and coronary heart disease in the VLA1553 group, and cerebellar hemorrhage and mental status change in the placebo group.

Among the 3 participants in the VLA1553 group who discontinued from the study, two participants (Participants (b) (6) were discontinued due to death and one participant (Participant (b) (6) was discontinued due to mild influenza that occurred at 5 days postvaccination and resolved in about 14 days. The narratives of the two participants in the VLA1553 group who discontinued from the study due to death are described in Section 6.1.12.3 of this review.

6.1.13 Study Summary and Conclusions

6.1.13.1 Immunogenicity

- Seroresponse rate, defined as a percentage of participants with a GMT titer ≥150, was 98.9% (95% CI: 96.7, 99.8) on Day 28 post-VLA1553 vaccination. The results met the pre-specified success criterion of LB of 95% CI >70%. Seroresponse rates remained at 98.0% and 96.3% on 84 days and 180 days postvaccination, respectively.
- Anti-CHIKV neutralizing antibody titer peaked at 28 days postvaccination with a GMT of 3,362, and subsequently decreased to 1,084 and 752 at Days 84 and 180 postvaccination, respectively.
- No statistically significant difference was observed in terms of GMTs and seroresponse rates among subgroups by age, sex, race, and ethnicity.

6.1.13.2 Safety

- Overall, 62.5% (1,926/3,082) of participants vaccinated with VLA1553 experienced any AE, including solicited adverse reactions, compared to 44.8% (463/1,033) after administration of placebo.
- Solicited adverse reactions were reported by 52.8% (1,628/3,082) of participants in the VLA1553 group compared to 32.0% (331/1,033) of participants in the placebo group.
- Solicited injection site reactions:
    - Solicited IS reactions were reported by 15.0% (463/3,082) participants vaccinated with VLA1553 and 11.1% (115/1,033) participants in placebo group.
    - The most common solicited IS reaction was tenderness, reported by 10.6% (328/3,082) of participants in the VLA1553 group vs. 8.1% (84/1,033) of participants in the placebo group.
    - Most solicited IS reactions were mild; one severe event of pain was reported in the VLA1553 group, and no severe events were reported in the placebo group.
- Solicited Systemic AEs:
    - Solicited systemic AEs were reported by 50.2% (1547/3,082) of participants vaccinated with VLA1553 vs. 26.9% (278/1,033) of participants in the placebo group.
    - Most solicited systemic AEs were mild or moderate; 2.1% (64/3,082) of participants in the VLA1553 group and 0.1% (1/1,033) of participants in the placebo group reported severe reactions.
    - The most common solicited systemic reactions were headache (27.9% in VLA1553 vs. 12.4% in placebo), fatigue (25.9% in VLA1553 vs 11.2% in placebo), myalgia (22.1% in VLA1553 vs. 6.8% in placebo), arthralgia (15.2% in VLA1553 vs. 4.5% in placebo) and fever (11.8% in VLA1553 vs. 0.6% in placebo).
- Unsolicited AEs in the 28 days following vaccination were reported in 22.3% (687/3,082) of participants in VLA1553 group and 13.4% (138/1,033) of participants in the placebo group.
- SAEs were reported by 1.5% (46/3,082) of participants in the VLA1553 group and by 0.8% (8/1,033) of participants in the placebo group.
    - Two related SAEs following VLA1553 were reported during the entire study period, including one event of myalgia and the events of atrial fibrillation with hypovolemic hyponatremia; both participants completely recovered (see also CHIK-like illness below).
- CHIK-like illness was reported by 11.7% (361/3,082) of participants in the VLA1553 group and 0.6% (6/1,033) of participants in the placebo group.
    - Most CHIK-like illnesses were mild or moderate. Forty-seven (1.5%) participants in the VLA1553 group and none in the placebo group experienced a severe CHIK-like illness.
    - The majority of events resolved with a mean and median duration of 6.2 days and 4.0 days, respectively, for overall CHIK-like illness, and mean and median duration of 8.6 days and 6.0 days, respectively, for severe CHIK-like illness.
    - Two VLA1553 recipients were hospitalized with serious CHIK-like illness, including severe myalgia with tachycardia and tachypnea, and atrial fibrillation and hypovolemic hyponatremia.
    - Fourteen VLA1553 recipients had prolonged (duration at least 30 days) chikungunya-like illness (median duration 94 days, range 30 days to at least 6 months). Prolonged fatigue, headache and myalgia were each reported by three participants. Prolonged arthralgia was reported by five participants, including a

46-year-old male who reported severe arthralgia and back pain that lasted for at least 51 days postvaccination and a 50-year-old female who reported polyarthralgia and nodular swelling of joints in fingers and foot that lasted for at least 6 months postvaccination.

6.1.13.3 Conclusion

Immunogenicity Conclusion
The results from the pivotal Study 301 demonstrated that 98.9% (95%CI: 96.7, 99.8) participants achieved an anti-CHIKV neutralizing antibody titer ≥150, a surrogate endpoint that is considered reasonably likely to predict a clinical benefit, at 28 days after a single dose vaccination with VLA1553. The results met the pre-specified success criterion for the primary endpoint, LB of 95% CI of seroresponse rate >70%.

Safety Conclusion
In general, the safety profile of VLA1553 was favorable. However, the AESIs of CHIK-like illness, including cardiac events and prolonged arthralgia, associated with VLA1553 administration, were severe, serious, and/or prolonged, and thus necessitate a warning and precaution and restricted indication in the product labeling, and warrant further postmarketing assessment (See Section 11.6).

6.2 Trial #2 (Study VLA1553-302)

NCT04786444
A randomized, double-blinded, pivotal 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 through 45 years.

6.2.1 Objectives

Primary objective
To demonstrate lot-to-lot manufacturing consistency of VLA1553 28 days following vaccination in a healthy population of adults 18-45 years of age after a single immunization.

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

6.2.2 Design Overview

This was a prospective, randomized, double-blind, multicenter Phase 3 clinical study designed to demonstrate manufacturing consistency of three manufacturing lots of VLA1553 at the final dose (target 1×10^4 $TCID_{50}$ per 0.5 mL), block-randomized in a ratio of 1:1:1.

6.2.3 Population

Eligible individuals were adults 18-45 years of age on the day of screening and generally healthy. Individuals of childbearing potential were eligible to participate if they had been using contraception during the month before screening, had a negative serum or urine pregnancy test, and agreed to use adequate contraception for the first 3 months postvaccination.

Individuals were not eligible for enrollment if they had had CHIKV infection in the past, including suspected CHIKV infection; were taking medication or other treatment for unresolved symptoms attributed to a previous CHIKV infection; or had participated in a clinical study involving an

investigational CHIKV vaccine. Individuals were also excluded for any of the following: acute infection at screening, positive test for HIV, HBsAg or HCV history of immune-mediated or clinically relevant arthritis/arthralgia, history of malignancy in the past 5 years, or congenital or acquired immunodeficiency, including infection with HIV.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study product was administered as a single IM vaccination in the deltoid region of the group of the participant with a pre-filled syringe containing VLA1553 1 x 10^4 $TCID_{50}$ per 0.5 mL. Batch numbers for each lot are as follows: Lot 1: 0010720, Lot 2: 0020720, and Lot 3: 0030720 Batch numbers refer to a single batch of each lot used throughout the study.

6.2.5 Directions for Use

VLA1553 was provided as a vaccine kit containing one single-use (b) (4) vial with the lyophilized vaccine powder and one prefilled syringe of 0.5 mL sterile water for reconstitution to an injectable volume of 0.5 mL. The full volume contained in the prefilled syringe was administered intramuscularly into the deltoid muscle as a single immunization on Day 1.

6.2.6 Sites and Centers

The study was conducted at 12 sites in the U.S.

6.2.7 Surveillance/Monitoring

Following vaccination, all participants were observed for at least 30 minutes at the study site. In addition, prior to discharge, vital signs including oral body temperature, pulse rate and resting blood pressure were measured, and any IS or systemic reactions were recorded. All participants were provided an eDiary and eMemory Aid and instructed on the use of the respective electronic Participant Questionnaire for documentation of solicited and unsolicited AEs until the end of study.

During each study visit the participants were asked about AEs and reminded about use of eDiary and eMemory Aid. The participants also had symptom-driven physical examinations, a hand stiffness test, and blood and urine laboratory exams to check for parameter changes.

All unsolicited AEs were documented in the respective AE section of the eCRF during respective study visits. The investigator followed-up on each AE until resolution or until the medical condition of the participant was stable. All relevant follow-up information was reported to the Applicant until the end of the study for each participant.

The following information was documented for each AE: severity, causality, outcome, seriousness, medically attended, action taken to treat AE, start and stop dates.

6.2.8 Endpoints and Criteria for Study Success

6.2.8.1 Primary Endpoint

Geometric mean titer (GMT) of CHIKV-specific neutralizing antibodies as determined by µPRNT assay on Day 29 postvaccination in participants who tested negative for CHIKV antibodies (as determined by (b) (4) at baseline.

Please refer to Section 6.2.9.2 for study success criteria.

6.2.8.2 Secondary Endpoints

Immunogenicity and safety measures considered as secondary endpoints are as listed.

Immunogenicity

1. Immune response as measured by CHIKV-specific neutralizing antibody titers on postvaccination Day 8, Day 29, Day 85, and Day 180 as determined by μPRNT assay
2. Percentage of participants with seroresponse defined as $\mu PRNT_{50}$ ≥150 (for baseline negative participants) at postvaccination Days 8, 29, 85, and 180.

Safety

1. Frequency and severity of solicited IS and systemic AEs within 10 days postvaccination
2. Frequency and severity of unsolicited AEs within 28 days postvaccination
3. Frequency and severity of any AESI within 30 days postvaccination
4. Frequency and severity of any AE during the entire study period
5. Frequency of any SAE during the entire study period.

6.2.9 Statistical Considerations & Statistical Analysis Plan

6.2.9.1 Study Hypotheses and Analyses of Primary Endpoint

A hypothesis test was defined for the primary immunogenicity analysis, using a two-sided significance level of 5%. Multiplicity adjustments were made for primary immunogenicity endpoints if statistical significance (p-value ≤ 0.05 for any of the comparisons between the 3 Lots) was reached. Please refer to the statistical review for details.

6.2.9.2 Sample Size Calculation

The sample size was selected to allow for a demonstration of Lot-to-Lot consistency based on the primary endpoint, CHIKV-specific neutralizing antibody titers as determined by μPRNT on postvaccination Day 29. The primary analysis was powered to demonstrate equivalence between the three lots based on anti-CHIKV GMTs. The sample size of 402 randomized participants (i.e., 134 per batch) ensured that the three pair-wise comparisons had an overall power of approximately 90% based on a two-sided significance level of 5%, an assumed SD of 0.32 (on a log10 scale), and acceptance margins of 0.67 and 1.5 for the GMT ratios, while correcting for an assumed drop-out rate of 10% and 5% of participants with major protocol deviations and 2% of participants expected to be baseline positive for CHIKV (as determined by (b) (4)

6.2.9.3 Methods of Handling Missing Data

All statistical analyses were generally based on observed values, missing values were not imputed, except for severity and causality of AE.

Any AE with missing severity was classified as severe. AEs with missing causality assessment were considered related unless further specified.

6.2.9.4 Interim Analysis

No interim analysis was conducted.

6.2.9.5 Safety Analyses

Safety tabulations were provided separately for solicited adverse reactions and unsolicited AEs, and for both types of events combined. Number and percentage of participants, and number of

events in each category were provided for all AEs, SOC and PT coded according to the MedDRA dictionary.

The numbers and percentages of participants were counted by participant, not by event, and participants were only counted once within each SOC or PT.

Where AEs were presented by severity (Mild, Moderate, Severe), SOC and PT, participants with multiple events within a particular SOC or PT were counted once under the category of their most severe event within that SOC or PT.

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

All AE tabulations were presented for the Safety analysis set.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

In total, 409 participants were randomized, of whom 136, 137, and 136 were randomized to the VLA1553 Lot 1, Lot 2, and Lot 3 groups, respectively. One participant in the VLA1553 Lot 3 group did not receive vaccination. Thus, the safety analysis set consists of 408 participants. All vaccinated participants were included in the Safety analysis set. A summary of the analysis sets is provided in Table 20.

Table 20. Analysis Sets, All Screened Participants, Study 302

Analysis Set	VLA1553 Lot 1	VLA1553 Lot 2	VLA1553 Lot 3	Total
Screened participants	-	-	-	668
Randomized participants (n)[a]	136	137	136	409
Vaccinated participants [n (%)]	136 (100)	137 (100)	135 (99.3)	408 (99.8)
Randomized but not vaccinated participants [n (%)]	0	0	1 (0.7)	1 (0.2)
Safety analysis set (SAS) [n (%)]	136 (100)	137 (100)	135 (99.3)	408 (99.8)
Full analysis set (FAS) [n (%)]	132 (97.1)	128 (93.4)	131 (96.3)	391 (95.6)
Per-Protocol analysis set (PP) [n (%)]	122 (89.7)	118 (86.1)	122 (89.7)	362 (88.5)
Sensitivity Per-Protocol analysis set 1 (sPP1) [n (%)][b]	120 (88.2)	119 (86.9)	122 (89.7)	361 (88.3)
Sensitivity Per-Protocol analysis set 2 (sPP2) [n (%)][c]	122 (89.7)	121 (88.3)	123 (90.4)	366 (89.5)

Source: adapted from Table 16 VLA-1553-302 CSR, p.90
Notes: a. Percentages are not included because participants were grouped according to treatment actually received and not randomized treatment
b. sPP1 analysis set included baseline μPRNT negative participants using $\mu PRNT_{50}$ <20
c. sPP2 analysis set included baseline μPRNT negative participants using $\mu PRNT_{50}$ ≤40
Percentages were calculated out of all randomized participants
Abbreviations: μPRNT, micro-plaque reduction neutralization test; n, number of participants

Table 21. Analysis Populations

Analysis Population	Definition
Safety *(Safety Analysis Set)*	• All participants that entered the study and received one vaccination. • This analysis set was the primary analysis set for all safety endpoints. • Participants were analyzed as treated.

Analysis Population	Definition
Full Analysis *(Full Analysis Set (FAS))*	• All participants who were randomized, received the vaccination, and had evaluable immunogenicity data at the time point for the primary endpoint. • Participants were analyzed as randomized.
Per-Protocol Population *(Per-Protocol Analysis Set (PPAS))*	• All participants who were baseline negative for CHIKV antibodies as determined by (b) (4) assay, had received the vaccination and had evaluable immunogenicity data at baseline and the time point for the primary endpoint without a major protocol deviation. • This analysis set was the primary analysis set for immunogenicity analyses. • Participants were analyzed in the PPAS according to the study group they had been randomized to.

6.2.10.1.1 Demographics

Baseline demographics are presented in Table 22. There was no significant difference in terms of age, sex, race, and ethnicity among the three groups.

Table 22. Demographic Characteristics, Safety Analysis Set, Study 302

Characteristic	VLA1553 Lot 1 (N=136)	VLA1553 Lot 2 (N=137)	VLA1553 Lot 3 (N=135)	Total (N=408)
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 (%)	-	-	-	-
American Indian or Alaska Native	4 (2.9)	1 (0.7)	0	5 (1.2)
Asian	6 (4.4)	5 (3.6)	7 (5.2)	18 (4.4)
Black or African American	21 (15.4)	22 (16.1)	19 (14.1)	62 (15.2)
Native Hawaiian or other Pacific Islander	0	1 (0.7)	0	1 (0.2)
White	103 (75.7)	106 (77.4)	106 (78.5)	315 (77.2)
Other	2 (1.5)	2 (1.5)	3 (2.2)	7 (1.7)
Ethnicity, n (%)	-	-	-	-
Hispanic or Latino	19 (14.0)	17 (12.4)	19 (14.1)	55 (13.5)
Not Hispanic or Latino	117 (86.0)	119 (86.0)	115 (85.2)	351 (86.0)
Unknown	0	1 (0.7)	1 (0.7)	2 (0.5)
Age (years)	-	-	-	-
Mean (standard deviation)	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
Q1, Q3	27.0, 39.0	27.0, 40.0	27.0, 40.0	27.0, 39.0
Minimum, maximum	18, 45	18, 45	18, 45	18, 45
Weight (kilograms)	-	-	-	-
Mean (standard deviation)	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
Q1, Q3	68.3, 95.1	71.1, 98.5	69.7, 99.3	69.9, 97.9
Minimum, maximum	49.2, 204.5	45.8, 171.4	45.5, 157.9	45.5, 204.5
Height (centimeters)	-	-	-	-
Mean (standard deviation)	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
Q1, Q3	164.6, 177.7	164.0, 177.8	165.0, 178.2	164.8, 177.8
Minimum, maximum	142.2, 189.5	149.9, 197.0	148.6, 194.0	142.2, 197.0

Characteristic	VLA1553 Lot 1 (N=136)	VLA1553 Lot 2 (N=137)	VLA1553 Lot 3 (N=135)	Total (N=408)
BMI (kg/m$^{2)}$	-	-	-	-
Mean (standard deviation)	29.4 (7.7)	29.6 (7.7)	29.1 (6.9)	29.4 (7.5)
Median	28.1	28.5	28.2	28.2
Q1, Q3	24.2, 33.5	24.8, 33.7	24.1, 32.9	24.2, 33.4
Minimum, maximum	17.5, 72.8	13.7, 61.8	14.0, 49.7	13.7, 72.8

Source: Adapted from Table 13 VLA-1553-302 CSR, p.86
Note: Unknown ethnicity category was as recorded on the CRF
Abbreviations: n, number of participants; BMI, body mass index; CRF, case report form; Std, standard deviation

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In the safety analysis set, of the 408 participants, 351 (86.0%) had medical history events. The most common medical history SOC was *Immune system disorders* (41.4%), followed by *Surgical and medical procedures* (37.5%), *Psychiatric disorders* (37.3%), *Gastrointestinal disorders* (18.4%), *Metabolism and nutrition disorders* (17.4%), *Nervous system disorders* (5.4%), *Infections and infestations* (13.7%), *Skin and subcutaneous tissue disorders* (13.5%), *Respiratory, thoracic, and mediastinal disorders* (13.0%), *Eye disorders* (12.5%), and *Musculoskeletal and connective tissue disorders* (12.0%). Of the 49 participants with AEs under SOC *Musculoskeletal and connective tissue disorders*, 2.2% reported arthralgia in their medical history. No significant difference in baseline medical history was observed among the three lot groups.

In the safety analysis set, 323 (79.2%) participants received concomitant medications. The most common (≥20%) concomitant medications for participants were psychoanaleptics (24.5%), anti-inflammatory and anti-rheumatic products (22.3%), and analgesics (21.6%). No significant difference was observed among the three groups.

6.2.10.1.3 Subject Disposition

Participant disposition is presented in Table 23. One participant randomized to VLA1553 Lot 3 did not receive vaccination.

Table 23. Disposition, Safety Analysis Set, Study 302

Disposition, n (%)	VLA1553 Lot 1 N=136	VLA1553 Lot 2 N=137	VLA1553 Lot 3 N=135	Total N=408
Screened	-	-	-	668
Screen failure	-	-	-	259
Randomized[a]	136	137	136	409
Completed study	121 (89.0)	120 (87.6)	123 (91.1)	364 (89.2)
Discontinued study	15 (11.0)	17 (12.4)	12 (8.9)	44 (10.8)
Withdrawal by participant	4 (2.9)	7 (5.1)	2 (1.5)	13 (3.2)
Lost to follow-up	11 (8.1)	9 (6.6)	10 (7.4)	30 (7.4)
Other	0	1 (0.7)	0	1 (0.2)

Source: Table 10 VLA1553-302 CSR, p. 82
Notes: a. Percentages are not included because participants were grouped according to treatment actually received and not randomized treatment
Reasons for discontinuation were based on the End of Study/Early Termination CRF page
Discontinued study includes all participants who discontinued early, prior to Visit 5 (Day 180/Month 6)
Percentages were calculated out of participants treated for each Lot
Abbreviations: N, number of participants who received vaccination; n, number of participants; CRF, case report form

Reviewer comment: *The screen failure rate (38.8%) was higher than generally expected. The Applicant stated that the most common reason for screen failures was failure to meet eligibility criteria. Withdrawal by participants was not due to AEs.*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The analyses of CHIKV-specific neutralizing antibody GMTs on Day 29 for the PP analysis set are presented in Table 24. The 95% CIs of the GMT ratios between any two lots were between 0.67 and 1.5, which met the pre-specified lot-to-lot consistency success criteria. Similar results were obtained in analyses with the Full Analysis Set (FAS) population.

