



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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Subject: Review of Pharmacovigilance Plan

Sponsor: Valneva Austria GmbH

Product: Chikungunya Vaccine, Live-Attenuated
(IXCHIQ)*

Application Type/Number BLA 125777/0

Proposed Indication Active immunization for the prevention of
disease caused by Chikungunya virus in
individuals 18 years and above

Submission Date: December 22, 2022

Action Due Date: August 22, 2023

*Referred to as VLA1553 throughout this memorandum

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original Biologics License Application (BLA or STN) 125777/0 based on the safety profile of the live-attenuated Chikungunya vaccine. Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for the Chikungunya vaccine, should the indication for this product be approved. Please refer to Appendix 1 for the complete list of materials reviewed.

2 BACKGROUND

Chikungunya disease is a mosquito-borne disease caused by the Chikungunya virus. Infection is characterized by an acute febrile illness with symptoms such as headache, muscle pain, skin rash, and arthralgia that may be chronic and incapacitating in infected individuals. The incubation period is 3 to 7 days (range 1 to 14 days), and signs and symptoms usually begin abruptly with fever and malaise. Death from Chikungunya is uncommon. Currently, no vaccine or antiviral therapies are available to treat Chikungunya virus infection.

The disease mostly frequently occurs in Africa, Asia, the Indian subcontinent, Brazil, and the Americas. Assessment of Chikungunya disease incidence is not well defined and often not accurate due to misdiagnosis to other circulating febrile diseases and the lack of serological confirmation. Chikungunya often occurs in outbreaks and epidemics may rapidly evolve. As of March 9, 2023, there are 114,181 cases worldwide and 43 deaths reported. Most cases are from Paraguay (82,240), Brazil (30,386), Argentina (655), Bolivia (300) and Thailand (259). All reported deaths occurred in Paraguay.¹

Chikungunya virus may be detected directly in blood samples collected during the first week of illness using tests such as reverse transcriptase-polymerase chain reaction or after the first week of infection to test for antibodies to the virus. Antibody levels are typically detectable by the first week after illness onset and can still be detected for about 2 months.²

The proposed vaccine acts by inducing antibodies that neutralize the live Chikungunya virus. Accumulated data from animal studies and human epidemiological studies indicate that a protective virus neutralizing antibody response, as measured in vitro in a 50% micro plaque-reduction neutralization antibody test (μ PRNT), is provided by a threshold μ PRNT titer of ≥ 150 and suggests evidence of protective immunity. The evaluation of vaccine effectiveness of the Chikungunya virus was therefore based on neutralizing antibody levels above a threshold μ PRNT titer of ≥ 150 .

3 PRODUCT INFORMATION

3.1 Product Description

The vaccine consists of a genetically engineered, attenuated Chikungunya La Reunion strain (LR-CHIKV clone LR2006-OPY1). A single injection of VLA1553 is administered intramuscularly as a suspension after reconstitution of targeted (b) (4) TCID₅₀ per 0.5

mL dose in a pre-filled syringe. Non-active excipients and buffer components of this lyophilized drug product includes di-potassium hydrogen phosphate, potassium di-hydrogen phosphate, trisodium citrate dihydrate, sucrose, magnesium chloride hexahydrate, D-sorbitol, L-methionine, and recombinant human albumin. The package will contain one single-use vial with the lyophilized powder of vaccine and one solvent consisting of 0.5 mL sterile water for injection in a prefilled syringe for reconstitution.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125777/0 is for active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years and above.

Reviewer Comment: The Division of Pharmacovigilance (DPV) defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

The Chikungunya vaccine is not currently marketed anywhere in the world. This product is also under Investigational New Drug application 017854.

Reviewer Comment: This vaccine is the first available for the prevention of Chikungunya virus and there are no foreign approvals.

5 DESCRIPTION OF CHIKUNGUNYA VACCINE CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data were reviewed from Summary of Clinical Safety, as well as individual study reports submitted to STN 125777/0. DPV defers to the product office on the final clinical review, safety and efficacy outcomes, and the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125777/0 be approved. Please refer to the package insert for the final clinical safety data. A summary of the three clinical studies contributing to the safety database is displayed below.

Table 1 Summary of clinical studies supporting the safety of Chikungunya vaccine

Study	N	Description
VLA1553-301	1,864 M /2,251 F	Placebo-controlled, randomized, double-blinded, multicenter pivotal phase 3 study in healthy adults. To evaluate the safety of the final dose of the live-attenuated Chikungunya virus vaccine (VLA1553) 28 and 180 days after a single immunization.

VLA1553-302	185 M/ 223 F	Lot-to-lot, randomized, double-blinded, multicenter phase 3 study in healthy adults. To evaluate the safety of VLA1553 up to 180 days after a single immunization.
VLA1553-101	106 M/ 14 F	Phase 1 dose-response study in healthy adults. To assess safety after a single immunization or re-vaccination at 6 or 12 months.