Table 24. GMTs for CHIKV-Specific Neutralizing Antibodies, Visit 3 (Day 29), Per-Protocol Analysis Set, Study 302

Time Point Statistic (Visit 3, Day 29)	VLA1553 Lot 1 N=122	VLA1553 Lot 2 N=118	VLA1553 Lot 3 N=122
n[a]	122	118	122
GMT (95% CI)	2556.7 (2094.32, 3121.07)	2767.7 (2259.58, 3390.01)	2613.7 (2141.05, 3190.70)
Difference in GMT[b]	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1
Difference in LS mean (SE)[c]	1.08 (1.16)	0.94 (1.16)	1.02 (1.15)
95% confidence interval[c]	0.81, 1.44	0.71, 1.26	0.77, 1.36

Source: Adapted from Table 17 VLA1553-302 CSR, p. 93
Notes: The ANCOVA model was applied to the log-transformed titers, and back-transformed results were displayed for the LS mean and difference. The difference in GMT was a ratio of the LS means
a. Number of baseline (b) (4) negative participants with non-missing titers at Day 29
b. LS means, standard errors, confidence intervals, and p-values were from an ANCOVA model with fixed factor for Lot and study center as a covariate
c. LS mean differences, and associated confidence intervals were presented for the comparison stated in each column
Abbreviations: ANCOVA, analysis of covariance; CHIKV, ch kungunya virus; n, number of participants with available result at the time point; GMT, geometric mean titer; CI, confidence interval; LS, least squares; SE, standard error

6.2.11.2 Analyses of Secondary Endpoints

Immune Response as Measured by CHIKV-Specific Neutralizing Antibodies Postvaccination
A summary of GMTs for CHIKV-specific neutralizing antibodies by visit for the PP analysis set is provided in Table 25. In the PP analysis set, at Day 8, anti-CHIKV neutralizing antibodies were barely detectable. The antibody titers peaked at Day 29 for all three groups, ranging from 2556.7 (Lot 1 group) to 2767.7 (Lot 2 group). From Day 29 to Day 180, titers decreased but remained about 700 for each group. No significant difference in anti-CHIKV GMTs was observed between the Lot groups at Days 29 and 85. However, the 95% CI for the GMT ratio of Lot 2/Lot 1 at Day 180 was 1.51, exceeding the success criterion of $\leq$1.5. Similar results were obtained in the FAS.

Reviewer comment: *Although the 95% CI on the GMT ratio of Lot 2/Lot 1 at Day 180 was not between 0.67 and 1.5, this has no impact on demonstration of Lot-to-Lot consistency because the lot-consistency was based on the primary endpoint (i.e., comparison of GMTs between Lots on Day 29 postvaccination).*

Table 25. GMTs For CHIKV-Specific Neutralizing Antibodies by Visit, Per-Protocol Analysis Set, Study 302

Time Point Statistic	VLA1553 Lot 1 N=122	VLA1553 Lot 2 N=118	VLA1553 Lot 3 N=122
Visit 1, Day 1 (n[a])	121	117	122
Geometric mean	10.2	10.1	10.2
95% CI[b] of GMT	9.94, 10.41	9.90, 10.38	9.95, 10.42
Difference in GMT[b]	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1
Difference in LS mean (SE)[c]	1.00 (1.02)	1.00 (1.02)	1.00 (1.02)
95% CI[c]	0.96, 1.03	0.97, 1.04	0.97, 1.03
Visit 2, Day 8 (n[a])	112	112	113
Geometric mean	13.0	12.0	11.4
95% CI[b] of GMT	11.88, 14.19	10.97, 13.11	10.45, 12.48
Difference in GMT[b]	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1
Difference in LS mean (SE)[c]	0.92 (1.07)	0.95 (1.07)	0.88 (1.07)
95% CI[c]	0.81, 1.05	0.84, 1.08	0.78, 1.00
Visit 3, Day 29 (n[a])	122	118	122
Geometric mean	2556.7	2767.7	2613.7
95% CI[b] of GMT	2094.32, 3121.07	2259.58, 3390.01	2141.05, 3190.70
Difference in GMT[b]	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1
Difference in LS mean (SE)[c]	1.08 (1.16)	0.94 (1.16)	1.02 (1.15)
95% CI[c]	0.81, 1.44	0.71, 1.26	0.77, 1.36
Visit 4, Day 85 (n[a])	110	109	117
Geometric mean	832.3	829.0	875.8
95% CI[b] of GMT	694.23, 997.86	690.86, 994.66	734.56, 1044.25
Difference in GMT[b]	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1
Difference in LS mean (SE)[c]	1.00 (1.14)	1.06 (1.14)	1.05 (1.14)
95% CI[c]	0.77, 1.29	0.82, 1.36	0.82, 1.35
Visit 5, Day 180 (n[a])	111	110	114
Geometric Mean	666.4	777.6	688.3
95% CI[b] of GMT	556.77, 797.73	649.10, 931.52	576.44, 821.98
Difference in GMT[b]	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1
Difference in LS Mean (SE)[c]	1.17 (1.14)	0.89 (1.14)	1.03 (1.14)
95% CI[c]	0.90, 1.51	0.69, 1.14	0.80, 1.33

Source: Adapted from Table 20 VLA1553-302 CSR, p. 96-97
Note: The ANCOVA model was applied to the log-transformed titers, and back-transformed results were displayed for the LS mean and difference. The difference in GMT was a ratio of the LS means.
a. Number of baseline (b) (4) negative participants with non-missing titers at Day 29; these are also the number of participants that contribute data at least once in the primary analysis model
b. LS means, standard errors, confidence intervals, were from an ANCOVA model with fixed factor for Lot and study center as a covariate
c. LS mean differences, and associated confidence intervals were presented for the comparison stated in each column
Abbreviations: GMT, geometric mean titer; CHIKV, chikungunya virus; N, total participants in each cohort; n, number of participants with available result at the time point; CI, confidence interval; LS, least squares; SE, standard error; ANCOVA, analysis of covariance

Percentage of Participants with Seroresponse Postvaccination

A summary of the seroresponse rate for CHIKV-specific neutralizing antibodies by visit for the PP analysis set is provided in Table 26.

In the PP analysis set, on Day 8, no participant reached the seroresponse CHIKV antibody level (defined as $\mu PRNT_{50}$ ≥150). By Day 29, 348/356 (97.8%) participants had seroresponse. No significant differences in seroresponse rates were observed between any two lots. Seroresponse rates remained above 94% for all lot groups at Days 85 and 180, and there was no significant difference in seroresponse rates among the three lots.

Table 26. Seroresponse Rate (Percentage) For CHIKV-Specific Neutralizing Antibodies by Visit, Per-Protocol Analysis Set, Study 302

Time Point[a]	VLA1553 LOT 1 N=122	VLA1553 LOT 2 N=118	VLA1553 LOT 3 N=122	Total N=362
Visit 2, Day 8 (n)	110	110	111	331
Seroresponse rate [% (95% CI)]	0 (0.0, 3.3)	0 (0.0, 3.3)	0 (0.0, 3.3)	0 (0.0, 1.1)
Difference in seroresponse rate[b]	-	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1	-
Difference	NC	NC	NC	-
95% CI	NC	NC	NC	-
Visit 3, Day 29 (n)	120	116	120	356
Seroresponse rate [% (95% CI)]	97.5 (92.9, 99.5)	98.3 (93.9, 99.8)	97.5 (92.9, 99.5)	97.8 (95.6, 99.0)
Difference in seroresponse rate[b]	-	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1	-
Difference	0.8	-0.8	0.0	-
95% CI	-2.9, 4.4	-4.4, 2.9	-4.0, 4.0	-
Visit 4, Day 85 (n)	108	107	115	330
Seroresponse rate [% (95% CI)]	98.1 (93.5, 99.8)	97.2 (92.0, 99.4)	96.5 (91.3, 99.0)	97.3 (94.9, 98.7)
Difference in seroresponse rate[b]	-	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1	-
Difference	-1.0	-0.7	-1.6	-
95% CI	-5.0, 3.1	-5.3, 3.9	-5.8, 2.6	-
Visit 5, Day 180 (n)	109	108	112	329
Seroresponse rate [% (95% CI)]	94.5 (88.4, 98.0)	98.1 (93.5, 99.8)	95.5 (89.9, 98.5)	96.0 (93.3, 97.9)
Difference in seroresponse rate[b]	-	-	-	-
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1	-
Difference	3.7	-2.6	1.0	-
95% CI	-1.3, 8.6	-7.2, 2.0	-4.7, 6.8	-

Source: Adapted from Table 21, VLA1553-302 CSR, p. 100
Notes: Percentages were based on the number of baseline µPRNT negative participants with non-missing titers at the visit.
Seroresponse was defined as $\mu PRNT_{50}$ ≥150 for baseline µPRNT negative (<20) participants.
a. Number of baseline µPRNT negative (<20) participants with non-missing titers at the specified time point.
b. Differences, p-values, and associated CIs were presented for the difference in seroresponse rate (percentage) between the Lots.
Abbreviations: CHIKV, chikungunya virus; N, total participants in each group; n, number of participants; NC, non-calculable; CI, confidence interval; µPRNT, micro-plaque reduction neutralization test; $\mu PRNT_{50}$, micro-plaque reduction neutralization test 50%

6.2.11.4 Dropouts and/or Discontinuations

The overall dropout rate for this study was around 10% and the dropout rate for the three groups were similar. The major reason for discontinuations was due to lost-to-follow-up (around

7%). The dropouts likely had no impact on the study conclusions of lot consistency because the dropout rates were similar among the three groups.

6.2.12 Safety Analyses

6.2.12.1 Methods

The safety analysis methods were the same as Study 301. Please refer to Section 6.1.12.1.

6.2.12.2 Overview of Adverse Events

An overall summary of AE, SAE, and AESI data, including solicited adverse reactions, is provided in Table 27. There was no difference in the percentage of participants reporting AEs, SAEs and AESIs among the three lot groups.

Table 27. Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest, Safety Analysis Set, Study 302

Adverse Event	VLA1553 LOT 1 N=136 n (%)	VLA1553 LOT 2 N=137 n (%)	VLA1553 LOT 3 N=135 n (%)	Total N=408 n (%)
Any adverse event	98 (72.1)	97 (70.8)	101 (74.8)	296 (72.5)
Any related adverse event	82 (60.3)	82 (59.9)	83 (61.5)	247 (60.5)
Any severe adverse event	8 (5.9)	4 (2.9)	4 (3.0)	16 (3.9)
Any related severe adverse event	5 (3.7)	3 (2.2)	3 (2.2)	11 (2.7)
Any serious adverse event	3 (2.2)	2 (1.5)	0	5 (1.2)
Any adverse event of special interest	13 (9.6)	16 (11.7)	17 (12.6)	46 (11.3)

Source: OCS Analysis Studio, Custom Table Tool.

Solicited Adverse Events

As shown in Table 28, solicited IS adverse reactions reported were similar across the 3 groups. Overall, all solicited IS reactions were mild or moderate, and none was severe. The most common injection-site reactions were tenderness (14.2%) followed by pain (6.4%).

The rates of participants reporting solicited systemic adverse reactions were also similar across the 3 groups (Table 28). Overall, most solicited systemic adverse reactions were mild or moderate in severity, and 2.7% participants experienced severe solicited systemic adverse reactions. The most common solicited adverse reactions overall were fatigue (38.0% of participants), followed by headache (35.8% of participants), myalgia (23.5% of participants), arthralgia (15.4% of participants), nausea (13.0% of participants) and fever (12.7% of participants).

The mean duration of solicited IS and systemic reactions ranged from 1.0 to 5.6 days. Most of the reactions resolved within 2-3 days.

Table 28. Solicited Systemic Reactions and Injection Site Reactions by Severity, Safety Population, Study 302

Preferred Term	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 AE	73 (53.7)	78 (56.9)	82 (60.7)	233 (57.1)
Any severe solicited systemic AE	5 (3.7)	3 (2.2)	3 (2.2)	11 (2.7)
Arthralgia	19 (14.0)	21 (15.3)	23 (17.0)	63 (15.4)
Severe arthralgia	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.5)
Fatigue	53 (39.0)	49 (35.8)	53 (39.3)	155 (38.0)
Severe fatigue	1 (0.7)	1 (0.7)	0 (0.0)	2 (0.5)
Headache	49 (36.0)	42 (30.7)	55 (40.7)	146 (35.8)
Severe headache	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
Myalgia	31 (22.8)	35 (25.5)	30 (22.2)	96 (23.5)
Severe myalgia	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Nausea	16 (11.8)	20 (14.6)	17 (12.6)	53 (13.0)
Fever	16 (11.8)	18 (13.1)	18 (13.3)	52 (12.7)
Severe fever	4 (2.9)	3 (2.2)	2 (1.5)	9 (2.2)
Rash	1 (0.7)	6 (4.4)	6 (4.4)	13 (3.2)
Vomiting	2 (1.5)	6 (4.4)	2 (1.5)	10 (2.5)
Any solicited injection site AE	23 (16.9)	30 (21.9)	26 (19.3)	79 (19.4)
Any severe solicited injection site AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tenderness	19 (14.0)	22 (16.1)	17 (12.6)	58 (14.2)
Pain	7 (5.1)	10 (7.3)	9 (6.7)	26 (6.4)
Erythema/redness	4 (2.9)	2 (1.5)	5 (3.7)	11 (2.7)
Induration	3 (2.2)	1 (0.7)	3 (2.2)	7 (1.7)
Swelling	2 (1.5)	0 (0.0)	2 (1.5)	4 (1.0)

Source: OCS Analysis Studio, Safety Explorer.

Reviewer comment: *A significant number of eDiary cards had missing information. This reviewer requested that the digital health technology reviewer, Dr. Hussein Ezzeldin, conduct an in-depth analysis of missing data. After multiple IRs to the Applicant, Dr. Ezzeldin concluded that no modification of data presented by the Applicant is necessary. Please refer to Dr. Ezzeldin's review for details.*

Unsolicited Adverse Events

Overall, 25.0% of participants reported any unsolicited AE through Day 29 (27.9%, 16.1%, and 31.1% of participants in the Lot 1, 2, and 3 groups, respectively). The most commonly reported (frequency ≥1%) unsolicited AEs through Day 29 in at least one study group by SOC, PT, and severity are provided in Table 29.

The most common unsolicited AEs were neutropenia (2.9% of participants), lymphadenopathy (1.7% of participants), arthralgia (1.7% of participants), chills (1.5% of participants), and oropharyngeal pain (1.2% of participants).

Overall, most unsolicited AEs were mild or moderate in severity. Severe AEs were reported by three participants (0.7%). All three severe unsolicited AEs were reported from the Lot 1 group. The three severe unsolicited AEs reported were appendicitis, COVID-19, and acute cholecystitis. These three severe AEs were considered unlikely related to the vaccine by the Applicant as well as this reviewer.

Reviewer comment: *Unsolicited AEs were collected via eMemory aid. The eMemory aid was reviewed by the digital health technology reviewer and no significant issue was identified.*

Table 29. Unsolicited Adverse Events up to Day 29 With a Frequency ≥1% in at Least One Study Group, by System Organ Class, Preferred Term, and Maximum Severity, Safety Analysis Set, Study 302

System Organ Class Preferred Term	VLA 1553 LOT 1 N=136 n (%)	VLA 1553 LOT 2 N=137 n (%)	VLA1553 LOT 3 N=135 n (%)	Total N=408 n (%)
Any unsolicited adverse event	39 (28.7)	23 (16.8)	41 (30.4)	103 (25.2)
Blood and lymphatic system disorders	11 (8.1)	6 (4.4)	12 (8.9)	29 (7.1)
Anemia	0 (0.0)	2 (1.5)	1 (0.7)	3 (0.7)
Lymphadenopathy	3 (2.2)	0 (0.0)	4 (3.0)	7 (1.7)
Lymphopenia	3 (2.2)	0 (0.0)	0 (0.0)	3 (0.7)
Neutropenia	4 (2.9)	3 (2.2)	5 (3.7)	12 (2.9)
Gastrointestinal disorders	6 (4.4)	2 (1.5)	4 (3.0)	12 (2.9)
Diarrhea	2 (1.5)	0 (0.0)	2 (1.5)	4 (1.0)
General disorders and administration site conditions	4 (2.9)	2 (1.5)	8 (5.9)	14 (3.4)
Chills	1 (0.7)	1 (0.7)	4 (3.0)	6 (1.5)
Infections and infestations	5 (3.7)	0 (0.0)	1 (0.7)	6 (1.5)
Investigations	7 (5.1)	3 (2.2)	5 (3.7)	15 (3.7)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.5)
Metabolism and nutrition disorders	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.5)
Musculoskeletal and connective tissue disorders	7 (5.1)	4 (2.9)	7 (5.2)	18 (4.4)
Arthralgia	4 (2.9)	1 (0.7)	2 (1.5)	7 (1.7)
Muscular weakness	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.5)
Myalgia	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.5)
Nervous system disorders	3 (2.2)	2 (1.5)	4 (3.0)	9 (2.2)
Dizziness	1 (0.7)	2 (1.5)	1 (0.7)	4 (1.0)
Headache	2 (1.5)	0 (0.0)	1 (0.7)	3 (0.7)
Psychiatric disorders	2 (1.5)	0 (0.0)	1 (0.7)	3 (0.7)
Respiratory, thoracic and mediastinal disorders	3 (2.2)	4 (2.9)	5 (3.7)	12 (2.9)
Cough	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.5)
Oropharyngeal pain	1 (0.7)	2 (1.5)	2 (1.5)	5 (1.2)
Rhinorrhea	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.5)
Skin and subcutaneous tissue disorders	0 (0.0)	3 (2.2)	2 (1.5)	5 (1.2)

Source: OCS Analysis Studio, Safety Explorer.

Reviewer comment: *The CSR did not specify the definitions of neutropenia and lymphopenia. This reviewer sent an IR to the Applicant asking for the definitions of neutropenia and lymphopenia; however, the Applicant did not address the IR.*

Medically-Attended Adverse Events

Overall, 47 (11.5%) participants experienced at least one MAAE during the study, with more participants in the Lot 1 (16.2%) and Lot 3 groups (11.9%) than in the Lot 2 group (6.6%). The most commonly reported MAAEs by SOC were musculoskeletal and connective tissue disorders (3.2% of overall [range: 1.5% to 6.6% across the 3 Lot groups]), infections and infestations (2.9% of overall [range: 0.7% to 5.1% across the 3 Lot groups]), nervous system disorders (2.0% of overall [range: 0.0% to 4.4% across the 3 Lot groups]), general disorders and administration site conditions (1.7% of overall [range: 0.7% to 3.7% across the 3 Lot groups]), and gastrointestinal disorders (1.5% of overall [range: 0.0% to 2.2% across the 3 Lot groups]).

Most MAAEs were mild or moderate. A total of six participants (1.5%) experienced at least one severe MAAE, including 2.9% of participants in the Lot 1 group, 0.7% of participants in the Lot 2 group, and 0.7% of participants in the Lot 3 group. The most common severe MAAE was pyrexia, occurring in two participants (0.5%; one each in the Lot 1 group and the Lot 3 group).

6.2.12.3 Deaths

No deaths occurred during the study.

6.2.12.4 Nonfatal Serious Adverse Events

Overall, 5 participants (1.2%) experienced nonfatal SAEs during the study (3 (2.2%) participants in the Lot 1 group and 2 (1.5%) participants in the Lot 2 group).

Two participants experienced spontaneous abortion and three participants were hospitalized due to acute appendicitis (two events) and acute cholecystitis (one events). All five events resolved. The Applicant considered the five cases of SAEs not related to the study vaccine.

Reviewer comment: *This reviewer agrees with the Applicant that the 2 cases of appendicitis (Participants* (b) (6) *and 1 case of cholecystitis (Participant* (b) (6) *were related to bacterial infections and were unlikely related to VLA-1553. This reviewer also agrees that one case of spontaneous abortion in Participant* (b) (6) *was unlikely related to the study vaccine due to lack of reasonable temporal association. However, the causality of the other spontaneous abortion in Participant* (b) (6) *could not be excluded due to its close temporal association with the vaccination administration. The 2 cases of spontaneous abortion are summarized below:*

1. Participant (b) (6) A 23-year-old White female experienced spontaneous abortion 55 days after she received VLA1553. The participant received VLA1553 from Lot 2, and her last menstrual period was 3 weeks before the vaccination. At 45 days postvaccination, she experienced cramping and a sonography showed an irregular gestational sac with debris and enlarged yolk sac, no detectable heartbeat, and a gestational age of 7 weeks and 4 days. Beta human chorionic gonadotropin (HCG) was 41705 mIU/mL, urine culture showed no growth, and *Chlamydia trachomatis* and *Neisseria gonorrhea* tests were negative. At 53 days postvaccination, sonography showed a blighted ovum, no fetal pole, and an irregular gestational sac. The participant experienced spontaneous abortion at 55 days postvaccination and underwent a dilation and curettage procedure the next day. The Applicant considered the event not related to VLA1553 because the spontaneous abortion occurred about 2 months postvaccination.

Reviewer comment: *This reviewer does not agree with the Applicant's conclusion of vaccine unrelatedness due to the event of spontaneous abortion occurring two months postvaccination. This reviewer considers the event was at least possibly related to VLA1553 because of close temporal association of the vaccination and gestational age of pregnancy (3 weeks at vaccination).*

2. Participant (b) (6) A 27-year-old White female experienced spontaneous abortion at 177 days postvaccination with VLA1553. She became pregnant at 106 days postvaccination. The estimated gestational age was 10 weeks and 1 day when the abortion occurred. The event resolved and was considered by the Applicant not related to the study vaccine.

Reviewer comment: *This reviewer agrees with the Applicant's causality assessment that the event was unlikely related to VLA1553 because the event occurred at 6 months postvaccination.*

6.2.12.5 Adverse Events of Special Interest (AESI)

AESIs were monitored and analyzed in the same way as in Study 301 (Section 6.1.12.5). Using the revised criteria to define events of CHIK-like illness, the results are presented in Table 30. Similar to Study 301, 11.3% of VLA1553 recipients developed CHIK-like illness and 2.5% off VLA1553 recipients had a severe CHIK-like illness. The mean duration of CHIK-like symptoms was 9.9 days with a range from 1 to 168 days. The mean duration of severe CHIK-like symptoms was 21.6 days with a range from 1 to 168 days. No serious events of CHIK-like illness were reported in this study.

Table 30. CHIK-like Symptoms, by System Organ Class and Preferred Term (≥0.1%), Safety Population, Study 302

CHIK-like Symptoms	VLA1553 N=408 n (%)
Any CHIK-like symptom	46 (11.3)
Any severe CHIK-like symptom	10 (2.5)
General disorders and administration site conditions	46 (11.3)
Pyrexia	46 (11.3)
Severe pyrexia	8 (2.0)
Fatigue	39 (9.6)
Severe fatigue	2 (0.5)
Chills	3 (0.7)
Nervous system disorders	40 (9.8)
Headache	40 (9.8)
Severe headache	1 (0.2)
Dizziness	2 (0.2)
Paresthesia	1 (0.2)
Musculoskeletal and connective tissue disorders	32 (7.8)
Myalgia	29 (7.1)
Severe myalgia	1 (0.2)
Arthralgia	18 (4.4)
Severe arthralgia	1 (0.2)
Skin and subcutaneous tissue disorders	3 (0.7)
Rash	3 (0.7)
Blood and lymphatic system disorders[a]	2 (0.5)
Lymph node pain	1 (0.2)
Lymphadenitis	1 (0.2)
Cardiac disorders	1 (0.2)
Palpitation	1 (0.2)

Source: Adapted from Table 1 (page 3-5), Module 1.11.3, STN125777/0.49.
Notes: a. Abnormal hematology parameters were not included in this analysis.
Abbreviations: N, number of participants in the group; n, number of participants with an indicated event.

Reviewer comment: *Although no serious CHIK-like illness was reported in this study, about 20% (10 out of 46 cases) of all the CHIK-like symptoms were severe. The frequency and severity of these reactions in this study support inclusion in Section 5 (Warnings and Precautions) of the PI, narrowing of the indication to those at risk of increased exposure to CHIKV, and further post-marketing assessment.*

6.2.12.6 Clinical Test Results

Participant hematology, clinical chemistry, and urinalysis were evaluated during study visits as specified in the clinical protocol and the changes from baseline in the laboratory safety parameters were similar to those observed in Study 301 (described in section 6.1.12.6). The changes were considered expected physiologic responses following vaccination with a live-attenuated vaccine and the clinical significance is unknown.

According to the protocol, participants who experienced Grade 3 fever or CHIK-like symptoms were to be tested for viremia. An exploratory retrospective analysis of viremia was conducted in 11 participants, 3 of whom were viremic at Day 8 (Participant (b) (6): 14,526 GCE/mL; Participant (b) (6): 132,129 GCE/mL; and Participant (b) (6): 4,739 GCE/mL), which became undetectable at Day 29. Participant (b) (6) experienced Grade 3 arthralgia, Grade 3 fatigue and Grade 3 myalgia at 5 days postvaccination and all the AEs lasted for 1 day. Participant (b) (6) (b) (6) experienced Grade 3 fever (Day 2 to 4) and Grade 2 headache (Days 5 to 29). Participant experienced Grade 3 fever (Days 6 to 11), Grade 1 arthralgia (Days 8 to 10), myalgia and headache (Days 8 to 13), and fatigue (Days 8 to 14).

6.2.12.7 Dropouts and/or Discontinuations

No participants experienced an AE leading to withdrawal from the study.

6.2.13 Study Summary and Conclusions

6.2.13.1 Immunogenicity

- The 95% CIs of the anti-CHIKV GMT ratios between any two lots at Day 29 were within 0.67 and 1.5, which met the pre-specified lot consistency success criteria.
- Overall, anti-CHIKV GMTs peaked at Day 29 with (GMT 2643.2 for all groups combined); GMTs subsequently decreased to 846.1 at Day 85 and 708.8 at Day 180. Similar GMTs and kinetics were observed for all 3 lots.
- Seroresponse rate was 97.8% on Day 29 and remained 96% through Day 180, and there was no significant difference among the 3 lots.

6.2.13.2 Safety

- Overall, 72.5% participants experienced any AE up to Day 180 following vaccination with VLA1553. No significant differences in any AE occurrences in terms of SOC and PT between the lots.
- A majority of participants (61.0%) reported solicited adverse reactions.
- Solicited Adverse Reactions:
  - Solicited IS reactions were reported by 19.4% of participants vaccinated with VLA1553
    - All solicited IS reactions were mild or moderate
    - The most common solicited IS reaction was tenderness (14.2% of participants)
  - Solicited systemic adverse reactions were reported by 57.1% of participants vaccinated with VLA1553
    - Most solicited systemic adverse reactions were mild or moderate, and 2.7% of the adverse reactions were severe
    - The most common solicited systemic reactions reported by participants were fatigue (38.0% of participants), followed by headache (35.8% of participants), myalgia (23.5% of participants), arthralgia (15.4% of participants), nausea (13.0% of participants), and fever (12.7% of participants).

- Unsolicited AEs were reported in 25.0% of participants in the 28 days postvaccination. Most unsolicited AEs were mild or moderate and 0.7% were severe.
- SAE: Overall, 5 SAEs were assessed as unrelated by the Investigator (2 cases of acute appendicitis, 1 case of acute cholecystitis, and 2 cases of spontaneous abortion). All cases were considered unrelated to vaccine by the Applicant. However, per this reviewer, causality cannot be ruled out for one spontaneous abortion case.
- AESIs: 11.3% of VLA1553 recipients developed acute CHIK-like illness. Most CHIK-like illness were mild to moderate. Ten participants (2.5%) experienced severe CHIK-like illness and no participant reported serious CHIK-like illness.

6.2.13.3 Conclusion

In conclusion, the safety profile of VLA1553 in this study is considered acceptable in the context of a restricted indication for use. However, the severity and duration of CHIK-like illness in this study are consistent with similar findings in Study 301, and support inclusion of this risk in the Warnings and Precautions section of the product labeling, an indication narrowed to those at high risk of exposure to CHIKV, as well as additional evaluation in postmarketing studies (see Section 11.6).

7. Integrated Overview of Efficacy

7.1 Indication

Active immunization for prevention of disease caused by CHIKV in adults ≥18 years of age who are at increased risk of exposure to CHIKV.

7.1.1 Methods of Integration

The Applicant submitted three clinical studies conducted in healthy adult volunteers to support licensure through accelerated approval (AA). The three studies include:

- Study VLA1553-301: a placebo-controlled immunogenicity and safety Phase 3 study
- Study VLA1553-302: a lot-to-lot consistency Phase 3 study
- Study VLA1553-101: a dose-response Phase 1 study

For VLA1553-301, the primary effectiveness endpoint was the percentage of baseline CHIKV seronegative participants with an anti-CHIKV neutralizing antibody GMT measured with μPRNT ≥150 28 days postvaccination. Immunogenicity data for Study 301 and Study 302 were analyzed by individual study and also pooled together. Since the immune assay used in the Phase 1 trial, (b) (4), was not validated and also different from μPRNT, and the doses and formulation of VLA1553 used in the Phase 1 trial were different from that used in the Phase 3 trials, immunogenicity data in the Phase 1 trial are not pooled in the ISE.

The analysis set for pooled immunogenicity data was from the per-protocol (PP) Population of Studies VLA1553-301 and VLA1553-302.

7.1.2 Demographics and Baseline Characteristics

Table 31 presents the demographics and the baseline characteristics of study participants enrolled in the clinical trials by treatment.

Table 31. Demographic and Other Baseline Characteristics, Per-Protocol Analysis Set, Studies 301 and 302

Treatment	VLA1553 N=656	Placebo N=103	All N=759
Sex, n (%)	**n=656**	**n=103**	**n=759**
Female	372 (56.7)	62 (60.2)	434 (57.2)
Male	284 (43.3)	41 (39.8)	325 (42.8)
Race, n (%)	**n=656**	**n=103**	**n=759**
White	517 (78.8)	89 (86.4)	606 (79.8)
Black/African American	96 (14.6)	10 (9.7)	106 (14.0)
Asian	20 (3.0)	2 (1.9)	22 (2.9)
American Indian/Alaska Native	6 (0.9)	0 (0.0)	6 (0.8)
Native Hawaiian/Pacific Islander	2 (0.3)	1 (1.0)	3 (0.4)
Other	15 (2.3)	1 (1.0)	16 (2.1)
Ethnicity	**n=656**	**n=103**	**n=759**
Hispanic or Latino	71 (10.8)	14 (13.6)	85 (11.2)
Non-Hispanic/non-Latino	579 (88.3)	87 (84.5)	666 (87.7)
Age (years)	**n=656**	**n=103**	**n=759**
Mean (SD)	41.2 (14.97)	51.1 (16.16)	42.5 (15.50)
Median	38.0	54.0	39.0
Range	18 / 81	21 / 78	18 / 81
Age category, n (%)	**n=656**	**n=103**	**n=759**
≥18 to 64 years	569 (86.7)	73 (70.9)	642 (84.6)
18 to 45 years	472 (72.0)	39 (37.9)	511 (67.3)
46 to 64 years	97 (14.8)	34 (33.0)	131 (17.3)
≥65 years	87 (13.3)	30 (29.1)	117 (15.4)
65 to 74 years	78 (11.9)	25 (24.3)	103 (13.6)
75 to 84 years	9 (1.4)	5 (4.9)	14 (1.8)
≥85 years	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m^2)	**n=654**	**n=103**	**n=757**
Mean (SD)	30.3 (8.03)	30.4 (6.98)	30.3 (7.89)
Median	28.8	29.5	28.9
Range	14 / 102	17 / 54	14 / 102
BMI category, n (%)	**n=654**	**n=103**	**n=757**
BMI<25 kg/m^2	156 (23.8)	19 (18.4)	175 (23.1)
BMI≥25 kg/m^2 and BMI<30 kg/m^2	211 (32.2)	35 (34.0)	246 (32.4)
BMI≥30 kg/m^2 and BMI<35 kg/m^2	138 (21.0)	27 (26.2)	165 (21.7)
BMI≥35 kg/m^2	149 (22.7)	22 (21.4)	171 (22.5)

Source: Module 5.3.5.3, Pooled Analysis, Table P.1.3.4
Abbreviations: BMI, body mass index; SD, standard deviation; PPAS, Per-Protocol analysis set

For both the vaccine and placebo groups, a majority of participants were White (78.8% in VLA1553 and 86.4% in placebo) and more females (57.2%) than males (42.8%). In general, the demographics and baseline characteristics were balanced except for participants in the 18 to 45 years age group. Because the integrated group of VLA1553 recipients included participants from VLA1553-302, which enrolled only participants 45 years of age and younger, the median age and percentage of participants in the older than 45 years of age groups was lower than that for the placebo group, which was enrolled entirely from VLA1553-301, and included participants up to 85 years of age.

7.1.3 Participant Disposition

Table 32 summarizes participant disposition in Studies 301 and 302. Please note that only a subset of participants for immunogenicity analyses in VLA1553-301 were included in the table.

Table 32. Disposition, Immunogenicity and Safety Populations, Studies 301 and 302

Disposition	Study 301 Placebo	Study 301 VLA1553	Study 302 VLA1553	Pooled VLA1553
Screened, n	6100[a]	6100[a]	668	6768[a]
Randomized, n	1035	3093	409	3502
Safety population, n	1033	3082	408	3490
IMM/ FAS/ ITT population, n	118	344	391	735
Completed, n (%)[b]	112 (94.9)	315 (91.6)	364 (89.2)	679 (92.4)
Early termination, n(%)[b], due to:	6 (5.1)	29 (8.4)	44 (10.8)	73 (9.9)
Lost to follow-up	4 (3.4)	15 (4.4)	30 (7.4)	45 (6.1)
Withdrawal by participant	1 (0.8)	11 (3.2)	13 (3.2)	24 (3.3)
Physician's decision	0	1 (0.3)	0	1 (0.1)
Death	0	1 (0.3)	0	1 (0.1)
AE	1 (0.8)	0	0	0
Other	0	1 (0.3)	1 (0.2)	2 (0.3)

Source: Adapted from Tables 14.1.1.1, and 14.1.1.3 2, VLA1553-301 CSR, and Tables 14.1.1.1 and 14.1.1.3, VLA1553-302 CSR
Notes: a. Total screened participants for Study VLA1533-301 (placebo and study group) were 6100; b. the denominator is IMM population.
Abbreviations: IMM, immunogenicity population; FAS, full analysis set, ITT, Intention-to-treat population, AE, adverse event; PP, Per-Protocol population

7.1.4 Analysis of Primary Endpoint

The primary immunogenicity endpoint for the ISE was anti-CHIKV seroresponse rate, which was defined as the percentage of participants who achieved an anti-CHIKV neutralizing antibody GMT ≥ 150 at 28 days postvaccination. The PP populations from Studies 301 and 302 were pooled together as an integrated Per-Protocol analysis set (PPAS) for the ISE primary endpoint analysis.

The assays used to determine CHIKV serostatus at baseline for inclusion in the PP populations were different for Studies 301 and 302. Baseline serostatus for CHIKV was measured with μPRNT in Study 301 and by (b) (4) in Study 302. In the ISE, μPRNT was uniformly used to determine baseline CHIKV serostatus, and thus the analysis population was designated as PPAS which included a definition of $\mu PRNT_{50}$ titer <20 at baseline applicable for all participants included in this analysis set from Studies 301 and 302.

Table 33 presents the primary endpoint analysis of the pooled data in PPAS. The results showed that 98.3% participants achieved a seroresponse at 28 days postvaccination with VLA1553, while no participant in the placebo achieved a seroresponse.

Table 33. Seroresponse Rate 28 Days After Vaccination, Pooled Per-Protocol Analysis Set, Studies 301 and 302

Treatment	n/N	Seroresponse Rate % (95% CI)
VLA1553	644/655	98.3 (97.0; 99.1)
Placebo	0/103	0.0 (0.0; 3.6)

Source: Adapted from Table 2.5-1 (page 51), Module 5.3.5.3--ISE, STN125777/0.3

7.1.5 Analysis of Secondary Endpoint(s)

Table 34 summarizes immune responses as expressed in GMTs and seroresponse rates in the PPAS populations at various time points following vaccination in the pooled dataset. Anti-CHIKV neutralizing antibody GMTs peaked at 28 days postvaccination and then decreased sharply at

85 days and then stabilized through 180 days. However, seroresponse rates from 28 days throughout 180 days postvaccination were ≥96.%.

Table 34. Immune Response Kinetics Following Vaccination with VLA1553, Pooled Per-Protocol Analysis Set, Studies 301 and 302,

Time Point	Placebo N=103	VLA1553 (Pooled dataset) N=656
GMT (95% CI)	-	-
Day 29	10 (10, 10)	2,954 (2,730, 3,197)
Day 85	10 (10, 10)	956 (888,1,029)
Day 180	10 (10, 10)	735 (682, 793)
SRR[a] % (95% CI)	-	-
Day 29	0.0 (0.0, 3.6)	98.3 (97.0, 99.1)
Day 85	1.0 (0.2, 5.6)	97.7 (96.2, 98.6)
Day 180	0.0 (0.0, 3.8)	96.4 (94.5, 97.6)

Source: Adapted from 2.5-1 (page 51), Module 5.3.5.3--ISE, STN125777/0.3.
Notes: a. Seroresponse rate was defined as a percentage of participants with an anti-CHIKV neutralizing antibody titer≥ 150.
Abbreviations: N, total number of participants in the group; GMT, geometric mean titer; CI, confidence interval; SRR, Seroresponse rate

7.1.7 Subpopulations

Pooled subgroup analyses of vaccine effective in terms of seroresponse rate and anti-CHIIKV neutralizing antibody GMTs 28 days postvaccination are presented in Table 35. No significant differences in seroresponse rates and anti-CHIKV neutralizing antibody GMTs were observed based on age, sex, race, and the ethnicity. However, for the subgroup analyses based on race, the data should be interpreted cautiously for the subgroup of American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander because of limited numbers of participants in these subgroups.

Table 35. Chikungunya-Specific Neutralizing Antibody Response Rate 28 Days Postvaccination, Pooled Per-Protocol Analysis Set

Subgroup	N	Seroresponse Rate % (95% CI)	GMT (95% CI)
Age	-	-	-
18 to 64 Years	568	98.1 (96.6, 98.9)	2869.5 (2630.1, 3130.6)
≥65 Years	87	100 (95.8, 100)	3571.3 (2997.2, 4255.3)
Sex	-	-	-
Female	371	97.8 (95.8, 98.9)	2873.5 (2568.1, 3215.3)
Male	284	98.9 (96.9, 99.6)	3062.8 (2746.7, 3415.3)
Race	-	-	-
White	516	99.2 (98.0, 99.7)	3091.9 (2862.6, 3339.7)
Black or African American	96	96.9 (91.2, 98.9)	2706.2 (2114.4, 3463.7)
Asian	20	95.0 (76.4, 99.1)	2275.9 (1180.9, 4386.4)
American Indian or Alaska Native	6	83.3 (43.6, 97.0)	1718.5 (115.2, 25629.5)
Native Hawaiian or other Pacific Islander	2	100 (34.2, 100)	2293.2 (2.0, 2,686,272)
Other	15	86.7 (62.1, 96.3)	1961.5 (587.4, 6550.5)

Subgroup	N	Seroresponse Rate % (95% CI)	GMT (95% CI)
Ethnicity	-	-	-
Hispanic or Latino	71	98.6 (92.4, 99.8)	3275.9 (2589.7, 4144.1)
Non-Hispanic or Latino	578	98.3 (96.8, 99.1)	2924.5 (2687.0, 3183.0)

Source: Adapted from Table 2 (page 7), Module 1.11.3 IR Response, STN125777/0.10.
Notes: Seroresponse of CHIKV-specific neutralizing antibody titer is defined as $\mu PRNT_{50} \geq 150$
Abbreviations: N, participants in each subgroup with non-missing neutralizing antibody titer result at Day 29; NC, not calculable; GMT, geometric mean titer; CI confidence interval.