Source: STN 125777/0, Module 2.7.4, Table 2.7.4-3, Summary of Clinical Safety for VLA1553. M=male. F=female.

There were 3,610 subjects in the pooled data population who received a single vaccination, of which 26 subjects were re-vaccinated after 6 months, and 68 subjects were re-vaccinated at 12 months.

All participants who entered in the study and received the single vaccination were included in the safety analysis. Subjects were provided with two types of questionnaires throughout the course of these studies. The subject eDiary was distributed to all participants for the collection of solicited safety information starting approximately eight hours after vaccination and for 10 days post-vaccination (studies VLA1553-301 and VLA1553-302) or 14 days post-vaccination (VLA1553-101). Information collected include temperature, injection site reactions, and systemic reactions. The eMemory Aid or Subject Diary 2 was distributed to all participants for the collection of unsolicited adverse event (AE)s outside the first 10 or 14 days post-vaccination until the next visit.

5.2 Adverse events (Pooled Safety Data)

5.2.1 Most Common AEs

The most common systemic adverse reactions (incidence $\geq 20\%$) in the pooled analysis of clinical studies (VLA1553-301, VLA1553-302 and VLA1553-101) were headache, fatigue, and myalgia. The most common injection site adverse reaction (incidence $\geq 10\%$) was tenderness. Solicited systemic AEs reported up to 14 days after vaccination with VLA1553 include headache, fatigue, myalgia, arthralgia, fever, nausea, and rash.

In the pooled analysis, unsolicited AEs occurring up to 28 days post-vaccination in the VLA1553 group were chills 2.0%, diarrhea 1.4%, leukopenia 1.2%, lymphadenopathy 1.1%, and neutropenia 1.7%. In the pooled analysis, the top 10 unsolicited AEs occurring up to 6 months post-vaccination in the VLA1553 arm were chills (74/3,610) 2.0%, arthralgia (71/3,610) 2.0%, COVID-19 (65/3,610) 1.8%, neutropenia (62/3,610) 1.7%, headache (61/3,610) 1.6%, diarrhea (56/3,610) 1.2%, back pain (53/3,610) 1.5%, leukopenia (42/3,610) 1.2%, lymphadenopathy (40/3,610) 1.1%, and urinary tract infection (35/3,610) 1.0%.

Reviewer Comment: An imbalance was observed in adverse events between the treatment arms with arthralgia/arthritis, neutropenia, and leukopenia, which are discussed further below.

Arthralgia/Arthritis

The solicited adverse event of arthralgia/joint pain occurred at 16.6% (599/3,610) compared to 4.8% (60/1,033) that received placebo in the pooled data analysis. Most cases were mild or moderate in severity. The mean duration of arthralgia was 4.5 days.

The prolonged arthralgia cases are summarized below:

1. Subject #1553-(b) (6). 46-year-old white male with a medical history of coronary artery disease and Crohn's disease received the study drug on (b) (6). He experienced Grade 2 (moderate) fever from (b) (6) Grade 1 (mild) lower back pain starting on December 9, 2020 and Grade 1 mild arthralgia starting on December 11, 2020 and discontinued early from the study on Day 51. Fever resolved on Day 6, while arthralgia and lower back pain were resolving at the time of last visit (Day 51, Early Termination Visit).
2. Subject #1553-(b) (6). 50-year-old white female with a medical history that includes obesity, hypothyroidism, back pain, right big toe and second toe fracture was vaccinated on (b) (6) and experienced Grade 1 (mild) fever from October 16, 2021-October 17, 2020, Grade 1 (mild) edema in fingers and right great toe from October 22, 2020-May 2021, and arthralgia/arthritis. Grade 1 mild arthralgia occurred from (b) (6) and resolved one day after vaccine. Grade 2 moderate arthralgia in the right phalanges and toe (4 days after vaccine), and in both hands occurred from October 19, 2020-May 2021. She tested positive for genetic predisposition marker for arthralgia/arthritis HLA-B*27. The total duration of arthralgia was 182 days. All symptoms resolved by the end of the study.
3. Subject #1553-(b) (6). 62-year-old white female with a medical history of cervical spinal stenosis, myalgia, irritable bowel syndrome, and anxiety received a single dose of VLA1553 on (b) (6). The subject reported arthralgia (moderate, possibly related) and myalgia (mild, probably related) starting on the day following vaccination; the event of arthralgia was ongoing at the subject's end of study, myalgia resolved the same day. Also reported were mild fatigue and nausea, synovitis (third metacarpophalangeal joint) starting on November 4, 2020 and ongoing, trigger finger starting on December 1, 2020, and bilateral fingertip paresthesia starting on November 4, 2020 and ongoing. Subject was referred to an arthritis and rheumatology clinic on January 20, 2021 for pain, swelling and stiffness in the third and fourth metacarpophalangeal joint of the right hand. Eight months after vaccination, the subject presented with inflammatory polyarthropathy of the third and fourth metacarpophalangeal joints. Unblinding was done several months after Visit 5 (last visit).