Reviewer comment: *Anti-CHIKV titers among younger age group 18-64 years of age appeared numerically lower than the older age group ≥65 years of age, which is not consistent with observations in other vaccine studies. This was because anti-CHIKV titers in Study 302 were lower [GMT (95% CI) =2643 (2354, 2968), at Day 29] than those in Study 301 [GMT (95% CI)=3362 (2994, 3775), at Day 29] and Study 302 only enrolled participants 18 through 45 years of age. In general, antibody titers among younger participants are higher than those among older participants. The lower anti-CHIKV neutralizing antibody titers observed in Study 302 were likely due to variability of the PRNT; however, the exact reason is unknown. Regardless of difference in the GMTs between the two studies, the seroresponse rates are similar between the two studies.*

7.1.8 Persistence of Efficacy

No evaluation of persistence of efficacy was conducted in the studies. However, anti-CHIKV neutralizing antibody persistence was assessed up to 6 months postvaccination. In the pooled analysis population from Study 301 and 302, seroresponse rates at Day 85 and Day 180 were 97.7% [95% CI (96.2, 98.6)] and 96.4% [95% CI (94.5, 97.6)], respectively.

7.1.9 Product-Product Interactions

Post-hoc subgroup analyses were conducted in the pooled data collected from VLA1553-treated participants of Studies 301 and 302 to assess potential impact of immunosuppressants and antipyretic products on immune responses of VLA1553.

In the PPAS, 124 participants received concomitant systemic medications with known or suspected immunosuppressive properties by anatomic therapeutic classification level 2, primarily consisting of medications not expected to impact the immune response. No remarkable differences in anti-CHIKV GMTs and seroresponse rates were noted between these participants and those who did not receive systemic immunosuppressants (N=532).

Reviewer comment: *Immunosuppressive therapies [e.g., systemic, or high dose inhaled (>800 µg/day of beclomethasone dipropionate or equivalent) corticosteroids, radiation treatment or other immunosuppressive or cytotoxic drugs] were not allowed during the studies and participants who received a prohibited concomitant medication which could influence the immune response were excluded from the PPAS. The concomitant medications with known or suspected "immunosuppressive properties" included anti-inflammatory and anti-rheumatic products, analgesics, psychoanaleptics, psycholeptics, sex hormones, and antihistamines. None of the listed medicines has known significant immunosuppresive effect. The results described above should be interpreted cautiously.*

In the PPAS, 99 participants received antipyretics in the first week postvaccination. No remarkable differences in anti-CHIKV GMTs and seroresponse rates were noted between these participants and those who did not receive antipyretic products (N=557) within the first week postvaccination.

7.1.10 Additional Efficacy Issues/Analyses

To assess cross-neutralization with other lineages and strains, stored samples from Study 101 were tested at the (b) (4) in (b) (4) assays to quantify neutralizing antibodies against the following wild type CHIKV strains:

- ECSA lineage (La-Reunion strain (b) (4)
- West African lineage (strain (b) (4)
- Asian lineage (b) (4)

The (b) (4) results for the 47 serum samples from Study 101 against the three CHIKV genotypes are presented in Table 36. The same samples were also quantified using the Asian strain (b) (4) based µPRNT and the results are also included in Table 36 as a comparator. The results showed that the antibodies generated following VLA1553 vaccination were able to neutralize all 3 tested CHIKV genotypes. The Applicant asserts that the results are consistent with other studies that showed that anti-CHIKV antibodies elicited by a vaccine candidate derived from one genotype were able to cross-neutralize other CHIKV genotypes (Rossi 2019; Folegatti, 2021; Goo, 2016).

Table 36. Comparison of Anti-CHIKV Neutralizing Antibody Geometric Mean Titers, by Reporter Virus, Study 101

Time Point (Day)	N	La Reunion (b) (4)	West African (b) (4)	(b) (4)	(b) (4) µPRNT50
0	12	<10	<10	<20	<20
14	5	80	320	105.6	2207.5
84	10	422.2	422.2	42.9	867.5
180	12	958.9	604.1	50.4	532.3

Source: Adapted from Table 2 (page 5), VIE-DR-0181 [01], Module 5.3.1.4, STN125777/0/3

Reviewer comment: *The antibody response kinetics measured by (b) (4) appeared to increase over time for the La Reunion and West African CHIKV strain based (b) (4) as compared with the decreasing antibody response kinetics measured with the (b) (4) based (b) (4) and the (b) (4) based µPRNT. Because the results are unusual, the clinical review team consulted with the CMC reviewers for additional insight. Per the CMC reviewer, 1) Although there may be three to four genetic lineages of the CHIKV there is only one "serotype", and there exists a substantial body of published work demonstrating cross-neutralization of heterologous CHIKV strains by convalescent sera. 2) The results from (b) (4) would be better interpreted as qualitative proof of generation of cross-neutralizing antibodies in vaccine recipients than as quantitative measurements of "protectiveness against different genotypes". This Clinical reviewer suggests that the Applicant provide cross-neutralization data using immune sera generated from the Phase 3 trials (i.e., VLA1553-301 or -302). However, based on the reasons above, the CMC team did not make a recommendation for cross-neutralization data using archived immune sera at this time. Please refer to the CMC review for details*

7.1.11 Efficacy Conclusions

The pivotal immunogenicity and safety Study 301 demonstrated that:

- Seroresponse rate, defined as a percentage of participants with a GMT titer ≥150, was 98.9% with a 95% CI of (96.7, 99.8) at 28 days postvaccination with VLA1553. The results met the pre-specific success criterion of LB of 95% CI >70%.

- Anti-CHIKV neutralizing antibody titer peaked at 28 days postvaccination with a GMT of 3,362, and subsequently decreased to 1,084 and 752 at postvaccination Days 84 and 180, respectively.
- Seroresponse rates remained at 97.7% and 96.4% on 84 days and 180 days postvaccination, respectively.
- No statistically significant difference was observed in terms of GMTs and seroresponse rates among subgroups by age, sex, race, and ethnicity 28 days postvaccination.

The lot-to-lot consistency Study 302 demonstrated that the 95% CIs of the anti-CHIKV GMT ratios between any two lots 28 days postvaccination were within 0.67 and 1.5, which met the pre-specified lot consistency criteria.

The integrated effectiveness analyses that pooled immunogenicity data from Study 301 and 302, showed similar results in seroresponse rate 28 days postvaccination as those of Study 301 alone.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Pooling of data can provide a larger database to detect lower frequency events and permit explorations of possible drug-demographic or drug-disease interactions in subgroups of the population. It is acknowledged that there are inherent weaknesses of pooling safety data from trials with heterogeneous study designs.

(b) (4) were used to conduct the analyses. In addition, (b) (4) was also used to modify datasets as needed. Multiple occurrences of the same event in the same participant were counted only once.

Solicited adverse reactions were collected via an e-diary for 14 days postvaccination in Study 101 and for 10 days postvaccination in Studies 301 and 302. For all studies, unsolicited AEs were collected via an eMemory Aid for 28 days and SAEs and AESIs were collected throughout the study period (at least 6 months postvaccination). All AEs that started before or on Day 180 were included.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The Integrated Summary of Safety included safety data from three completed clinical studies in healthy adult participants (Studies 101, 301 and 302). Please refer to Table 4 in Section 5.3 for details.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The Pooled Safety Population consists of 4,643 participants from the three clinical studies: 3,610 participants were vaccinated with VLA1553 (3,082, 408, and 120 participants, respectively) and 1,033 participants received placebo (all participants in the placebo group were from VLA1553-301) (Table 37).

All vaccinated participants were included in the Pooled Safety Population, except for one participant in Study 301 who was randomized at two different sites, vaccinated twice with VLA1533, and was thus excluded from the Pooled Safety Population under each participant identification (ID) (Participant with a participant ID of (b) (6) was the same participant) due to violation of GCP. Another participant in Study 301 was randomized to the placebo group but was vaccinated with VLA1553 and was thus allocated to the actual treatment received (VLA1553) in the Pooled Safety Population.

Table 37. Participant Overview, Pooled Safety Population, Studies 301, 302 and 101

Participant Overview	Pooled VLA1553	Placebo
Vaccinated participants, n	3609[a]	1034
Pooled safety population, n	3610[b]	1033[b]
Day 29[c], n (%)	3442 (95.3)	991 (95.9)
Day 180[c], n (%)	3196 (88.5)	918 (88.9)
Completed study, n (%)	3179 (88.1)	921 (89.1)
Discontinued study, n (%)	430 (11.9)	113 (10.9)

Source: Adapted from Table 5, Pooled ISS, p 22
Notes: a. One participant in Study VLA1553-301 was randomized at two different sites and was vaccinated twice with VLA1553 and thus excluded from the pooled safety population under each participant ID due to violation of GCP
b. One participant in Study VLA1553-301 was randomized to the placebo group but was vaccinated with VLA1553 and was thus allocated to the VLA1553 in the pooled safety population
c. Participants are included at the timepoint if they have data entered in the eCRF at that visit or an early termination visit within the visit window
Abbreviations: n (%), number and percentage of participants; ID, identification; GCP, Good Clinical Practice; eCRF, electronic case report form

The demographic and baseline characteristics of the pooled safety population and safety cohorts for Studies 101, 301 and 302 are provided in Table 38.

Table 38. Demographic and Baseline Characteristics, Pooled Safety Population, Studies 301, 302 and 101

Treatment	Pooled Studies[a] VLA1553 (N=3610)	VLA1553-301 VLA1553 (N=3082)	VLA1553-302 Total (N=408)	VLA1553-101 Total (N=120)	VLA1553-301 Placebo (N=1033)
Sex, n (%)	--	--	--	--	--
Female	1919 (53.2)	1682 (54.6)	223 (54.7)	14 (11.7)	569 (55.1)
Male	1691 (46.8)	1400 (45.4)	185 (45.3)	106 (88.3)	464 (44.9)
Race, n (%)	--	--			--
White	2867 (79.4)	2456 (79.7)	315 (77.2)	96 (80.0)	853 (82.6)
Black or African American	530 (14.7)	451 (14.6)	62 (15.2)	17 (14.2)	122 (11.8)
Asian	74 (2.0)	51 (1.7)	18 (4.4)	5 (4.2)	17 (1.6)
Other	92 (2.5)	84 (2.7)	7 (1.7)	1 (0.8)	31 (3.0)
American Indian or Alaska Native	33 (0.9)	27 (0.9)	5 (1.2)	1 (0.8)	5 (0.5)
Native Hawaiian or Other Pacific Islander	14 (0.4)	13 (0.4)	1 (0.2)	0	5 (0.5)
Age[b] (years)	--	--	--	--	--
Mean (SD)	43.3 (15.1)	45.1 (15.4)	33.2 (7.4)	32.5 (6.6)	45.0 (15.6)
Median	42.0	45.0	34.0	33.0	45.0
Min, Max	18, 88	18, 88	18, 45	19, 45	18, 94
Age Category[b], n (%)	--	--	--	--	--
≥18 to 64 years	3264 (90.4)	2736 (88.8)	408 (100)	120 (100)	916 (88.7)
≥65 years	346 (9.6)	346 (11.2)	0	0	117 (11.3)

Treatment	Pooled Studies[a] VLA1553 (N=3610)	VLA1553-301 VLA1553 (N=3082)	VLA1553-302 Total (N=408)	VLA1553-101 Total (N=120)	VLA1553-301 Placebo (N=1033)
Mean (SD)	30.2 (7.4)	30.5 (7.4)	29.4 (7.5)	25.8 (2.9)	30.0 (7.1)
Median	29.0	29.4	28.2	25.8	28.9
Min, Max	14.0, 102.0	14.1, 102.3	13.7, 72.8	19.0, 29.9[b]	16.6, 63.1

Source: Module 5.3.5.3, Pooled Analysis, Table P.1.3.1, Module 5.3.5.1, study VLA1553-301, Table 14.1.2.1, Module 5.3.1.2, study VLA1553-302, Table 14.1.2.1, and Module 5.3.5.1, study VLA1553-101, Table 3.2.1.1
Notes:
a. Studies VLA1553-301, VLA1553-302, and VLA1553-101
b. In studies VLA1553-302 and VLA1553-101, the upper age limit was set at 45 years of age, whereas in study VLA1553-301, no upper age limit was established.
Abbreviations: Max, maximum; Min, minimum; SD, standard deviation

8.2.3 Categorization of Adverse Events

All verbatim terms for reported AE in VLA1553-301 and -302 were coded using the Medical Dictionary for Regulatory Activities version 24.1 (MedDRA v24.1) and verbatim terms for reported AEs in Study 101 were coded using MedDRA v22.0, and the resulting SOC and PTs were used for tabulation of rates.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Among the three studies, VLA1553-301 was the only placebo-controlled, randomized clinical trial. Thus, comparisons of safety data between the pooled VLA1553 and placebo should be interpreted with extreme caution.

Furthermore, the open study design in terms of treatment in the non-randomized studies may have resulted in reporting bias. Study 101 had a different collection window for solicited adverse reactions (10 days for Studies 301 and 302 vs. 14 days for Study 101). Considering that the three studies had similar study populations, AE definitions (i.e., solicited AEs, unsolicited AEs, SAEs and AESIs), AE collection tools and approaches, and duration of follow-up, the pooling of the safety data from these three studies was deemed appropriate. Although Study 101 had a different collection window for solicited adverse reactions, the majority of solicited adverse reactions occurred within 10 days following vaccination. Only two solicited reactions were documented later than 10 days postvaccination in Study 101. Hence, the difference in the collection window for solicited reactions in Study 101 did not have a significant impact on rate of solicited reactions in the pooled data.

8.4 Safety Results

8.4.1 Deaths

A total of three deaths were reported: 2/3610 (0.1%) participants in the pooled VLA1553 group and 1/1033 (0.1%) participant in the placebo group. All deaths were reported in Study 301. Please refer to Section 6.1.12.3 for details.

8.4.2 Nonfatal Serious Adverse Events

Overall, 1.4% (52/3610) of participants in the pooled VLA1553 group and 0.8% (8/1033) of participants in the placebo group reported a total of 79 and 10 SAEs, respectively. Of the 52 VLA1553 recipients reporting SAEs, 46 were enrolled in Study 301, 5 were enrolled in Study 302, and 1 was enrolled in Study 101. Of these SAEs, 2 (0.1%) participants in the pooled

VLA1553 group and none in the placebo group had SAEs considered to be related to vaccination by the Applicant.

8.4.2.1 Summary of Non-Fatal Serious Adverse Events

A summary of any SAEs by SOC and PT in the pooled population is presented in Table 39. The results were similar to those obtained in Study 301. One SAE (atrial fibrillation) was reported in Study 101 but was not included in the Applicant's analysis, because the Applicant stated that they only included AEs occurring after a single vaccination. This case is included in Table 39 and described below:

- Participant 1553-(b) (6): A 40-year-old White male with a medical history of bradycardia, hypertension, COPD and asthma was enrolled in Study 101 and experienced an SAE of supraventricular extrasystole ectopy at Day 62 after the second dose of VLA1553. He was then hospitalized due to atrial fibrillation. He had a cardiac ablation in hospital and recovered after the procedure. He had another cardiac ablation using cauterization about 53 days after his first cardiac ablation. The SAE of supraventricular extrasystoles was assessed as not related to VLA1553 by the Applicant.

Reviewer comment: *This reviewer does not agree with the Applicant's causality assessment that the atrial fibrillation was not related to VLA1553. This reviewer considers the event was possibly related to VLA1553 because of the temporal association between the event and vaccination, and another case of atrial fibrillation with Participant* (b) (6) *in Study 301 was considered likely related to VLA1553 (see Section 6.2.12.4). In addition, atrial fibrillation has been reported to be associated with natural CHIKV infection (Cotella, 2021; Traverse, 2021).*

All the related SAEs were reported in VLA1553-301 and their narratives are provided in Section 6.1.12.4. No related SAE was reported from Study 302.

Table 39. Serious Adverse Events (≥0.1% participants in either the pooled or placebo group) by System Organ Class Preferred Term, Integrated Summary of Safety Population, Studies 301, 302, and 101

System Organ Class Preferred Term	Pooled VLA1553 N=3610 n (%)	Study 301 VLA1553 N=3082 n (%)	Study 302 VLA1553 N=408 n (%)	Study 101 VLA1553 N=120 n (%)	Study 301 Placebo N=1033 n (%)
Any Serious Adverse Event	53 (1.5)	46 (1.5)	5 (1.2)	2 (1.8)	8 (0.8)
Cardiac disorders	6 (0.2)	5 (0.2)	0 (0.0)	1 (0.8)	0 (0.0)
Atrial fibrillation	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.8)[a]	0 (0.0)
Gastrointestinal disorders	3 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Hepatobiliary disorders	2 (0.1)	1 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Infections and infestations	11 (0.3)	9 (0.3)	2 (0.5)	0 (0.0)	3 (0.3)
Appendicitis	3 (0.1)	1 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
COVID-19	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Kidney infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications	9 (0.2)	8 (0.3)	0 (0.0)	1 (0.8)	1 (0.1)
Ankle fracture	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Multiple injuries	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Road traffic accident	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Tibia fracture	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	Pooled VLA1553 N=3610 n (%)	Study 301 VLA1553 N=3082 n (%)	Study 302 VLA1553 N=408 n (%)	Study 101 VLA1553 N=120 n (%)	Study 301 Placebo N=1033 n (%)
Musculoskeletal and connective tissue disorders	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	4 (0.1)	4 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Cerebellar hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pregnancy, puerperium and perinatal conditions	5 (0.1)	3 (0.1)	2 (0.5)	0 (0.0)	0 (0.0)
Abortion spontaneous	4 (0.1)	2 (0.1)	2 (0.5)	0 (0.0)	0 (0.0)
Psychiatric disorders	7 (0.2)	7 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Depression	3 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Mental status changes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Suicidal ideation	3 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Renal and urinary disorders	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Notes: a, Atrial fibrillation occurred after re-vaccination
Abbreviations: N, Total number of participants, n, number of participants with events.

8.4.2.2 Subgroup Analyses of Non-Fatal Serious Adverse Events

Subgroup analyses of non-fatal SAEs are presented in Table 40. The rate of SAEs was low in the pooled ISS population and data in the respective subgroups need to be interpreted with caution when comparing the percentage of participants with SAEs between the subgroups. Additionally, given the heterogenous study designs of the pooled trials, comparisons are limited to within study groups. Conclusions cannot be made between study groups (i.e., VLA1553 vs. placebo) because only one of the pooled studies had a placebo group.

In the VLA1553 group, 1.2% (40/3264) of participants 18-64 years of age and 3.5% (12/346) of participants aged ≥65 years had SAEs. Similar trends in SAE rates were also observed in the placebo group (participants 18-64 years of age: 0.7%; participants ≥65 years of age: 1.7%). However, SAEs appeared more common in older adults compared to younger adults who received VLA1553 compared with the placebo group.

The percentage of participants with SAEs was comparable between males and females (male: 1.2% vs female: 1.7%).

In general, SAEs appeared to be comparable among the race subgroups [White (1.6%), Black/African American (1.1%), and Asian (1.4%) participants], and in the ethnicity subgroups [Hispanic/Latino ethnicity (0.7%) vs non-Hispanic/Latino ethnicity (1.6%)]. The numerical differences in SAE rate among the subgroups were likely due to the small number of SAEs reported in the studies (Table 40).

Table 40. Serious Adverse Events in Pooled Integrated Summary of Safety Population

Subgroup	VLA1553 (N=3610) n/N (%)	Placebo (N=1033) n/N (%)
Age	-	-
18 to 64 years	40/3264 (1.2)	6/916 (0.7)
≥65 years	12/346 (3.5)	2/117 (1.7)
Sex	-	-
Male	20/1691 (1.2)	5/464 (1.1)
Female	32/1919 (1.7)	3/569 (0.5)
Race	-	-
White	45/2867 (1.6)	8/853 (0.9)
Black or African American	6/530 (1.1)	0/122 (0.0)
Asian	1/74 (1.4)	0/17 (0.0)
American Indian or Alaska Native	0/33 (0.0)	0/5 (0.0)
Native Hawaiian or other Pacific Islander	0/14 (0.0)	0/5 (0.0)
Other	0/92 (0.0)	0/31 (0.0)
Ethnicity	-	-
Hispanic or Latino	4/608 (0.7)	1/177 (0.6)
Non-Hispanic or Latino	48/2961 (1.6)	7/840 (0.8)

Source: Table 6 (page 9), Module 1.11.3_IR Response File (to IR#23), STN125777/0.24
Notes: percentages are based on N
Abbreviations: n, number of participants with event

8.4.3 Study Dropouts/Discontinuations

Study participants who dropped out or discontinued from the studies and the corresponding reasons for withdrawal in the pooled ISS population are summarized in Table 41. The overall discontinuation rates were similar in the VLA1553 (11.9%) and placebo group (10.9%). The most common reasons for discontinuation were lost to follow-up and withdrawal by participant.

Table 41. Summary of Participant Disposition, Pooled Integrated Summary of Safety Population

Disposition	VLA1553 N=3610 n/N (%)	Placebo N=1033 n/N (%)
Randomized participants	3590/3610 (99.4)	1033/1033 (100)
Participants who completed the studies	3180/3610 (88.1)	920/1033 (89.1)
Participants who discontinued the studies	430/3610 (11.9)	113/1033 (10.9)
Reason for study discontinuation	-	-
Adverse Event	2/430 (0.5)	1/113 (0.9)
Death	2/430 (0.5)	1/113 (0.9)
Lost to follow-up	222/430 (51.6)	63/113 (55.8)
Other	18/430 (4.2)	5/113 (4.4)
Physician decision	8/430 (1.9)	2/113 (1.8)
Withdrawal by participant	158/430 (36.7)	41/113 (36.3)
Withdrawal of consent	20/430 (4.7)	0/113 (0.0)

Source: Table 1 (page 3), Module 1.11.3_IR Response File (to IR#23), STN125777/0.24
Abbreviations: n, number of participants

8.4.4 Common Adverse Events

8.4.4.1 Overview of Unsolicited Adverse Events

The incidence (≥1% of participants in any group) of unsolicited AEs up to 28 days following vaccination is presented in Table 42. The overall frequency of unsolicited AEs among VLA1553

vaccinated participants in the pooled population was 23.5% and the incidence among the placebo recipients was 13.4%, which was consistent with the results from the placebo-controlled VLA1553-301 Study (frequency of unsolicited AEs in VLA1553 and placebo was 22.3% and 13.4%, respectively). The unsolicited AEs that had a noticeably higher frequency in the VLA1553 group included chills, neutropenia, diarrhea, leukopenia, and lymphadenopathy.

Table 42. Incidence (≥1%) of Unsolicited Adverse Events up to 28 Days Following Vaccination, Integrated Summary of Safety Population, Studies 301, 302, and 101

System Organ Class Preferred Term	Pooled Studies VLA1553 N=3610 n (%)	Study 301 VLA1553 N=3082 n (%)	Study 302 VLA1553 N=408 n (%)	Study 101 VLA1553 N=120 n (%)	Study 301 Placebo N=1033 n (%)
Any AE	849 (23.5)	687 (22.3)	103 (25.2)	59 (49.2)	138 (13.4)
Blood and lymphatic system disorders	141 (3.9)	84 (2.7)	29 (7.1)	28 (23.3)	7 (0.7)
Cardiac disorders	6 (0.2)	5 (0.2)	1 (0.2)	0 (0.0)	1 (0.1)
Congenital, familial and genetic disorders	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ear and labyrinth disorders	13 (0.4)	13 (0.4)	0 (0.0)	0 (0.0)	2 (0.2)
Endocrine disorders	3 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	27 (0.7)	24 (0.8)	3 (0.7)	0 (0.0)	5 (0.5)
Gastrointestinal disorders	110 (3.0)	91 (3.0)	12 (2.9)	7 (5.8)	15 (1.5)
General disorders and administration site conditions	135 (3.7)	111 (3.6)	14 (3.4)	10 (8.3)	17 (1.6)
Hepatobiliary disorders	5 (0.1)	3 (0.1)	2 (0.5)	0 (0.0)	0 (0.0)
Immune system disorders	8 (0.2)	6 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)
Infections and infestations	124 (3.4)	116 (3.8)	6 (1.5)	2 (1.7)	27 (2.6)
Injury, poisoning and procedural complications	48 (1.3)	43 (1.4)	3 (0.7)	2 (1.7)	10 (1.0)
Investigations	76 (2.1)	55 (1.8)	15 (3.7)	6 (5.0)	7 (0.7)
Metabolism and nutrition disorders	33 (0.9)	25 (0.8)	2 (0.5)	6 (5.0)	5 (0.5)
Musculoskeletal and connective tissue disorders	168 (4.7)	143 (4.6)	18 (4.4)	7 (5.8)	37 (3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	97 (2.7)	84 (2.7)	9 (2.2)	4 (3.3)	22 (2.1)
Psychiatric disorders	27 (0.7)	23 (0.7)	3 (0.7)	1 (0.8)	4 (0.4)
Renal and urinary disorders	17 (0.5)	14 (0.5)	2 (0.5)	1 (0.8)	2 (0.2)
Reproductive system and breast disorders	8 (0.2)	6 (0.2)	2 (0.5)	0 (0.0)	2 (0.2)
Respiratory, thoracic and mediastinal disorders	74 (2.0)	58 (1.9)	12 (2.9)	4 (3.3)	8 (0.8)
Skin and subcutaneous tissue disorders	49 (1.4)	39 (1.3)	5 (1.2)	5 (4.2)	11 (1.1)
Vascular disorders	12 (0.3)	11 (0.4)	1 (0.2)	0 (0.0)	2 (0.2)

Source: OCS Analysis Studio, Safety Explorer.

8.4.4.2 Subgroup Analysis of Unsolicited Adverse Events

Subgroup analyses of unsolicited AEs up to Day 29 (i.e., 28 days postvaccination) by age, sex, race, and ethnicity are presented in Table 43.

In the VLA1553 group of the pooled ISS population, the percentage of participants with unsolicited AEs up to Day 29 was generally comparable when stratified by age, sex, race, and ethnicity. For the race subgroups, Black/African American participants had a numerically lower unsolicited AE rate (17.9%) compared with the other race subgroups (21.2% to 24.6%).

In the placebo group, the percentage of participants with unsolicited AEs was generally comparable among different race groups and ethnicity groups. The older age subgroup (≥65 years of age) and female subgroup appeared to have a higher percentage of participants experiencing an unsolicited AE.

Reviewer comment: *It would be expected that older age subgroup would have a higher percentage of participants reporting an AE, and women generally report more AEs in vaccine trials than males.*

Table 43. Frequency of Unsolicited Adverse Events to Day 29, by Demographic Subgroup, Pooled Integrated Summary of Safety Population

Subgroup	VLA1553 N=3610 n/N (%)	Placebo N=1033 n/N (%)
Age	-	-
18 to 64 years	779/3264 (23.9)	115/916 (12.6)
≥65 years	70/346 (20.2)	23/117 (19.7)
Sex	-	-
Male	385/1691 (22.8)	42/464 (9.1)
Female	464/1919 (24.2)	96/569 (16.9)
Race	-	-
White	704/2867 (24.6)	117/853 (13.7)
Black or African American	95/530 (17.9)	13/122 (10.7)
Asian	18/74 (24.3)	2/17 (11.8)
American Indian or Alaska Native	7/33 (21.2)	0/5 (0.0)
Native Hawaiian or other Pacific Islander	3/14 (21.4)	1/5 (20.0)
Other	22/92 (23.9)	5/31 (16.1)
Ethnicity	-	-
Hispanic or Latino	127/608 (20.9)	19/177 (10.7)
Non-Hispanic or Latino	715/2961 (24.1)	116/840 (13.8)

Source: Table 4 (page 7), Module 1.11.3_IR Response File (to IR#23), STN125777/0.24
Abbreviations: n, number of participants

8.4.4.3 Summary of Medically Attended Adverse Events

MAAEs up to 6 months occurred in 12.3% (445/3610) participants in the pooled VLA1553 group and 11.3% (117/1,033) participants in the placebo group. The frequency of MAAEs reported by ≥1% of participants in either group are presented by SOC and PT below:

- MAAEs reported by ≥1% of participants by SOC:
  - Infections and Infestations: 3.9% (141/3,610) in the pooled VLA1553 group and 4.2% (43/1,033) in the placebo group
  - Musculoskeletal and Connective Tissue Disorders: 2.2% (81/3,610) in the pooled VLA1553 group and 1.6% (17/1,033) in the placebo group

  - Injury, Poisoning and Procedural Complications: 1.9% (69/3,610) in the pooled VLA1553 group and 1.9% 20/1,033 in the placebo group
  - Nervous system disorders: 1.5% (53/3,610) in the pooled VLA1553 group and 0.9% (9/1,033) in the placebo group
  - Gastrointestinal disorders: 1.1% (41/3,610) in the pooled VLA1553 group and 0.8% (8/1,033) in the placebo group
  - General disorders and administration site conditions: 1.1% (40/3,610) in the pooled VLA1553 group and 0.4% (4/1,033) in the placebo group
- MAAEs reported by ≥1% of participants by PT:
  - Headache, 1.0% (36/3,610) in the VLA1553 group versus 0.3% (3/1,033) in the placebo group

8.4.6 Systemic Adverse Events

8.4.6.1 Overview of Solicited Systemic Adverse Reactions

An overview summary of the pooled solicited systemic reactions among the ISS population is presented in Table 44. As comparison, the incidence rates among the individual studies are also presented in the table. Please note that solicited adverse reactions were collected through Day 10 in Studies 301 and 302, and through Day 14 for Study 101, after a single vaccination.

The incidence of solicited systemic adverse reactions in the pooled VLA1553 group was 51.1% and 26.9% in the Study 301 placebo recipients. In general, the rates of solicited systemic reactions among the participants vaccinated with VLA1553 in the two Phase 3 trial as well as the high dose group (Group H) in the Study 101 were comparable (Table 54).

Most solicited systemic reactions were of mild or moderate severity. Severe solicited systemic reactions were reported by 2.3% of participants in the pooled VLA1553 group and by 0.1% of participants in the placebo group from Study 30.

Table 44. Solicited Systemic Adverse Reactions, Safety Population

Preferred Term	Pooled VLA1553 N=3610 n (%)	Study 301 VLA1553 N=3082 n (%)	Study 302 VLA1553 N=408 n (%)	Study 101 VLA1553 N=120 n (%)	Study 301 Placebo N=1033 n (%)
Any Solicited Systemic Reactions	1843 (51.1)	1547 (50.2)	233 (57.1)	63 (52.5)	278 (26.9)
Any Severe Solicited Systemic Reactions	82 (2.3)	64 (2.1)	11 (2.7)	7 (5.8)	1 (0.1)
Arthralgia	599 (16.6)	520 (16.9)	63 (15.4)	16 (13.3)	50 (4.8)
Severe Arthralgia	10 (0.3)	9 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Fatigue	1063 (29.4)	879 (28.5)	155 (38.0)	29 (24.2)	130 (12.6)
Severe Fatigue	7 (0.2)	5 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)
Fever	498 (13.8)	414 (13.4)	52 (12.7)	32 (26.7)	8 (0.8)
Severe Fever	60 (1.7)	44 (1.4)	9 (2.2)	7 (5.8)	0 (0.0)
Headache	1154 (32.0)	969 (31.4)	146 (35.8)	39 (32.5)	151 (14.6)
Severe Headache	5 (0.1)	3 (0.1)	1 (0.2)	0 (0.0)	1 (0.1)
Myalgia	855 (23.7)	735 (23.8)	96 (23.5)	24 (20.0)	76 (7.4)
Severe Myalgia	9 (0.2)	8 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)

Preferred Term	Pooled VLA1553 N=3610 n (%)	Study 301 VLA1553 N=3082 n (%)	Study 302 VLA1553 N=408 n (%)	Study 101 VLA1553 N=120 n (%)	Study 301 Placebo N=1033 n (%)
Nausea	411 (11.4)	345 (11.2)	53 (13.0)	13 (10.8)	58 (5.6)
Severe Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Rash	85 (2.4)	70 (2.3)	13 (3.2)	2 (1.7)	5 (0.5)
Vomiting	73 (2.0)	58 (1.9)	10 (2.5)	5 (4.2)	10 (1.0)
Severe Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Source: OCS Analysis Studio, Safety Explorer.

8.4.6.2 Subgroup Analyses of Solicited Systemic Adverse Reaction

In the VLA1553 group of the pooled ISS population, male and female participants had comparable rates for solicited systemic reactions (51.2% and 51.0%). A slightly lower rate for solicited systemic reactions was seen in participants ≥65 years of age (43.6%) compared to those 18-64 years of age (51.8%). A slightly lower rate of solicited systemic reactions was also seen in the Hispanic/Latino population (44.1%) compared to the Non-Hispanic/Latino population (52.5%) (Table 45).

Table 45. Solicited Systemic Adverse Reactions, Pooled Integrated Summary of Safety Population

Subgroup	VLA1553 N=3610 n/N (%)	Placebo N=1033 n/N (%)
Age	-	-
18 to 64 years	1692/3264 (51.8)	254/916 (27.7)
≥65 years	151/346 (43.6)	24/117 (20.5)
Sex	-	-
Male	865/1691 (51.2)	106/464 (22.8)
Female	978/1919 (51.0)	172/569 (30.2)
Race	-	-
White	1540/2867 (53.7)	228/853 (26.7)
Black or African American	199/530 (37.5)	32/122 (26.2)
Asian	38/74 (51.4)	5/17 (29.4)
American Indian or Alaska Native	14/33 (42.4)	3/5 (60.0)
Native Hawaiian or other Pacific Islander	6/14 (42.9)	1/5 (20.0)
Other	46/92 (50.0)	9/31 (29.0)
Ethnicity	-	-
Hispanic or Latino	268/608 (44.1)	32/177 (18.1)
Non-Hispanic or Latino	1556/2961 (52.5)	242/840 (28.8)

Source: Table 3 (page 6), Module 1.11.3_IR Response File (to IR#23), STN125777/0.24
Abbreviations: n, number of participants

8.4.7 Local Reactogenicity

8.4.7.1 Overview of Solicited Injection-Site Adverse Reactions

A summary of solicited IS reactions in the pooled population as well as the individual studies is presented in Table 46. The overall frequency of solicited IS reactions was 15.2% in the pooled VLA1553 group and 11.1% in the Study 301 placebo group. All solicited IS reactions were mild or moderate except for a single case of solicited IS pain in one participant (USUBJID:(b) (6) vaccinated with VLA1553 in Study 301.

Table 46. Summary of Solicited Injection Site Adverse Reactions, Safety Population

Preferred Term	Pooled VLA1553 N=3610 n (%)	Study 301 VLA1553 N=3082 n (%)	Study 302 VLA1553 N=408 n (%)	Study 101 VLA1553 N=120 n (%)	Study 301 Placebo N=1033 n (%)
Any Solicited Injection Site Reactions	549 (15.2)	463 (15.0)	79 (19.4)	7 (5.8)	115 (11.1)
Any Severe Solicited Injection Site Reactions	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema/redness	59 (1.6)	46 (1.5)	11 (2.7)	2 (1.7)	15 (1.5)
Induration	51 (1.4)	44 (1.4)	7 (1.7)	0 (0.0)	8 (0.8)
Pain	219 (6.1)	191 (6.2)	26 (6.4)	2 (1.7)	38 (3.7)
Severe Pain	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	25 (0.7)	21 (0.7)	4 (1.0)	0 (0.0)	8 (0.8)
Tenderness	390 (10.8)	328 (10.6)	58 (14.2)	4 (3.3)	84 (8.1)

Source: OCS Analysis Studio, Safety Explorer.

8.4.7.2 Subgroup Analyses of Solicited Injection-Site Reactions

Subgroup analyses of solicited local reactions are presented in below. In the VLA1553 group, a slightly lower rate for solicited local reactions was seen in participants ≥65 years of age (10.7%) compared to those 18-64 years of age (15.7%). In the VLA1553 group, a slightly lower rate for solicited local reactions was seen in male participants (12.7%) compared to female participants (17.4%). Variations in incidence rates among the race groups were larger likely due to the small numbers of participants in some race groups. Black/African American and Hispanic or Latino participants both reported lower rates of solicited local AEs (for both, 11.3%) (Table 47).

Table 47. Solicited Local Reactions, Pooled Integrated Summary of Safety Population

Subgroup	VLA1553 N=3610 n/N (%)	Placebo N=1033 n/N (%)
Age	-	-
18 to 64 years	512/3264 (15.7)	105/916 (11.5)
≥65 years	37/346 (10.7)	10/117 (8.5)
Sex	-	-
Male	215/1691 (12.7)	49/464 (10.6)
Female	334/1919 (17.4)	66/569 (11.6)
Race	-	-
White	448/2867 (15.6)	98/853 (11.5)
Black or African American	60/530 (11.3)	8/122 (6.6)
Asian	19/74 (25.7)	1/17 (5.9)
American Indian or Alaska Native	3/33 (9.1)	2/5 (40.0)
Native Hawaiian or other Pacific Islander	2/14 (14.3)	0/5 (0.0)
Other	17/92 (18.5)	6/31 (19.4)
Ethnicity	-	-
Hispanic or Latino	69/608 (11.3)	18/177 (10.2)
Non-Hispanic or Latino	478/2961 (16.1)	96/840 (11.4)

Source: Table 2 (page 5), Module 1.11.3_IR Response File (to IR#23), STN125777/0.24
Abbreviations: n, number of participants

8.4.8 Adverse Events of Special Interest

8.4.8.1 Summary of Adverse Events of Special Interest

Frequency, Severity, Seriousness, and Duration of Events of CHIK-like Illness
AESIs reported among VLA1553 recipients are pooled from the safety datasets of the three studies. Summary of the CHIK-like symptoms by SOC and PT in the pooled data as well as in individual studies is presented in . SOCs, PTs, or severe PTs without reported AEs in any individual studies were omitted from the table.