Reviewer Comment: The third potential case of prolonged arthralgia (Subject #1553-(b) (6)) was identified in a subject who was unblinded. Details of this case narrative were provided in a sponsor IR response submitted to STN1257777/0.68.

Arthralgia/arthritis, including prolonged cases, were discussed with the OVR clinical review team. This safety concern will be addressed by enhanced pharmacovigilance, which is discussed in Section 6 below.

Neutropenia/Leukopenia

Unsolicited adverse events up to 6 months after vaccination revealed an imbalance in neutropenia and leukopenia. Neutropenia occurred at (34/3,082) 1.1% in the VLA1553 arm compared to (1/1,033) 0.1% in the placebo arm of study VLA1553-301. Of note, safety laboratory samples were only taken from the immunogenicity subset of Study VLA1553-301 (i.e., 501 participants) and percentages were calculated for the entire safety population by the sponsor. Thus, if calculated in the immunogenicity subset, the actual frequency of neutropenia was (34/374) 9.0% in the VLA1553 arm compared to (1/126) 0.8% in the placebo arm. Leukopenia also occurred at a higher frequency in the VLA1553 treatment arm at 18/3,082 (0.6%) compared to no cases in placebo in study VLA1553-301.

Reviewer Comment: A higher frequency of neutropenia and leukopenia appears in the VLA1553 arm in unsolicited adverse events. Neutropenia and leukopenia were reported as clinically relevant laboratory parameter deviations, without associated clinical signs or symptoms. Neutropenia and leukopenia resolved by day 28. The risk of neutropenia and leukopenia can be addressed by the product labeling.

5.2.2 Withdrawals Due to AEs

A total of 5/3,610 (0.1%) withdrawals were due to AEs in the pooled analysis. There were three adverse events (COVID-19, influenza, and coronary heart disease) leading to withdrawal in the VLA1553 arm and two (cerebellar hemorrhage and mental status change) in the placebo arm.

Reviewer Comment: No concerns were identified with the cases of withdrawals due to adverse events.

5.2.3 Serious Adverse Event (SAE)s

There were 1.4% (52/3,610) of subjects in the pooled VLA1553 arm and 0.8% (8/1,033) of subjects in the placebo arm that reported 79 and 10 SAEs, respectively. SAEs occurred most frequently in Infections and Infestations. This class included pneumonia 2/3,082 (0.1%) VLA1553 vs. 1/1,033 (0.1%) placebo. Other SAEs in this class included appendicitis, bacterial arthritis, complicated appendicitis, diverticulitis, kidney infection, and pyelonephritis.

Reviewer comment: An imbalance with SAEs for cardiac events and spontaneous abortions was noted. Cardiac disorders are discussed below. Safety in pregnancy, including the imbalance in spontaneous abortions, is discussed in Section 5.2.6. In addition, there was one case of Guillain-Barre Syndrome (GBS) in the vaccine group compared to none in the placebo group, which is discussed below. No other imbalances in SAEs were noted based on PT review.

Cardiac disorders

Chikungunya virus has been associated with cardiovascular (CV) involvement such as myocarditis, pericarditis, heart failure, and acute myocardial infarction. CV involvement in Chikungunya infection remains the most frequent atypical presentation of this disease and may have severe manifestations. Timely diagnosis and appropriate management help improve patient outcomes.³ There was an imbalance in cardiac events between treatment arms, with five events in the VLA1553 arm (all from Study VLA1553-301) and none in the placebo arm. These five events include two events of atrial fibrillation, one event of cardiac arrest, one event of cardiomyopathy, and one case of CAD. There was an additional cardiac event of atrial fibrillation (supraventricular extrasystoles) in Study VLA1553-101 not included in the initial safety analysis set. The narratives of these cases are included below.