Table 48. CHIK-like symptoms by System Organ Class, Preferred Term, and Severity, Integrated Summary of Safety Population, Studies 301, 302, and 101

CHIK-like symptoms	Pooled VLA1553 N=3610	Study 301 VLA1553 N=3082	Study 302 VLA1553 N=408	Study 101 VLA1553 N=120	Study 301 Placebo N=1033
Any CHIK-like symptoms, %	12.1	11.7	11.3	24.2	0.6
Any severe CHIK-like symptoms, %	1.8	1.5	2.5	6.7	0.0
General disorders and administration site conditions, n (%)	436 (12.1)	361 (11.7)	46 (11.3)	29 (24.2)	6 (0.6)
Pyrexia, n (%)	436 (12.1)	361 (11.7)	46 (11.3)	29 (24.2)	6 (0.6)
Severe pyrexia, n (%)	54 (1.5)	39 (1.3)	8 (2.0)	7 (5.8) 7	0 (0.0)
Fatigue, n (%)	321 (8.9)	264 (8.6)	39 (9.6)	18 (15.0)	5 (0.5)
Severe fatigue, n (%)	4 (0.1)	2 (0.1)	2 (0.5)	0 (0.0)	0 (0.0)
Chills, n (%)	37 (1.0)	29 (0.9)	3 (0.7)	5 (4.2)	0 (0.0)
Pain, n (%)	6 (0.2)	4 (0.1)	0 (0.0)	2 (1.7)	0 (0.0)
Asthenia, n (%)	2 (0.1)	1 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Oedema peripheral, n (%)	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Chest pain, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Feeling abnormal, n (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza like illness, n (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders, n (%)	342 (9.5)	282 (9.1)	40 (9.8)	20 (16.7)	5 (0.5)
Headache, n (%)	340 (9.4)	280 (9.1)	40 (9.8)	20 (16.7)	5 (0.5)
Severe headache, n (%)	3 (0.1)	1 (0.0)	1 (0.2)	1 (0.8)	0 (0.0)
Dizziness, n (%)	9 (0.2)	6 (0.2)	2 (0.5)	1 (0.8)	0 (0.0)
Paresthesia, n (%)	4 (0.1)	3 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Syncope, n (%)	2 (0.1)	1 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Ataxia, n (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoesthesia, n (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral, n (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders, n (%)	299 (8.3)	249 (8.1)	32 (7.8)	18 (15.0)	2 (0.2)
Myalgia, n (%)	258 (7.1)	215 (7.0)	29 (7.1)	14 (11.7)	1 (0.1)
Severe myalgia, n (%)	4 (0.1)	3 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Arthralgia, n (%)	186 (5.2)	159 (5.2)	18 (4.4)	9 (7.5)	2 (0.2)
Severe arthralgia, n (%)	5 (0.1)	4 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)

CHIK-like symptoms	Pooled VLA1553 N=3610	Study 301 VLA1553 N=3082	Study 302 VLA1553 N=408	Study 101 VLA1553 N=120	Study 301 Placebo N=1033
Back pain, n (%)	16 (0.4)	13 (0.4)	0 (0.0)	3 (2.5)	0 (0.0)
Severe back pain, n (%)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Skin and subcutaneous tissue disorders, n (%)	31 (0.9)	25 (0.8)	3 (0.7)	3 (2.5)	0 (0.0)
Rash, n (%)	26 (0.7)	22 (0.7)	3 (0.7)	1 (0.8)	0 (0.0)
Hyperhidrosis, n (%)	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)
Cold sweat, n (%)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Rash erythematous, n (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders n (%)	13 (0.4)	9 (0.3)	2 (0.5)	2 (1.7)	0 (0.0)
Lymphadenopathy, n (%)	11 (0.3)	9 (0.3)	0 (0.0)	2 (1.7)	0 (0.0)
Lymph node pain, n (%)	1 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Lymphadenitis, n (%)	1 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac disorders n (%)	2 (0.1)	1 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Atrial fibrillation n (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe atrial fibrillation n (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations n (%)	1 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Source: Table 1 (page 3-5), Module 1.11.3, STN125777/0/49
Notes: Percentages are based on N
Abbreviations: n, number of participants with event; AESI, adverse events of special interest

Vaccine Viremia Results

For Study VLA1553-101, all participants were tested for vaccine viremia at 3, 7 and 14 days after the first vaccination. The results are reviewed and presented in the Appendix. Among the 15 participants with severe CHIK-like signs and symptoms, 12 out the 15 participants (80%) had viremia at 3 days postvaccination, 4 of the 15 participants (26.7%) had quantifiable or detectable viremia at 7 days postvaccination.

Vaccine viremia was tested at Day 8 among participants with severe CHIK-like symptoms in Studies VLA1553-301 and VLA1553-302. The viremia results are presented below:

- VLA1553-301: 9 out of the 61 participants (14.8%) with severe AEs were tested viremia at Day 8, 2 of the 9 participants had viremia >1 X 10^5 GCE/mL.
- VLA1553-302: 5 of the 11 participants with severe AE had viremia, 3 of them had viremia ranged from 4,739 to 132,129 GCE/mL and 2 of them had detectable but not quantifiable viremia at Day 8.

In total, 18 out 87 participants (20.7%) with severe AEs among the three clinical trials had viremia at 7 days postvaccination.

Evidence for causality

There is a high likelihood that these AESIs of CHIK-like illness were related to vaccination, given their temporal relationship, symptomatology consistent with known manifestations of CHIK, and the viremia associated with CHIK-like illness Data from the clinical development program associating viremia with the events of CHIK-like illness that supports this causal relationship include:

- In the Phase 1 study (VLA1553-101), 30 participants received the medium dose (3.2 x 10^4 $TCID_{50}$/dose), which is similar to the to-be-marketed dose of IXCHIQ, and vaccine viremia was present in 90% and 17% of participants at Days 3 and 7, respectively.

- In the ISS of safety population (VLA1553-101, VLA1553-301, VLA1553-302), 87 VLA1553 recipients who experienced a severe AESI were assessed for viremia on Day 8, 18 (20.7%) of whom were viremic.
- Participant (b) (6) experienced high fever, myalgia, high level of BNP, increased troponin, high level of vaccine viremia (on Day 8), and serious events of atrial fibrillation and hypovolemic hyponatremia around 10 days postvaccination (additional details in Section 6.1.12.4). We consider the hypovolemic hyponatremia was caused by high-level BNP. In the face of high levels of vaccine viremia, this participant manifested almost all the atypical features of cardiac events following natural CHIKV infection as reported in the literature (Traverse, 2021; Cotella, 2021; Alvarez, 2017). This case was deemed serious by FDA as well as Valneva and was considered related to VLA1553 by FDA.

Reviewer comments**:** *This causal relationship, in association with severe and serious events, is sufficient to justify a warning in Section 5 of product labeling for these events. Per the 2011 FDA Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format | FDA, the WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.*

8.4.8.2 Standardized MedDRA Query Analyses of Arthritis, Rash, and Cardiac Arrythmias and Cardiomyopathy

Arthritis and Rash (SMQ)
Due to the observation of an imbalance in events of arthralgia and rash in the VLA1553 group compared to placebo recipients, the broad SMQs of *Arthritis* and *Rash* (SMQ) were used to query the safety database. The results of the search did not show noticeable difference between the VLA1553 and placebo groups in the frequency of reported PTs, with the exception of the PTs of A*rthralgia* and *Rash*. The percentages of participants with arthralgia and rash in VLA1553 group were 17.8% and 3.4%, respectively, while the percentage of participants with arthralgia and rash in the placebo group were 6.1% and 1.7%, respectively.

Cardiac Arrythmias and Cardiomyopathy (SMQ)
There was an imbalance in cardiac-related SAEs in the pivotal clinical trial and cardiac toxicity has been reported following natural CHIKV infection. To ensure identification of all potential cases of cardiac manifestations, additional cardiac-specific safety analyses were conducted using the broad SMQs of *Cardiac arrythmia* and *Cardiomyopathy*. No additional cardiac concern is identified from the SMQs.

8.4.8.3 Subgroup Analysis of Adverse Events of Special Interest

Subgroup analyses of AESIs by age, sex, race, and ethnicity in the Safety Population are presented in Table 49.

In the pooled VLA1553 group, the rates of AESIs or CHIK-like illness, were comparable between the younger participants 18-64 years of age and the older participants ≥65 years of age (12.2% and 10.7%, respectively) and ethnicity subgroups. Female participants had slightly lower rates of CHIK-like illness compared to males (9.5% and 15.0%, respectively). Differences

by race can only be interpreted in a meaningful way for Black/African American, White, and Hispanic or Latino Ethnicity; all other subgroups are too small.

In conclusion, there are numerical differences in the rates of CHIK-like illness among some subgroups, however, it is unknown if these differences are clinically meaningful, due to small numbers of participants in some subgroups.

Table 49. CHIK-like Illness, Integrated Summary of Safety Population, Studies 301, 302, and 101

Subgroups	Pooled VLA1553[b] N=3610 n/N[a] (%)	Study 301 VLA1553 N=3082 n/N[a] (%)	Study 302 VLA1553 N=408 n/N[a] (%)	Study 101 VLA1553 N=120 n/N[a] (%)	Study 301 Placebo N=1033 n/N[a] (%)
Age	-	-	-	-	-
18-64 years	399/3264 (12.2)	324/2736 (11.8)	46/408 (11.3)	29/120 (24.2)	6/916 (0.7)
≥65 years	37/346 (10.7)	37/346 (10.7)	0/0 (NC)	0/0 (NC)	0/117 (0.0)
Sex	-	-	-	-	-
Male	254/1691 (15.0)	196/1400 (14.0)	29/185 (15.7)	29/106 (27.4)	1/464 (0.2)
Female	182/1919 (9.5)	165/1682 (9.8)	17/223 (7.6)	0/14 (0.0)	5/569 (0.9)
Race	-	-	-	-	-
White	362/2867 (12.6)	303/2456 (12.3)	38/315 (12.1)	21/96 (21.9)	4/853 (0.5)
Black or African American	48/530 (9.1)	40/451 (8.9)	3/62 (4.8)	5/17 (29.4)	2/122 (1.6)
Asian	11/74 (14.9)	5/51 (9.8)	4/18 (22.2)	2/5 (40.0)	0/17 (0.0)
American Indian or Alaska Native	3/33 (9.1)	2/27 (7.4)	0/5 (0.0)	1/1 (100)	0/5 (0.0)
Native Hawaiian or Other Pacific Islander	1/14 (7.1)	1/13 (7.7)	0/1 (0.0)	0/0 (NC)	0/5 (0.0)
Other	11/92 (12.0)	10/84 (11.9)	1/7 (14.3)	0/1 (0.0)	0/31 (0.0)
Ethnicity	-	-	-	-	-
Hispanic or Latino	67/608 (11.0)	58/545 (10.6)	8/55 (14.5)	1/8 (12.5)	0/177 (0.0)
Non-Hispanic or Latino	365/2961 (12.3)	300/2498 (12.0)	37/351 (10.5)	28/112 (25.0)	6/840 (0.7)

Source: Table 6 (page 11), Module 1.11.3, STN125777/0/49
Notes: a. Percentages are based on subgroup N;
b. VLA1553 Pooled group is all three studies combined
Abbreviations: n, number of participants with event; N, total number of participants; NC, not calculable

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

In the Phase 1 trial (Study 101), participants who received the high-dose vaccine experienced significantly higher solicited adverse reactions in the 14 days (67.8.0%, 35.5% and 40.0% in high dose, low dose, and medium dose groups, respectively) and unsolicited AEs in the 28 days (78.0%, 58.1% and 46.7% in high dose, low dose, and medium dose groups, respectively) after a single vaccination. Participants in the high dose groups tended to have more severe solicited reactions and unsolicited AEs compared to those in low dose and medium dose groups.

Solicited IS reactions were rare and solicited systemic reactions were less common after re-vaccination compared with the first dose vaccination. Please refer to the summary of Study 101 in Appendix A.

8.5.2 Person-to-Person Transmission, Shedding

No person-to-person transmission of vaccine virus was reported. One participant was reported to shed the vaccine virus in urine in Study 101, and no shedding study was conducted in the Phase 3 trials.

8.6 Safety Conclusions

Safety of VLA1553 was assessed in the U.S. in 3,610 healthy participants ≥18 years of age who received at least one dose of VLA1553 at 3.2 x 10^3 to 3.2 x 10^5 $TCID_{50}$ in three studies under the vaccine development program. The three studies included a dose ranging (3.2 x 10^3, 3.2 x 10^4 and 3.2 x 10^5 $TCID_{50}$) Phase 1 trial with 120 participants (Study 101), a pivotal safety and immunogenicity Phase 3 trial with 3,082 participants (VLA1553-301) and a lot-consistency Phase 3 trial with 408 participants (Study 302). The Applicant-proposed dose regimen for market approval was a single dose of VLA1553 at 1 x 10^4 $TCID_{50}$ which was assessed in the two Phase 3 trials. Safety issues associated with VLA1553 include CHIKV-like illness, such as arthritis/arthralgia and atrial fibrillation. However, in general, the safety profile of the Applicant-proposed dose regimen of VLA1553 is considered favorable in the setting of CHIKV outbreaks.

8.6.1 Serious Adverse Events

There were total of three deaths reported among the three studies, including two in the pooled VLA1553 group (one death was due to coronary artery disease and the other due to COVID-19) and one death in the placebo group (due to anoxic brain injury). All deaths were reported in Study 301. None of the three deaths were considered to be related to treatment.

Overall, non-fatal SAEs among VLA1553 recipients were similar in the pooled analyses and individual studies. For the placebo-controlled Study 301, 1.5% of participants in the VLA1553 group and 0.8% of participants in the placebo group reported non-fatal SAEs. Two (0.1%) participants in the pooled VLA1553 group had SAEs considered to be related to vaccination. The 2 related SAEs, considered to be events of CHIK-like illness, included an event of severe myalgia, and events of atrial fibrillation with hypovolemic hyponatremia, both leading to hospitalization.

8.6.2 Unsolicited Adverse Events

An imbalance in the overall frequency of unsolicited AEs was observed between the treatment groups. The overall frequency of unsolicited AEs occurring up to 28 days in the pooled VLA1553 group was 23.5% compared to 13.4% in the placebo group. The most common unsolicited AEs following vaccination with VLA1553 were chills (2.0%), diarrhea (1.4%), and lymphadenopathy (1.1%).

8.6.3 Solicited Adverse Reactions

Single vaccination with VLA1553 was associated with a significantly higher overall frequency of solicited systemic adverse reactions compared with placebo (51.1% after VLA1553 versus 26.9% after placebo). Most of the solicited systemic reactions were mild to moderate, and a significantly higher frequency of severe systemic reactions were reported in VLA1553 group (2.3%) compared with the placebo group (0.1%).

The most common systemic reactions following vaccination with VLA1553 included headache (32.0% of participants), fatigue (29.4% of participants), myalgia (23.7% of participants), arthralgia (16.6% of participants), fever (13.8% of participants), nausea (11.4% of participants) and rash (2.4% of participants). The percentage of individuals with systemic reactions among VLA1553 recipients was higher than that among the placebo recipients.

Solicited IS reactions occurred at an overall higher percentage in the pooled VLA1553 group (15.2%) vs the placebo group (11.1%). The most common injection site reactions among VLA1553 recipients were tenderness (10.8%) followed by pain (6.1%). All the injection site reactions were mild or moderate, except for one VLA1553 recipient who experienced severe pain following vaccination.

8.6.4 AESIs

The percentage of VLA1553 recipients with CHIK-like illness was similarly in the pooled analyses and individual studies. In the pooled analyses, 436 participants (12.1%) experienced CHIK-like illness, and of them, 65 participants (1.8%) had severe CHIK-like illness. Fourteen VLA1553 recipients had prolonged (duration at least 30 days) chikungunya-like illness (median duration 94 days, range 30 days to at least 6 months). Prolonged fatigue, headache and myalgia were each reported by 3 participants. Prolonged arthralgia was reported by 5 participants, including a 46-year-old male who reported severe arthralgia and back pain that lasted for at least 51 days postvaccination, and a 50-year-old female who reported polyarthralgia and nodular swelling of joints in fingers and foot that lasted for at least 6 months postvaccination.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Eighteen pregnancies were recorded for female participants, including 15 pregnancies in Study 301 (13 in the VLA1553 group and two in the placebo group) and three pregnancies in Study 302. There was no report of pregnancy in Study 101.

The pregnancy outcomes for the placebo recipients included delivery of a full term healthy baby and a pregnancy outcome lost to follow-up.

Pregnancy outcomes for the 16 female VLA1553 recipients are described below:

- 10 (62.5%) full term healthy babies were born. Of them, 8 babies and mothers had their 3-month safety follow-up.
- One (6.2%) participant was lost to follow-up.
- Five participants (31.3%) reported spontaneous abortion, which were reported as SAEs.
    - One fetal death due to Turner syndrome 45 X (genetic disorder).
    - One female participant had a BMI of 60 kg/m^2 and a history of two previous miscarriages.
    - Two spontaneous abortions had no identified other reasons. One spontaneous abortion occurred in a participant who became pregnant about 105 days postvaccination and experienced spontaneous abortion at 8 weeks of gestation.

The Applicant stated that the DSMB reviewed all the events of spontaneous abortion in detail and could not identify any safety concerns.

Reviewer comment: *When calculating the percentage of participants with spontaneous abortions during the studies, the Applicant restricted the spontaneous abortions to the first 3 months postvaccination, which this reviewer found acceptable. Therefore, Participant* (b) (6) *with a spontaneous abortion at 177 days postvaccination (about 8 weeks of gestation) was excluded. Thus, the percentage of pregnant participants with spontaneous abortions per the Applicant was 25%.*

A summary of spontaneous abortions is presented in Table 50.

Table 50. Participants With Spontaneous Abortion or Intrauterine Fetal Death, Integrated Summary of Safety Population

Participant ID	Age at Pregnancy (Years)	Time of Onset Spontaneous Abortion (Days Postvaccination)	Estimated Gestational Age (Weeks)	Potential Confounding Factors
(b) (6)	36	59	10 to 14	Not identified
(b) (6)	33	99	5 to 6	BMI at screening 60.0 kg/m^2 and two previous spontaneous abortions
(b) (6)	28	177	10	BMI at screening 35 kg/m^2
(b) (6)	23	55	8	Not identified. Blighted ovum (i.e., anembryonic pregnancy)
(b) (6)	22	101	11	Turner Syndrome, intrauterine fetal death.

Source: Derived from the Applicant's responses to CBER IR #18, Module 1.11.3, STN125777/0.19.
Abbreviations: ID, identification; BMI, body mass index

Reviewer comment: *The observed rate of spontaneous abortions during the first 3 months postvaccination) was 25.0%, which is higher than typically seen in the general population (approximately 11% to 16%) (Lang, 2012; Rossen, 2018; Magnus, 2019) or in women vaccinated with mRNA COVID-19 vaccine (14.1%) (Zauche, 2021).*

Previous studies suggest that CHIKV infection is associated with adverse pregnancy outcomes (Gupta, 2019; Ali, 2022). During a CHIKV epidemic in 2018 in Kassala, Sudan, 93 pregnant women with confirmed CHIK infection were enrolled in a maternal and perinatal outcomes study (Ali, 2022). Of the 93 pregnant women, 58 (62.4%) delivered a live infant at term and 18 (19.4%), 13 (13.9%), and 4 (4.3%) women experienced miscarriage, preterm birth, and stillbirth, respectively.

In a prospective study conducted during an outbreak of CHIKV, vertical transmission of wild-type CHIKV to neonates from infected pregnant individuals was assessed. Among pregnant individuals infected prepartum (N=22) or intrapartum (N=39) (symptomatic between day -7 and day -3, or day -2 and day 2 around delivery, respectively and concomitant positive serum CHIKV RT-PCR or IgM serology when PCR not available) vertical transmission occurred in 19, all with an intrapartum infection (vertical transmission rate of 48.7% for intrapartum infections). Severe CHIKV disease was reported in 52.6% (10/19) of these infected neonates. Among 678 pregnant individuals infected antepartum (symptomatic between conception and the week preceding labor and positive serum CHIKV RT-PCR or IgM serology) fetal death attributed to CHIKV occurred in three (0.4%). In these three cases, onset of CHIKV symptoms in the pregnant individual ranged from approximately 12 weeks to 15 weeks gestation and the fetal death occurred approximately two weeks later. For these fetal deaths, amniotic fluid before fetal

death was CHIKV RT-PCR positive. CHIKV RNA was detected in the placenta and in the fetal brain for two (Gérardin, 2008).

Although the small sample size for pregnancy outcomes in this application precludes a clinically meaningful conclusion whether the vaccine would impact pregnancy outcome adversely, vertical transmission of wild-type CHIKV to neonates from pregnant individuals with viremia at delivery is common and can cause severe, potentially fatal CHIKV disease in neonates as described above. Decisions to administer VLA1553 during pregnancy should take into consideration the individual's risk of exposure to wild-type CHIKV, gestational age, and risks to the fetus or neonate from vertical transmission of wild-type CHIKV. A postmarketing commitment study is warranted to further address the concern of potential adverse pregnancy outcomes.

9.1.2 Use During Lactation

No data available.

9.1.3 Pediatric Use and PREA Considerations

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups. The Applicant requested a deferral for the pediatric assessment for children <17 years of age. CBER agreed to grant the deferral request, and the application included an agreed iPSP.

9.1.4 Immunocompromised Patient

The safety and effectiveness of VLA1553 have not been evaluated in immunocompromised patient populations.

9.1.5 Geriatric Use

The studies to support this application evaluated the safety and immunogenicity of VLA1553 in 346 participants ≥65 years of age. The safety profile of VLA1553 in this population was similar to the population 18 to 64 years of age in terms of percentages of participants with solicited AE and unsolicited AEs. However, the percentage of participants with SAEs was numerically higher in participants ≥65 years of age (3.5% of participants) than in the younger population 18 through 54 years of age (1.2% of participants). Please refer to Section 8.4.2 for details. The anti-CHIKV neutralizing antibody titers and antibody response kinetics were similar to those among the younger populations. Please refer to Section 6.1 for details.

10. CONCLUSIONS

10.1 Vaccine Effectiveness

The pivotal immunogenicity Study 301 demonstrated that 98.9% (95% CI: 96.7, 99.8) of participants achieved an anti-CHIKV neutralizing antibody titer ≥150 at Day 28 following a single dose vaccination with VLA1553, which is considered reasonably likely to predict clinical benefit. The seroresponse rate remained at 96.3% at Day 180 (6 months) postvaccination. Results of integrated analyses of pooled immunogenicity data from Studies 301 and 302 were similar to results from Study 301.

In conclusion, immunogenicity data from Studies 301 and 302 indicate that a single intramuscular injection of VLA1553 is likely effective in preventing disease caused by CHIKV

based on the surrogate endpoint of seroresponse rates; however, a postmarketing confirmatory study will be needed to confirm clinical benefit.

10.2 Safety

Safety of VLA1553 was assessed in the U.S. in 3,610 healthy participants ≥18 years of age who received at least one dose of VLA1553 in three clinical studies under the vaccine development program. The safety data of VLA1553 demonstrated:

- Increased frequency and severity of solicited systemic adverse reactions with slightly higher solicited IS adverse reactions
- Increased frequency of unsolicited adverse events
- Increased frequency of leukopenia, lymphopenia, and neutropenia
- Slightly higher rate of SAEs, mainly driven by cardiac related events
- Increased rate of CHIK-like illness: Most of them were fever and arthralgia, 14 VLA1553 recipients had prolonged CHIK-like symptoms lasting up to at least 6 months, and 2 participants experienced serious adverse events of sever myalgia and atrial fibrillation with hypovolemic hyponatremia, respectively, that led to hospitalization.

As described above, the frequency, severity, and duration of CHIK-like illness necessitates risk mitigation, including a warning statement in Section 5 of the PI, restriction of the indication those at increased risk of exposure to CHIKV, and postmarketing safety assessments. Overall, the safety profile of VLA1553 is considered favorable in the setting of CHIKV outbreaks.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk Benefit Considerations

Table 51. Risk Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CHIKV often causes sudden large outbreaks affecting approximately 33 to 75% of the population in areas where the virus is circulating. • CHIK manifests as a highly heterogenous spectrum of symptoms and severity of disease. • Up to 97% of infected individuals become symptomatic and up to 70% experience debilitating polyarthritis or polyarthralgia. • 1.6 to 57% infected individuals may develop recurrent arthralgia lasting for months to years after infection. • CHIK affects all age groups and both sexes in areas of ongoing transmission. • Uncertainties include an incomplete understanding of mechanisms of pathogenesis of chronic arthralgia and risk for severe disease (e.g., virulence of different CHIKV lineages, environmental factors, pre-existing medical conditions).	• While the mortality rate due to CHIKV infection is low (<0.1%), the frequency and severity of morbidity is high (30% to 70%). • Acute arthralgia caused by CHIKV infection may be incapacitating. • Chronic disease usually manifests as disabling polyarthritis or polyarthralgia, significantly affecting day-to-day functioning. • CHIK is generally considered a serious medical condition.
Unmet Medical Need	• No vaccine is available to prevent CHIK or CHIKV infection. • Prevention is limited to mosquito control and restricting exposure to vector mosquitos such as wearing long sleeves and pants, and use of insect repellants. • Treatment is mainly supportive, such as bed rest and symptomatic relief by using analgesics and antipyretics. • Uncertainties: In some reports, CHIK did not appear to be a serious condition. It is unknown whether disease severity is associated with specific CHIKV lineages.	• An unmet medical need exists for effective prevention of CHIK (and CHIKV infection).

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• Vaccine efficacy study to demonstrate disease prevention has not yet been assessed due to unpredictable CHIKV outbreaks. • An anti-CHIKV neutralizing antibody titer ≥1:150, estimated based on prevention of CHIKV viremia in a passive transfer challenge NHP model, was used as a surrogate endpoint that is reasonably likely to predict a clinical benefit. • The Phase 3 immunogenicity trial demonstrated that over 98% participants achieved an anti-CHIKV neutralizing antibody titer ≥150 at 28 days after a single dose of VLA1553. • Uncertainties: The surrogate endpoint was estimated based on its prevention of CHIKV viremia but not disease in the NHP model. Other nonclinical studies showed that anti-CHIKV neutralizing antibodies prevented CHIKV viremia but not CHIKV in joints and had insignificant effect on joint pathology.	• VLA1553 is reasonably likely to prevent CHIK • Uncertainties need to be addressed in adequate and well-controlled postmarketing confirmatory studies.
Risk & Risk Management	• The most substantial and common risks of vaccination with VLA1553 are headache, fatigue, myalgia, arthralgia, fever, and injection site pain. Most of the reactions are mild to moderate and resolve in a few days without sequelae. • Four hundred and thirty-six participants (12.1%) experienced CHIK-like illnesses, most of them were mild to moderate and self-limited, and 65 participants (1.8%) experienced severe CHIK-like illness with a mean duration of 8.6 days. • Fourteen participants experienced prolonged myalgia • Two participants were hospitalized: one due to severe myalgia; and another due to atrial fibrillation with hypovolemic hyponatremia • Serious cardiac events were disproportionally reported in VLA1553 recipients • More than expected pregnant women experienced spontaneous abortions. However, the number of pregnancies were limited.	• VLA1553 is reactogenic and the reactogenicity is generally similar to other live-attenuated vaccines. • VLA1553 may cause severe CHIK-like illness including prolonged arthralgia and atypical presentation of CHIK such as cardiac events. • Cardiac disorders such as arrhythmias and myocarditis may be a rare but serious vaccine associated AE. • The safety of VLA1553 in immune-compromised population was not assessed. • Risk mitigation strategies for VLA1553 include communication of risks and benefits by adding information on the risk of CHIK-like adverse reactions in Section 5 of the PI (Warnings and Precautions), an indication for individuals at increased risk of CHIKV infection, directed counseling prior to vaccination according to individual risks and benefits, and a pharmacovigilance plan. • The results from postmarketing confirmatory studies and postmarketing commitment studies will also be critical to updating benefit-risk assessments.

11.2 Risk-Benefit Summary and Assessment

Infection by CHIKV typically results in mild and self-limiting disease in infected humans, characterized by fever, skin rash, myalgia, and arthralgia that can last weeks to months. Although fatal CHIKV infection is rare, severe arthralgia and chronic polyarthralgia are the hallmark presentations. Serious atypical presentations of CHIK including cardiac- and neurologic-related events occur rarely. In addition, manifestations of CHIK are highly heterogeneous in terms of the frequency, severity, and spectrum of signs and clinical symptoms. Reported rated of asymptomatic infections vary greatly from 3% to 82% (Bustos, 2019; Yoon, 2015) and are believed to be lineage dependent, with more asymptomatic infections appearing to be associated with the Asian lineage than ECSA lineage (Bustos, 2019).

Similarly, the prevalence of patients with severe arthralgia or chronic arthralgia has been reported to range from 4.1% to 78.6% (Khongwichit, 2021), while other studies did not identify any severe cases following natural CHIKV infection (Yoon, 2015; Yoon, 2020; Langsjoen, 2016). Interestingly, Gordon et al. reported that even two successive outbreaks in Nicaragua during 2014 to 2016 demonstrated differences in transmission and disease severity (Gordon, 2018). The reasons for this variability remain unclear. Some investigators postulated that the variability may be due to persistent virus infection or virus RNA or proteins in joint tissues, immune response mediated tissue injury, exacerbation of a pre-existing joint condition, genetic susceptibility, and differential virulence of CHIKV lineages (Hawman, 2013; Burt, 2014; Vairo, 2019; Langsjoen 2016).

The Phase 3 immunogenicity trial demonstrated that over 98% participants achieved an anti-CHIKV neutralizing antibody titer ≥150 at 28 days after a single dose of VLA1553 and the anti-CHIKV neutralizing antibody response persisted for at least 6 months after the single dose vaccination, indicating that vaccination with VLA1553 is reasonably likely to prevent disease caused by CHIKV infection. Some of the residual uncertainty of relying upon anti-CHIKV neutralizing antibody responses as a surrogate reasonably likely to predict clinical benefit come from nonclinical studies in a NHP model (Pal, 2014). reported that a single dose of passively transferred anti-CHIKV neutralizing antibodies completely prevented CHIKV viremia but did not prevent high CHIKV titers (similar to control group) in joints, muscles, and lymph tissues. The PMR confirmatory studies are designed to address this uncertainty.

Risks of vaccination with VLA1553 include local and systemic reactogenicity. An additional risk includes CHIK-like adverse reactions (12.1% VLA1553 recipients developed CHIK-like illness). Severe, serious, and prolonged CHIK-like illness was reported following vaccination with VLA1553, including chronic disease and atypical presentations such as cardiac events. In addition, the studies demonstrated disproportionately higher incidences of spontaneous abortion in VLA1553 recipients compared with participants in the placebo group. Because the available evidence is insufficient to establish or exclude a vaccine-associated risk, postmarketing assessment is warranted.

Uncertainties in the quantitative benefit-risk assessment include severity of CHIK during actual outbreaks and the effect of VLA1553 on prevention of disease caused by CHIKV, especially on prevention of severe manifestations of CHIK, in the context of the risk of CHIK-like illness caused by the vaccine. It is possible that the benefit-risk profile could become less favorable or even unfavorable if the disease caused by CHIKV is only mild and moderate as reported by some investigators (Yoon, 2020; Langsjoen, 2016) or if VLA1553 has no significant effect on severe manifestations of the disease and chronic arthralgia.

In addition, the observed imbalance in spontaneous abortion in a limited small sample size in this application and the reports regarding vertical transmission of wild-type CHIKV to neonates from pregnant individuals with viremia at delivery that cause severe, potentially fatal CHIK disease in neonates necessitates risk mitigation considering the individual's risk of exposure to wild-type CHIKV at delivery and vaccination benefit and a postmarketing commitment study to further address the concern of potential adverse pregnancy outcomes.

The currently available data support a benefit-risk profile that is favorable for approving VLA1553 for use in individuals 18 years of age and older at increased risk of exposure to CHIKV under an accelerated approval pathway. Mitigation of the observed risks and uncertainties will be accomplished through labeling (including statements regarding uncertainties of the clinical benefit and risks of CHIK-like adverse reactions, potential cardiac events and spontaneous abortions), and through adequate and well-controlled postmarketing confirmatory studies to confirm clinical benefit and continued safety surveillance and postmarketing studies to further assess and understand these risks. Please refer to Section 11.5 for recommended labeling changes and Section 11.6 for postmarketing requirement and commitment studies.

11.3 Discussion of Regulatory Options

The Applicant is seeking accelerated approval of VLA1553 for the indication of prevention of disease caused by CHIKV. Accelerated approval of VLA1553 under this regulatory pathway will require the Applicant to carry out postmarketing confirmatory studies to verify and describe the clinical benefit of VLA1553 with due diligence. Due to the unpredictability of CHIK outbreaks, it is uncertain when such confirmatory studies could be implemented.

11.4 Recommendations on Regulatory Actions

CHIK is generally considered a serious condition, and there is no currently approved preventative vaccine. A single dose of VLA1553 induced in >98% of participants an anti-CHIKV neutralizing antibody titer that is considered reasonably likely to predict a clinical benefit. The safety profile of VLA1553 is considered acceptable for an indication restricted to individuals at increased risk of exposure to CHIKV. In the opinion of this reviewer, the data provided in this application support accelerated approval of VLA1553 for the proposed restricted indication.

Please refer to Section 11.6 for recommended postmarketing actions to fulfill the regulatory requirement for product under accelerated approval.

11.5 Labeling Review and Recommendations

At the time this review was finalized, labeling negotiations with the Applicant was still ongoing. Major recommendations for the package insert include:

- Adding safety data on CHIK-like adverse reactions caused by the vaccine virus, highlighting serious and prolonged CHIK symptoms (e.g., arthritis/arthralgia) and cardiac events.
- An indication for individuals at increased risk of CHIKV infection.
- Inclusion of CHIK-like adverse reactions in Section 5 (Warnings and Precautions).
- Presentation of data on neutropenia, leukopenia, and lymphopenia from the immunogenicity subset of Study 301.
- Presentation of comparative safety data from Study 301 only, rather than pooled analyses.

- Focusing on seroresponse data at Day 28 and including seroresponse data at Day 180 in narrative, when applicable.

11.6 Recommendations on Postmarketing Actions

11.6.1 Postmarketing Requirement Studies

Confirmatory Clinical Studies to Verify Clinical Benefit
In accordance with the accelerated approval regulations, adequate and well-controlled confirmatory studies to verify and describe clinical benefit must be conducted with due diligence to fulfill the regulatory requirements. The Applicant submitted a test-negative case control observational study protocol (b) (4) -402 to verify clinical benefit. To address concerns associated with potential limitations of the test-negative study design, the Applicant submitted a concept protocol upon CBER request for a randomized controlled PMR study to verify clinical benefit (b) (4) -404), which will also serve to further address the safety concern of CHIK-like illness associated with the vaccine. The totality of the evidence from these studies will inform our postmarketing assessment of benefit-risk.

Study (b) (4) -402 is an observational Test Negative Design (TND) study to estimate the vaccine effectiveness of (b) (4) in Brazil, to be conducted (b) (4) in the country. This study will be initiated after implementation of the vaccine (b) (4) in selected municipalities as part of a pilot vaccination program, once vaccination coverage reaches 20% of the eligible population in these municipalities, and an increase in CHIKV transmission has been detected through CHIKV routine epidemiological surveillance in these areas. We anticipate that this study design will allow collection of data to confirm efficacy through an adjusted comparison of the (b) (4) vaccination rates between cases and controls. Although it is not possible to prospectively identify all limitations and biases in this TND field study, some potential limitations of this study design may include:

- Inclusion of participants with unidentified prior CHIK infection, which may influence efficacy results, mainly because of the possibility that the rate of unidentified prior CHIKV infection could be different between the vaccine recipients and the unvaccinated individuals. To determine the effect of this potential imbalance, and in response to CBER's request, the Applicant has agreed to perform an additional serological study including approximately 1,000 individuals vaccinated with (b) (4) and 1,000 not vaccinated with (b) (4) from each municipality included in the TND study, using dry blood spot testing. To quantify the potential bias resulting from unmeasured confounding due to potential differences in prior unidentified CHIKV infection, the Applicant will perform a probabilistic bias analysis using data from the seroprevalence surveys.
- Selection bias: Although the TND implicitly accounts for selection bias associated with differences in the likelihood of seeking care when sick, the possibility of selection bias that may result in an overestimation of vaccine efficacy if vaccinated participants are more likely to avoid disease may still exist.
- Inability to predict protection against chronic disease.
- Inability to address the safety concerns of CHIK-like illness potentially caused the by vaccine virus.

Study (b) (4) -404 is a pragmatic randomized controlled trial assessing a primary endpoint of vaccine effectiveness (VE) against symptomatic virologically confirmed CHIKV disease in vaccine recipients compared to controls (individuals receiving either placebo or another vaccine such as tetanus vaccine). Secondary objectives include assessment of VE against chronic and

severe CHIKV disease and assessment of safety, in particular the characterization of the frequency and severity of AESIs of CHIK-like illness. We anticipate that this randomized controlled design will allow collection of rigorous data to confirm efficacy.

Reviewer comment**:** *To conduct the studies with due diligence, the Applicant should collaborate with other stakeholders including government agencies to identify CHIKV outbreaks worldwide. To facilitate rapid implementation of these studies, the Applicant should have the protocol cleared by IRBs in advance and have the vaccine and study teams ready to launch the trials immediately, once an outbreak is identified.*

In summary, both studies will contribute to the totality of our understanding of the benefit-risk profile of VLA-1553, through both confirmation of clinical benefit and additional data to characterize AESIs of CHIK-like adverse reactions and any other safety concerns that may emerge in the post-market setting.

Pediatric Studies
According to the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)), the Applicant requested deferred pediatric studies for all pediatric population. The following proposed deferred pediatric studies are agreed upon by the Agency:

1. VLA1553-321: Safety and immunogenicity study in children (12 to <17 years of age)
2. VLA1553-221: Dose-finding safety and immunogenicity study in children (1 to <12 years of age)
3. VLA1553-322: Dose-confirmation safety and immunogenicity study in children (1 to <12 years of age)
4. VLA1553-222: Dose-finding safety and immunogenicity study in neonates and infants (<1 year of age)
5. VLA1553-323: Dose-confirmation safety and immunogenicity study in neonates and infants (<1 year of age)

11.6.2 Postmarketing Commitment Study

Since there was an imbalance in spontaneous abortions between VLA1553 and placebo groups, the clinical review team recommends postmarketing commitment studies for pregnancy outcomes to address the potential safety concerns. The Applicant proposed to conduct an observational study (b) (4) -403) to evaluate the safety of the vaccine in at least 90 women 18-45 years of age exposed to the vaccine prior to or during pregnancy compared to a group of pregnant women who have not been exposed to the vaccine. Please refer to the review memo of the PMC by the OBPV reviewers.

12. APPENDIX A

Review of Dose Ranging Study 101

Study Title: "A randomized, observer-blinded, dose-escalation Phase 1 study to assess the safety and immunogenicity of three different dose levels of a live-attenuated Chikungunya virus vaccine candidate (VLA1553) in healthy volunteers aged 18 to 45 years."

Study Period: March 5, 2018 to July 23, 2019

Study Sites

- Optimal Research LLC, 2089 Cecil Ashburn Drive SE, Suite 203, Huntsville, AL 35802, U.S.
- Optimal Research, LLC, 4911 Executive Drive, Peoria, IL 61614, U.S.

Primary Objective

- To assess the safety and tolerability of VLA1553 in a healthy adult population aged 18 to 45 years of age after a single immunization

Secondary Objectives

- To assess the immunogenicity of VLA1553 in a healthy adult population aged 18 to 45 years of age after a single immunization
- To identify the optimal dose level(s) of VLA1553 in a healthy adult population aged 18 to 45 years of age
- To assess safety and immunogenicity of VLA1553 in a healthy adult population aged 18 to 45 years of age, after a re-vaccination at 6 or 12 months
- To assess long-term safety of and antibody persistence to a single vaccination with VLA1553 up to 1 year

Study Design

The proposed study was a randomized, observer-blind, multicenter, dose-escalation Phase 1 clinical trial to assess the safety and immunogenicity of VLA1553 in 120 healthy adults 18 through 45 years of age. The investigational product was administered by intramuscular injection. Participants were randomized into 3 groups:

- Group L (Low dose): VLA1553 3.2×10^3 50% tissue culture infectious dose ($TCID_{50}$) on Day 0 (0.1 mL of 3.2×10^4 $TCID_{50}$/mL) and 3.2×10^5 $TCID_{50}$ at Month 12 (1 mL of 3.2×10^5 $TCID_{50}$/mL)
- Group M (Medium dose): VLA1553 3.2×10^4 $TCID_{50}$ (1 mL of 3.2×10^4 $TCID_{50}$//mL) on Day 0 and 3.2×10^5 $TCID_{50}$ at Month 12
- Group H (High dose): VLA1553 3.2×10^5 $TCID_{50}$ on Day 0 and at Month 12 (Group H1) or at Month 6 (Group H2)

Participants were enrolled in a staggered manner: 20 sentinel participants (five participants each per low and medium dose group, ten participants in the high dose group) were assessed in an open-label dose escalation fashion, and the remaining 100 participants were enrolled simultaneously in a randomized observer-blind manner. Dose escalation started with five sentinel participants in Group L (3.210^3 $TCID_{50}$/dose). Escalation to the next higher dose group was started after acceptable 14 day postvaccination safety data was available in the lower dose group. Thereafter, the remaining participants were randomized at 1:1:2 (Group L: Group M: Group H) into the three study groups.