1. Subject (b) (6) : 85-year-old white male with a medical history of atrial fibrillation since 2005 experienced three events of worsening of atrial fibrillation. He enrolled in study VLA1553-301 on (b) (6) and received a single dose of VLA1553 on (b) (6). On (b) (6), the subject experienced the first Grade 2 atrial fibrillation, 117 days after study drug administration. The event was classified as an SAE due to hospitalization. On (b) (6), the event resolved, and the subject was discharged. On (b) (6), the subject experienced the second Grade 2 atrial fibrillation, 132 days after study drug administration. On (b) (6), the event resolved, and the subject was discharged from hospital. On (b) (6), the subject experienced the third Grade 2 atrial fibrillation, 164 days after study drug administration. On (b) (6), a new dual chamber pacemaker pulse generator was inserted. On (b) (6), the subject had persistent atrial fibrillation, and cardioversion was unsuccessful. On (b) (6), the event resolved, the subject was discharged, and completed the study on (b) (6) (Study Day 177).
2. Subject (b) (6) : 66-year-old white male experienced atrial fibrillation. The subject experienced Grade 3 pyrexia on (b) (6), five days after study drug administration. The subject experienced Grade 3 atrial fibrillation on (b) (6), 10 days after study drug administration. The event of atrial fibrillation recovered/resolved on (b) (6). The subject experienced Grade 3 inappropriate antidiuretic hormone secretion on (b) (6), 10 days after study drug administration. On (b) (6), the subject developed diffuse myalgia (Grade 2), injection site pain (Grade 1), and injection site tenderness (Grade 1). On (b) (6), he additionally developed nausea (Grade 1) and fever greater than 100.4°F. On (b) (6), he had headaches and double vision (Grade 1). On (b) (6), he experienced diarrhea (Grade 1) without abdominal pain or blood in stool. On (b) (6), he still had a fever of 102.1°F. He called a home service provider on (b) (6) and the home nurse noted a very fast and irregular pulse. On (b) (6), 10 days after receiving blinded study drug, he went to the emergency room and was hospitalized due to rapid atrial fibrillation with a heart rate as high as 180 bpm. The subject had severe

hyponatremia. According to the investigator, urine osmolality and serum osmolality were consistent with the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) and hypothyroidism was ruled out as cause of hyponatremia. The subject completed the study on (b) (6) (Study Day 323). Based on follow-up information from August 4, 2021 provided by the investigator, the diagnostic parameters to confirm the diagnosis SIADH and provide a reliable differential diagnosis versus hypovolemic hyponatremia are missing, e.g., uric acid in serum, a blood gas analysis, and an assessment of the volume status or urine sodium during control visits. The subject was dehydrated after fever and diarrhea, and blood pressure stabilized after fluid supplementation. The DSMB recommended to follow-up the subject by analyzing the missing laboratory parameters to re-evaluate the diagnosis SIADH. SIADH cannot be completely ruled out, although hypovolemic hyponatremia may be possible. The sponsor considers the SAE in Subject #553-(b) (6) related to vaccination.

3. Subject (b) (6): 77-year-old white male experienced cardiac arrest on (b) (6), 32 days after study drug administration on (b) (6). The event was classified as an SAE due to hospitalization; life-threatening criterion and Grade 3. The subject suddenly collapsed. After initiating cardiopulmonary resuscitation (CPR), neighbors called the emergency medical service. He experienced ventricular fibrillation, was shocked three times, regained a pulse, then developed pulseless electrical activity in the emergency department and received CPR before regaining a pulse again. The subject was admitted to the ICU and underwent cooling protocol and treated with epinephrine initially. Coronary angiogram showed a negative result for significant coronary artery disease. A transthoracic echocardiography (TTE) showed normal left ventricular function apical akinesis which was also seen on a prior TTE. The etiology of ventricular fibrillation arrest remained unclear. The subject received an implantable cardioverter defibrillator (ICD) on (b) (6) for secondary prevention and was treated with aspirin and IV furosemide. The subject was also found to have a left pleural effusion as well as hematoma and mediastinal/abutting the pericardium, likely secondary to CPR while on anticoagulation. The subject has had left-sided thoracentesis on (b) (6) to drain this fluid.

Reviewer Comment: This subject (b) (6) has a previous cardiac history given he had a TEE earlier and was on anticoagulation.

4. Subject (b) (6): 38-year-old black female experienced cardiomyopathy. The subject received VLA1553 on (b) (6). Subject experienced Grade 3 acute respiratory failure with hypoxia, Grade 3 pneumonia secondary to COVID-19 infection, Grade 3 cardiomyopathy, Grade 3 acute respiratory failure with hypoxia, Grade 3 cardiomyopathy, Grade 3 pulmonary embolism, and tested positive for COVID-19 on (b) (6), 162 days after study drug administration. The events were each classified as an SAE due to hospitalization.

The event of cardiomyopathy was classified as an SAE due to meeting the life-threatening criterion. The events of acute respiratory failure, COVID-19 pneumonia, cardiomyopathy hypoxia, and pulmonary embolism recovered/resolved on (b) (6). The subject completed the study on (b) (6) (Study Day 187).

5. DEATH-Subject (b) (6): 52-year-old male experienced severe coronary artery disease (b) (6) days after study drug administration, which was fatal on the same day. Medical history included hypertension, hypercholesterolemia, and obesity. Subject (b) (6) experienced Grade 3 coronary artery disease (described as coronary artery disease) on (b) (6) days after study drug administration. The event was classified as a fatal event and SAE.
6. Subject #1553-(b) (6) was hospitalized due to atrial fibrillation reported in the phase 1 study VLA1553-101. This event was not reported in the safety analysis set (ISS) as the sponsor stated that the event occurred after revaccination and the ISS only included safety data up to Day 180 in those subjects who received one dose of VLA1553 and did not include revaccination. The 41-year-old white male subject was vaccinated on (b) (6) and received revaccination on Day 180 on (b) (6). The subject experience an SAE of supraventricular extrasystoles two months after revaccination. He went to the emergency room with intermittent palpitations and presyncope on (b) (6). Medical history includes sinus bradycardia since June 11, 2018, hypertension, chronic obstructive pulmonary disease, and asthma. Atrial fibrillation is documented from February 13, 2019.

Reviewer Comment: This case appears new onset of atrial fibrillation. However, it is noteworthy that this subject in a study of healthy volunteers has a medical history which includes hypertension, sinus bradycardia, chronic obstructive pulmonary disease, and asthma at 41 years of age. It is unclear whether there may have been any other risk factors in the past medical history that could have contributed to atrial fibrillation.

Reviewer comment: One case of a cardiac event (subject (b) (6)) is possibly related to vaccination due to the close temporal association. The remaining cases of cardiac events had medical comorbidities that may have contributed to the event or occurred at a long-time frame after vaccination. These cases were discussed with the OVR clinical review team and enhanced pharmacovigilance activities are planned to address this safety concern. Pharmacovigilance recommendations for cardiac events are discussed in Section 6 below.

Guillain-Barre Syndrome

In study VLA1553-301, Subject (b) (6), a 56-year-old white male received a single dose of VLA1553 on (b) (6) and developed GBS on (b) (6) (70 days after vaccination). He was hospitalized after collapsing and diagnosed with Grade 3 GBS and COVID-19. The subject was discharged from hospital on (b) (6).

(b) (6) with improvement in extremity strength. He was treated with intravenous immunoglobulin for GBS. The subject completed the study on Day 183. Vaccination history is listed as none. Past medical history includes umbilical hernia in 2014, plantar fasciitis in 2020, and insomnia, environmental and cheese allergies since 1964.

Reviewer Comment: There was one SAE of GBS reported in this study. GBS occurs worldwide with an overall incidence of only 1 to 2 cases per 100,000 per year^{4 5 6 7}. One case occurring after vaccination in an otherwise healthy individual in the VLA1553 study population of 3,610 persons raised interest in comparison to no cases in the placebo group and one case per 100,000 persons in the general population. There are confounders that make attribution to the vaccine less likely, such as infection with COVID-19. The usual risk window for Guillain-Barre syndrome is 42 days and this case occurred 70 days after the study vaccine. Thus, this case of GBS is likely not attributable to IXCHIQ. No pharmacovigilance actions are needed for GBS.

5.2.4 Deaths

A total of three deaths occurred and all deaths were in study VLA1553-301. A summary of the deaths are as follows:

1. 52-year-old man (Subject #1553-(b) (6)) [176cm, 124 kg] experienced severe coronary artery disease (CAD) (b) (6) days after study drug administration (VLA1553), which was fatal on the same day. Medical history included hypertension since 2000 and hypercholesterolemia since 2011. This case is discussed in detail in Section 5.2.3 above.
2. 57-year-old woman (Subject #1553-(b) (6)) experienced severe COVID-19 165 days after study drug administration (VLA1553), which was fatal on Day (b) (6).
3. 63-year-old man (Subject #1553-(b) (6)) experienced severe mental status changes (anoxic brain injury) 151 days after study drug administration (placebo), which was fatal on Day (b) (6). No treatment was reported for this event.

Reviewer Comment: All deaths occurred several months after vaccination. Subject #1553-(b) (6) had a history of hypertension, hypercholesterolemia and was overweight and these risk factors possibly may have contributed to CAD and subsequent death. Subject #1553-(b) (6) death was attributed to COVID-19 and is unlikely related to the Chikungunya vaccine. Subject #1553-(b) (6) received placebo, therefore there is no causality related to the vaccine.

5.2.5 Adverse Events of Special Interest (AESI)s

AESIs include fever, acute (poly)arthralgia/arthritis most frequently in the extremities (wrists, ankles, phalanges, often symmetric), back pain and/or neurological symptoms (e.g., confusion, optic neuritis, meningoencephalitis, or polyneuropathy) and/or cardiac symptoms (e.g., myocarditis), and rash. AESIs were reported in 11 subjects 11/3,610 (0.3%) subjects in the pooled VLA1553 arm and 1/1,033 (0.1%) in the placebo arm.

Reviewer comment: The imbalance in arthritis/arthralgia is discussed in Section 5.2.1, and a case of GBS is discussed in Section 5.2.3 above.

5.2.6 Safety in Pregnancy

Eighteen pregnancies were recorded for female participants: 15 pregnancies in study VLA1553-301 (13 in the VLA1553 arm and two in the placebo arm) and three in study VLA1553-302. There were no reports of pregnancy in VLA 1553-101. Pregnancy outcomes were reported for 16 female subjects vaccinated with VLA1553. There were 10/16 (62.5%) healthy babies were born, and 8 infants and their mothers had a 3-month safety follow-up. One subject (6.2%) was lost to follow up.