Participants in Groups L and M were re-vaccinated with VLA1553 (3.2×10^5 $TCID_{50}$) at Month 12 (Day 365), and participants in Study Group H were re-randomized (1:1) to receive a dose of VLA1553 (3.2×10^5 $TCID_{50}$) at either Month 6 or Month 12.

Solicited injection-site and systemic adverse reactions were collected for 14 days after each vaccination and viremia were measured at baseline and at Days 3, 7, and 14. If a participant presented with viremia on Day 14 postvaccination, weekly tests were performed until viremia resolved. SAEs were monitored throughout the study duration and were continued to be followed until 6 months after the last re-vaccination. Anti-CHIKV neutralizing antibody titer was assessed as scheduled in the protocol. The study duration was approximately 13 months.

Reviewer comment: *Anti-CHIKV neutralizing antibodies were determined by* (b) (4) *assay. The assay was not validated.*

Results of Immune Responses

A summary of anti-CHIKV neutralizing antibody GMTs following the first and second vaccination (or re-vaccination) by study group is presented in Table 52 for the PP population. After the first dose of VLA1553 anti-CHIKV neutralizing antibody titers were not detectable at postvaccination Day 3 but started to increase at postvaccination Day 7 (data not shown). As shown in Table 52, anti-CHIKV neutralizing antibody titers reached their peak at Day 28, and the peak titers were similar among the three dose groups following the first vaccination. For all three groups, anti-CHIKV neutralizing antibody titers reached their nadir at Day 84, started to increase at Day 180, and were similar to their peak titers at Day 365. These unusual immune response kinetics were likely due to the variability of the assay (the assay was not validated), per the Applicant.

Re-vaccination at either 6 months after the first vaccination (for Group H2) or 12 months after the first vaccination (for Groups L, M and H1) had no impact on anti-CHIKV neutralizing antibody titers measured at 28 days after the re-vaccination compared with the pre-re-vaccination titers (Day 180 for H2 and Day 365 for Groups L, M, and H1).

Table 52. Anti-CHIKV Neutralizing Antibody GMTs After VLA1553, PP Population

Time Point	Group L N=23 GMT ± SD	Group M N=23 GMT ± SD	Group H1 N=20 GMT ± SD	Group H2 N=25 GMT ± SD
Day 0 (Baseline)	10.0 ± 0.0	10.0 ± 0.0	10.0 ± 0.0	10.0 ± 0.0
1st vaccination	-	-	-	-
Day 14 postvaccination	244.0 ± 0.37	419.7 ± 0.25	398.3 ± 0.35	541.9 ± 0.28
Day 28 postvaccination	659.6 ± 0.32	660.5 ± 0.38	761.1 ± 0.36	605.5 ± 0.31
Day 84 postvaccination	301.3 ± 0.37	310.5 ± 0.35	278.6 ± 0.35	311.2 ± 0.35
Day 180 postvaccination	419.7 ± 0.36	584.7 ± 0.61	468.5 ± 0.61	458.9 ± 0.48
Day 365 postvaccination	602.6 ± 0.39	1005.8 ± 0.32	735.2 ± 0.47	588.9 ± 0.25
2nd Vaccination[a]	-	-	-	-
Day 28 postvaccination	600.9 ± 0.31	964.0 ± 0.34	870.9 ± 0.36	512.7 ± 0.36

Source: Section 14, Table 3.3.1.2 (page 114-117), VLA1553-101 CSR, Module 5.3.5.1, STN125777/0.3
Notes: a. Re-vaccination with VLA 1553 (3.2×10^5 $TCID_{50}$) was administered on Day 180 for Group H2 and on Day 365 for Groups L, M and H1.
Abbreviations: PP, Per-Protocol; N, number of participants in the group; GMT, geometric mean titer; SD, standard deviation

Safety Results

Safety overview of VLA1553

A summary of AEs after the single vaccination by study group is presented in Table 53. Between 63% and 78% of participants reported any AE during the study period across study groups, and participants in the high dose group had the highest incidence of AEs. The

percentage of participants reporting solicited local and systemic events was dose-dependent, with the highest percentage of participants with these events, including severe solicited events, in the high-dose group.

AESIs were not specifically solicited in this study; however, no AESI was reported in this study.

Table 53. Adverse Events Throughout 12 Months After Single Vaccination With VLA1553, Safety Population

Adverse Events	Group L N=31 % (95% CI)	Group M N=30 % (95% CI)	Group H N=59 % (95% CI)
Any AE	67.7 (50.1, 81.4)	63.3 (45.5, 78.1)	78.0 (65.9, 86.6)
Any SAE	12.9 (5.1, 28.9)	10.0 (3.5, 25.6)	15.3 (8.2, 26.5)
Any solicited reaction	35.5 (21.1, 53.1)	40.0 (24.6, 57.7)	67.8 (55.1, 78.3)
Any severe solicited reaction	3.2 (0.6, 16.2)	3.3 (0.6, 16, 7)	11.9 (5.9, 22.5)
Any solicited local reaction	3.2 (0.6, 16.2)	6.7 (1.8, 21.3)	10.2 (4.7, 20.5)
Any severe local reaction	0.0 (0.0, 11.0)	0.0 (0.0, 11.4)	0.0 (0.0, 6.1)
Any solicited systemic reaction	35.5 (21.1, 53.1	40.0 (24.6, 57.7)	67.8 (55.1, 78.3)
Any severe systemic reaction	3.2 (0.6, 16.2)	3.3 (0.6, 16.7)	11.9 (5.9, 22.5)
Unsolicited AE	58.1 (40.8, 73.6)	50.0 (33.2, 44.4)	64.4 (51.7, 75.4)
Any severe unsolicited AE	9.7 (3.3, 24.9)	6.7 (1.8, 21.3)	3.4 (0.9, 11.5)
Any medically attended AE	6.5 (1.8, 20.7)	16.7 (7.3, 33.6)	20.8 (9.2, 40.5)
Any SAE	0.0 (0.0, 11.0)	3.3 (0.6, 16.7)	0.0 (0.0, 6.1)
Any AE leading to discontinuation (from re-vaccination)	0.0 (0.0, 11.0)	0.0 (0.0, 11.4)	1.7 (0.3, 9.0)

Source: Adapted from Table 3.4.1 (page 193-195), Section 14 of VLA1553-101 CSR, Module 5.3.5.1, STN125777/0.3
Abbreviations: AE, adverse event; SAE, serious adverse event

Solicited Adverse Reactions
A summary of solicited local and systemic adverse reactions after a single vaccination of VLA1553 is presented in Table 54.

Within 14 days after a single vaccination, tenderness was the most common solicited local reaction, reported by one (3.3%) participant in the medium dose group (Group M) and three (5.1%) participants in the high dose group (Group H). This was followed by redness (reported by one participant each in Groups L and M) and pain (reported by one participant each in Groups M and H). No participants reported any solicited local AE of swelling or induration. None of the local reactions was severe. There was no significant difference in the incidence of any category of solicited local AEs.

The most frequently reported solicited systemic reactions was headache, followed by fever, fatigue, muscle pain, joint pain, and nausea. Overall, most solicited systemic AEs were mild or moderate. Seven participants (one each in Group L and M and five participants in Group H) experienced severe fever. The severe fever occurred 2–4 days after the single vaccination; all resolved within 2 days. One participant in Group H experienced a severe headache. The incidence rates and severity of all the solicited systemic reactions appeared to correlate with the vaccine dose level.

Table 54. Solicited Adverse Reactions within 14 Days After Single Vaccination With VLA1553, Safety Population

Adverse Reactions	Group L N=31 % (95% CI)	Group M N=30 % (95% CI)	Group H N=59 % (95% CI)
Solicited Local Reaction	-	-	-
Tenderness	0.0 (0.0, 11.0)	3.3 (0.6, 16.7)	5.1 (1.7, 13.9)
Redness	3.2 (0.6, 16.2)	3.3 (0.6, 16.7)	0.0 (0.0, 6.1)
Pain	0.0 (0.0, 11.0)	3.3 (0.6, 16.7)	1.7 (0.3, 9.0)
Induration	0.0 (0.0, 11.0)	0.0 (0.0, 11.4)	0.0 (0.0, 6.1)
Swelling	(0.0, 11.0)	0.0 (0.0, 11.4)	0.0 (0.0, 6.1)
Systemic Reactions	-	-	-
Headache	25.8 (13.7, 43.2)	26.7 (14.2, 44.4)	39.0 (27.6, 51.7)
Severe headache	0.0 (0.0, 11.0)	0.0 (0.0, 11.4)	1.7 (0.3, 9.0)
Fever	12.9 (5.1, 28.9)	20.0 (9.5, 37.3)	37.3 (26.1, 50.0)
Severe fever	3.2 (0.6, 16.2)	3.3 (0.6, 16.7)	8.5 (3.7, 18.4)
Fatigue	16.1 (7.1, 32.6)	20.0 (9.5, 37.3)	30.5 (20.3, 43.1)
Muscle pain	3.2 (0.6, 16.2)	16.7 (7.3, 33.6)	30.5 (20.3, 43.1)
Joint pain	6.5 (1.8, 20.7)	13.3 (5.3, 29.7)	16.9 (9.5, 28.5)
Nausea	3.2 (0.6, 16.2)	13.3 (5.3, 29.7)	13.6 (7.0, 24.5)
Vomiting	3.2 (0.6, 16.2)	6.7 (1.8, 21.3)	3.4 (0.9, 11.5)
Rash	0.0 (0.0, 11.0)	3.3 (0.6, 16.7)	1.7 (0.3, 9.0)

Source: Adapted from Table 35 (page 136), Table 36 (page 137) and Table 38 (page 140-141), VLA1553-101 CSR, Module 5.3.5.1, STN125777/0.3.

Solicited local reactions following re-vaccination either at 6 or 12 months after the first vaccination were rare. No participant in Group H2 reported solicited local reactions after the Month 6 re-vaccination. No participant in Group L and M experienced solicited local reaction, 1 participant reported a mild swelling, and 1 participant reported a mild tenderness in Group H1, following the Month 12 re-vaccination.

Solicited systemic reactions following re-vaccination were less common as compared with the first vaccination. For participants in H2 group who received re-vaccination at 6 months after the first vaccination, two (7.7%) participants reported severe nausea, and one (3.8%) participant reported mild fatigue for 14 days following re-vaccination.

For participants who were re-vaccinated at 12 months after the first vaccination, only 1 participant in Group H1 reported a mild joint pain and moderate headache, no participant in Group L or M reported any solicited systemic reactions during 14 days after re-vaccination.

Unsolicited AEs

Up to 12 months after the single vaccination, unsolicited AEs were reported in 17 (54.8%), 15 (50.0%), and 36 (61.0%) participants in Groups L, M, and H, respectively. Of all participants who reported any unsolicited AEs, 13 (41.9%), 8 (26.7%), and 29 (49.2%) participants in Groups L, M, and H without H2, respectively, experienced at least one unsolicited AE that was considered related to the vaccination. Related AEs were observed most frequently in the high dose group (Group H).

Across the study groups, two (3.4% in Group H and 6.7% in Group M) to three (9.7%; Group L) participants reported severe unsolicited AEs, including neutropenia (one participant in Group M and two participants in Group L), lymphopenia (two participants in Group H), back pain (one participant in Group L), and multiple injuries (related to car accident; reported by one participant in Group M). All severe AEs were considered related to the vaccination except for one AE

(multiple injuries) reported by one participant in Group M. One (3.3%) participant in Group M reported one SAE (multiple trauma related to car accident) and one (3.2%) participant in Group L reported one related medically attended unsolicited AE.

Overall, no study group was observed to experience significantly more of any of unsolicited AEs (overall or severe AEs) than any other study group.

The most frequent unsolicited SOC was blood and lymphatic system disorders, reported by 4 (13.3%; Group M) to 18 (30.5%; Group H) participants. The most frequently reported unsolicited AE was leukopenia, reported by 2 (6.7%; Group M) to 14 (23.7%; Group H) participants, followed by neutropenia, reported by 1 (3.3%; Group M) to 10 (16.9%; Group H) participants.

Serious AEs, Including Deaths
No death occurred during the study.
Two non-fatal SAEs were reported by 2 participants during the study:

- Participant 1553-(b) (6) (Group M): A 30-year-old White female enrolled in Group M experienced an SAE of multiple injuries due to a car accident. Approximately 110 days postvaccination, the participant was involved in a car accident and admitted to the hospital intensive care unit with five broken ribs and a punctured lung. She was discharged 2 days later. The SAE of multiple injuries was considered not related to VLA1553.
- Participant (b) (6): A 40-year-old White male initially enrolled in Group H and re-randomized to Group H2 on Day 180 experienced an SAE of supraventricular extrasystole ectopy. He had a medical history of bradycardia, hypertension, COPD and asthma. The participant was hospitalized due to atrial fibrillation 62 days after the second dose of VLA1553. He had a cardiac ablation in hospital and recovered after the procedure. He had another cardiac ablation using cauterization about 53 days after his first cardiac ablation. The SAE of supraventricular extrasystoles was assessed as not related to VLA1553.

Reviewer comment: *This reviewer agrees with the Applicant the multiple injuries was not related to the vaccine. However, the causality of the atrial fibrillation to the vaccine could not be excluded because there were temporal association and biological plausibility (atrial fibrillation was reported in individuals after natural CHIKV infection and also reported in a VLA1553 recipient (Participant* (b) (6) *in Study VLA1553-301 [described in Section 6.1.12.4].*

AEs Leading to Withdrawal
Two participants in the high dose group (Group H) experienced unsolicited AEs leading to withdrawal from re-vaccination, one of whom was also withdrawn from the study due to the AE.

- Participant 1553-(b) (6): A female initially enrolled in Group H and re-randomized to Group H1 on Day 180 experienced Hashimoto's Disease on Day 320 after the first vaccination. The participant had a partial left-side thyroidectomy 5 days later. She was withdrawn from re-vaccination and from the study. The AE of autoimmune thyroiditis was assessed as mild and not related to VLA1553 by the investigator. The DSMB also confirmed that this AE of autoimmune thyroiditis was not related to the vaccination. The AE of autoimmune thyroiditis was still ongoing when the participant completed the final examination at the early termination visit.
- Participant 1553-(b) (6) (Group H): The participant enrolled in Group H experienced syncope on Day 7 after a single vaccination. This participant had a medical history of mild sinus arrhythmia. The participant recovered on the same day, but he did not return

for any other visits or re-vaccination. The AE of syncope was assessed as not related to VLA1553 by the investigator and DSMB.

Reviewer comment: *This reviewer agrees that the two AEs described above were unlikely to be related to the vaccine.*

Viremia and Shedding Assessment
Viremia was analyzed in blood and shedding in urine samples obtained on the day of vaccinations and on postvaccination Days 3, 7, and 14. The concentration of detected viral RNA was measured in genome copy equivalents (GCE)/mL by (b) (4) . The sensitivity of this assay was 1087 GCE/mL (limit of detection, LOD) and the lower limit of quantification (LLOQ) was 3261 GCE/mL. Any samples with viremia or shedding results below the LLOQ were not reported.

Reviewer comment: *The* (b) (4) *used in the Phase 1 study was not validated.*

Plasma viremia results after the single vaccination on Days 0, 3, 7, and 14 by study group is summarized in Table 55. The levels of viremia appeared to be vaccine dose dependent and peaked at Day 3 and reduced significantly at Day 7 for all dose groups. No participant in any dose group showed a reportable viremia result on Day 14.

Table 55. Plasma Viremia (GCE/mL) Results Days 3, 7, And 14 After Single Vaccination, Safety Population, Study 101

Visit	VLA1553 Group L (N=31)	VLA1553 Group M (N=30)	VLA1553 Group H (N=59)
Day 3	-	-	-
Participants at visit (n)	31	30	59
Below LLOQ, n (%)	2 (6.5)	1 (3.3)	1 (1.7)
Below LOD, n (%)	3 (9.7)	1 (3.3)	2 (3.4)
Not detected, n (%)	1 (3.2)	1 (3.3)	0 (0.0)
Report result, n (%)	25 (80.6)	27 (90.0)	56 (94.9)
Mean	73,601.2	89,353.7	229,224.1
SD	152,151.0	107,203.8	332,163.6
Median	26,508.0	47,810.0	146,548.5
Q1 / Q3	10,559.0 / 43,882.0	19,009.0 / 119,009.0	62,638.0 / 276,450.5
Min / Max	3542.0 / 751,113.0	3267.0 / 410,728.0	3739.0 / 1,884,885
Day 7	-	-	-
Participants at visit (n)	30	30	58
Below LLOQ, n (%)	8 (26.7)	6 (20.0)	5 (8.6)
Below LOD, n (%)	12 (40.0)	6 (20.0)	22 (37.9)
Not detected, n(%)	4 (13.3)	13 (43.3)	27 (46.6)
Report result, n (%)	6 (20.0)	5 (16.7)	4 (6.9)
Mean	8814.0	15,725.2	27,028.0
SD	8541.9	17,471.2	33,386.1
Median	4827.0	6062.0	13,409.0
Q1 / Q3	4305.0 / 9424.0	5847.0 / 15,470.0	5470.0 / 48,586.0
Min / Max	3756.0 / 25,745.0	5203.0 / 46,044.0	5460.0 / 75,834.0

Visit	VLA1553 Group L (N=31)	VLA1553 Group M (N=30)	VLA1553 Group H (N=59)
Day 14	-	-	-
Participants at visit (n)	30	30	56
Below LLOQ, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Below LOD, n (%)	0 (0.0)	0 (0.0)	2 (3.6)
Not detected, n(%)	30 (100)	30 (100)	54 (96.4)
Report result, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Mean	N/A	N/A	N/A
SD	N/A	N/A	N/A
Median	N/A	N/A	N/A
Q1 / Q3	N/A / N/A	N/A / N/A	N/A / N/A
Min / Max	N/A / N/A	N/A / N/A	N/A / N/A

Source: Section 14, Table 3.4.55.1 VLA1553-101 CSR
Note: Percentages were based on non-missing observations (Total); Limit of detection: 1087 GCE/mL; Lower limit of quantification: 3261 GCE/mL.
Abbreviations: GCE, genome copy equivalent; LLOQ, lower limit of qualification; n, number of participants with available result; LOD, limit of detection; SD, standard deviation; Q, quartile; Min, minimum; Max, maximum; N/A, not applicable

After the Month 6 or Month 12 re-vaccinations, none of the participants in any study group showed any reportable plasma viremia results within 14 days after the re-vaccination. Urinary shedding of vaccine virus was only observed in one participant in the low dose study group (Group L) 7 days after the first vaccination. After re-vaccination, none of the participants showed any reportable urinary shedding of vaccine virus within 14 days postvaccination.

Conclusion

Safety:

- Safety profile of VLA1553 was generally acceptable in all dose levels, and the low dose and medium dose of VLA1553 had a superior reactogenicity profile (including viremia) compared with the high dose group.
- The local tolerability profile at all dose levels was considered favorable. Notable systemic AEs included short-term fever, headache, and muscle pain. Rates were significantly lower in the low and medium dose groups compared with the high dose group.
- No AESI or vaccine-related SAE was reported.
- Over 80% (80.6% to 94.9% depending on dose levels) of study participants had vaccine viremia at 3 days following a single dose of VLA1553. The magnitude of viremia significantly reduced 7 days postvaccination and no participants had a detectable viremia at 14 days postvaccination.

Immunogenicity:

- VLA1553 was immunogenic in all dose group as demonstrated by significant levels of CHIKV-specific neutralizing antibody titers at 28 days after a single dose of VLA1553.
- There was a dose-dependent response and the second dose at either 6 or 12 months after the first vaccination did not boost CHIKV-specific antibody responses.