There were 5/16 (31.3%) miscarriages that occurred with less than gestation week 20. There was one fetus with Turner syndrome 45X, one subject was severely obese with BMI 60 mg/m² with a history of two previous miscarriages, and another subject had a blighted ovum anembryonic pregnancy. One subject (6.2%) became pregnant 3 months after vaccination and miscarried at week 8. A summary of these cases is as follows in the table below.

Table 2 Spontaneous Abortion Cases

Subject #/Study	Age	Onset of SAB After VLA1553 Vaccine	Gestational Age	Reasons
(b) (6) VLA1553-301	36	Spontaneous abortion 59 days (~2 months)	9-13 weeks	Not identified
(b) (6) VLA1553-301	33	Spontaneous abortion 99 days (~3 months)	5 weeks	Obesity BMI 60 kg/m ² . 2 previous miscarriages.
(b) (6) VLA1553-302	28	Spontaneous abortion 177 days (~6 months; pregnancy at 3 months after vaccination)	10 weeks	Overweight
(b) (6) VLA1553-302	23	Spontaneous abortion 55 days (~2 months)	8 weeks	Blighted ovum/ anembryonic pregnancy
(b) (6) VLA1553-301	22	Fetal death 101 days (~3.3 months)	11 weeks	Cytogenetic analysis on fetal tissue-single X-chromosome (45, X) consistent with Turner syndrome. COVID-19 vaccine administered (b) (6) approximately 1.5 months after VLA1553 (b) (6) One previous miscarriage.

Source: STN125777/0.19, Module 1.11.3, IR #18

Reviewer Comment: The rate of spontaneous abortion was higher (5/16, 31.3%) in the treatment arm in comparison to the general population (15–20%). Note that if pregnancies that occurred >45 days following vaccination are excluded, then there were 4/7 spontaneous abortions. Of the four spontaneous abortions, three cases had the following risk factors presenting alternate etiologies: Turner Syndrome (45, X); blighted ovum/ anembryonic pregnancy; morbid obesity with prior history of miscarriages.

No effects on pregnancy and fetal development were observed in animal studies. The Data Safety Monitoring Board reviewed the data on the miscarriage cases and did not identify any safety concerns. The ages of the subjects with miscarriages were between 23-36 years of age. The observed rate of miscarriages post-vaccination was slightly higher than typically seen in the general population.^{8 9 10} This observation led to a recommendation to further evaluate spontaneous abortions and pregnancy in a dedicated post marketing study and enhanced pharmacovigilance activities (see Section 6 below).

6 SPONSOR'S PHARMACOVIGILANCE PLAN

A summary of the sponsor's pharmacovigilance plan (PVP) is provided in the table below. The sponsor will perform routine pharmacovigilance for all adverse events per the requirements of 21 CFR 600.80.

Table 3 Summary of Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Action
Identified	No risks have been identified by the sponsor	--
Potential	Vaccine-associated arthritis	-Cases of arthralgia and arthritis will be followed-up via a dedicated questionnaire. -All spontaneous reports of arthritis or arthralgia, including prolonged cases of arthralgia, will be submitted as expedited reports (i.e., submission of 15-day reports) to VAERS, regardless of label status or seriousness for three years post-approval. In addition, a summary and analysis of all reports of arthritis and arthralgia (including prolonged cases) will be included in periodic safety reports for both interval and cumulative data for three years post-licensure.
Potential	Leukopenia, especially neutropenia	-Cases of leukopenia and neutropenia will be followed-up via a dedicated questionnaire.
Potential	Cardiac events	-Cases of cardiac events in the post marketing setting will be followed-up via a dedicated questionnaire if reporter information is available. - Submit all spontaneous reports of cardiac adverse events, including atrial fibrillation, as expedited reports (i.e., submission of 15-day reports) to VAERS, regardless of label status or seriousness, for three years post-licensure, and a summary and analysis of all reports of spontaneous cardiac adverse events (including atrial fibrillation) in periodic safety reports for interval and cumulative data.

Missing	Safety in pregnant women or breastfeeding women	-Targeted follow-up questionnaire. -Post-marketing safety study of pregnancy outcomes. -Submit all spontaneous reports of spontaneous abortion to VAERS as expedited reports, regardless of label status or seriousness, for three years post-licensure and assessment (based on interval and cumulative data) including a summary and analysis of safety in pregnancy in periodic safety reports.
Missing	Use in patients with autoimmune or inflammatory disorders	-Safety data will be collected in individuals with autoimmune or chronic inflammatory diseases, including those on immunosuppressants, in the voluntary post-marketing safety study and through routine pharmacovigilance.
Missing	Safety in frail patients with acute or progressive, unstable, or uncontrolled clinical conditions, e.g., cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions	-Safety data will be collected from individuals who are frail with acute or progressive, unstable, or uncontrolled clinical conditions in the voluntary post-marketing safety study and through routine pharmacovigilance.
Missing	Long-term safety	-Safety data are being collected in ongoing Study VLA1553-303 six months to two years following immunization with IXCHIQ, in the ongoing adolescent study VLA1553-321 in the endemic country Brazil (12 months follow-up). Further long-term safety data will be collected in the voluntary post-market safety study.
Missing	Interaction with other vaccines	-Data on concomitant vaccination will be collected in the voluntary post-market safety study and through routine pharmacovigilance.

Source: STN 125777/0, Risk Management Plan, pages 29-32 of 85, and Table 15, SVII 3.2, page 34-35 of 85. STN125777/0.55, 6-16-2023, updated Risk Management Plan. STN125777/0.32 4-28-32 IR #32.

Reviewer Comment: The pharmacovigilance plan submitted to STN125777/0.55 does not include the pregnancy safety study in Brazil (b) (4) -403). On July 19, 2023, DPV sent an information request to the sponsor asking they add the pregnancy safety study (b) (4) -403 and any other pregnancy studies the sponsor plans to perform to their PVP. The sponsor updated their PVP in the IR response submitted to STN125777/0.72.

6.1 Enhanced Pharmacovigilance

The sponsor will perform expedited reporting to VAERS regardless of seriousness or label status and summaries of both interval and cumulative data in the periodic safety reports for spontaneous abortions/pregnancies, arthralgias/arthritis, and cardiac events.

The sponsor will also use follow-up questionnaires to facilitate collection of structured data for vaccine associated arthralgia/arthritis, leukopenia and neutropenia, pregnancies, and cardiac events.

Reviewer comment: The sponsor acknowledged FDA's required enhanced pharmacovigilance activities in the IR response submitted to STN125777/0.55.

6.2 Safety-related Post Marketing Studies

The sponsor proposes a post-marketing safety study to evaluate the incidence of medically attended AESIs. Additionally, there is a dedicated post marketing pregnancy study as a PMC to evaluate safety in pregnancy.

6.2.1 “A post-marketing safety study of live-attenuated chikungunya virus vaccine (VLA1553) routinely administered in adults aged 18 years and above in the U.S. planning to travel to endemic areas”

This is a prospective, observational, multicenter, non-interventional, post-marketing study to evaluate the safety of the live-attenuated Chikungunya vaccine. This study plans to enroll 5,000 U.S. adult travelers planning to travel to endemic areas that will be followed for six months. Subjects enrolled will receive a single injection of live-attenuated Chikungunya virus vaccine to prevent disease.

It is estimated that 500 study travel clinic sites will participate. Study subjects will be followed via mobile app, email, and call centers with targeted questionnaires at Weeks 1, 2, 4, 8, 12, and 24. Subjects must be enrolled in the study within five days of receiving the vaccine.

Primary objective: To estimate the incidence of medically attended AESIs, including laboratory-confirmed infection with Chikungunya virus following the administration of the live-attenuated Chikungunya virus vaccine (VLA1553) in adults aged 18 years and above, residing in the U.S. and planning to travel to endemic areas.

Reviewer Comment: The primary analysis will compare rates of adverse events with background rates. Such a comparison may be biased as travelers to high-risk areas may not be representative of the general U.S. population. On July 19, 2023, FDA suggested the sponsor use the SCRI (self-controlled risk interval) analysis as the main analysis instead. The SCRI will be less biased, especially regarding time fixed confounders, and the sponsor may consider using time-related changes in the background incidence of the events of interest in the region of interest for time-varying adjustments if needed (using the area under the curve, for instance). The sponsor acknowledged this recommendation in the IR response submitted to STN125777/0.72.

Secondary objectives:

- To compare the observed incidence rate with the expected rate in the population for each medically attended AESI.
- To quantify the relative risk associated with VLA1553 and each medically attended AESI for which a risk window after vaccination can be defined.

- To describe the risk of medically attended AESIs following live-attenuated Chikungunya virus vaccine (VLA1553) administration, and interaction with other vaccines.
- To describe the use of the live-attenuated Chikungunya virus vaccine (VLA1553) and the risk of medically attended AESIs in individuals aged ≥ 65 years, HIV positive, patients with autoimmune or inflammatory disorders, patients with acute or progressive, unstable, or uncontrolled clinical conditions, pregnant or breastfeeding women, subjects with an infection in the past three days from the index date or with known or suspected defect of the immune system.

Study duration: The study duration is estimated as 42 months total. Participants will be enrolled for an estimated 36 months from marketing (estimated 2024) and data collection will occur until the last enrolled subject is followed for six months.

Inclusion criteria:

- Vaccination with VLA1553 at a participating travel clinic
- Subjects planning to travel to Chikungunya virus endemic areas within 60 days from the index date
- Age ≥ 18 years at the time of vaccination

Exclusion Criteria:

- Enrollment in the study more than 5 days after the index vaccine dose was received
- Subjects participating in another clinical study involving an investigational Chikungunya virus vaccine

Adverse Event of Special Interest (AESI): AESIs that will be followed in this study include rheumatoid arthritis, polyarthritis, polyarthralgia, spondyloarthropathy, myalgia, fibromyalgia, fever, anaphylaxis, seizure, rash, disseminated intravascular coagulation, venous thromboembolism, hemorrhagic stroke, syndrome of inappropriate antidiuretic hormone secretion, colonic diverticulitis, leukopenia, neutropenia, aseptic meningitis, Bell's Palsy, myelitis transverse, encephalitis, encephalomyelitis, acute disseminated encephalomyelitis, Guillain-Barré syndrome, optic neuritis, central nervous system inflammation, and sudden death.

Pregnancy outcomes:

A dedicated pregnancy and birth outcomes questionnaire will be used. Occurrence of inadvertent vaccination with VLA1553 vaccine during pregnancy or lactation or within 30 days preceding their last menstrual period (i.e., peri-conceptional period) or up to 24 weeks after receiving the vaccine will be followed via either mobile app, email or a call center with pregnancy and birth specific questionnaires until the end of the pregnancy. The sponsor proposes to collect baseline demographics, medical history including pregnancy or breastfeeding status, concomitant medications, vaccinations, information on travel, adverse events, hospitalizations, gestational age, vaccine details, pregnancy complications and neonate complications.

The pregnancy questionnaire will collect self-reported pregnancy outcomes (as applicable) during follow-up:

- Spontaneous abortion (miscarriage) (≤ 20 gestational weeks)
- Elective or therapeutic termination
- Live birth
- Stillbirth (> 20 gestational weeks, prior to delivery)
- Ectopic pregnancy (a pregnancy outside the uterus)
- Molar pregnancy (a non-viable fertilized egg implant in the uterus)
- Date of pregnancy outcome
- Gestational age at pregnancy outcome (weeks)

Data Collection: The following data will be collected directly from study participants at pre-specified follow-up points at weeks 1, 2, 4, 6, 8, 12 and 24:

- Pregnancy status (female participants of childbearing age only), breastfeeding status, and pregnancy and birth outcomes
- Details on occurrence of medically attended AESIs since the last follow up
- Other medication exposure, such as any new concomitant medication and changes in medication taken after vaccination as well as any other vaccines received
- Any changes in contact information
- Changes in preferred follow-up method—telephone interview or web/app-based questionnaire
- Reasons for discontinuation.

Study Milestones: Sponsor proposes to start on January 1, 2024, with the last date of enrollment on December 31, 2026 and End of Study on June 30, 2027.

Reviewer Comment: The above post-market study to assess the safety of IXCHIQ will be a voluntary study.

This study does include evaluation of pregnancy outcomes. However, use in pregnancy is not recommended since this is a live vaccine and thus exposure during pregnancy would likely be unintentional and prior to the patient being aware of the pregnancy. A U.S. travel vaccine is unlikely to yield many pregnancy cases after vaccine exposure due to limited uptake. Thus, DPV recommended a study outside of the U.S. in countries where the vaccine is more likely to be used on a routine basis. The sponsor proposed two potential pregnancy studies, one in Brazil and a claims-based study in Puerto Rico (response to IR submitted to STN125777/0.32), which are discussed below.

6.2.2 “Observational study to evaluate the safety of live attenuated chikungunya virus vaccine (b) (4) in pregnant women aged 18-45 years exposed to the vaccine”.

This is a prospective observational cohort multi-center, non-interventional, post marketing study to evaluate the safety of the live-attenuated CHIKV vaccine (b) (4) in pregnant women residing in Brazil and their offspring (submitted to STN125777/0.42).

Primary Objective: To assess the incidence of pregnancy outcomes in women aged 18 to 45 years vaccinated with (b) (4) up to 30 days before their last menstrual period, at any point during pregnancy, or from pregnancies reported within 24 weeks after vaccination.

Reviewer Comment: The primary study objective includes women who become pregnant within 24 weeks after vaccination. On July 11, 2023, an IR was sent to the sponsor to provide rationale for 24 weeks. The sponsor responded to the IR (submitted to STN125777/0.63) suggesting a 30 day period after vaccination for studying reported pregnancies. The rationale for studying pregnancies reported within 24 weeks after vaccination is to align with the follow-up proposed voluntary post-marketing U.S. travel study and covers the time period with the miscarriage reported in the Phase 3 studies, with the longest temporal distance from vaccination in a subject who became pregnant more than 3 months after vaccination. On July 19, 2023 in an IR, the FDA recommended the pregnancy safety studies include women with IXCHIQ exposure up to 30 days before the last menstrual period or at any point during pregnancy, which was acknowledged by the sponsor in the IR response submitted to STN125777/0.72.

Secondary Objective:

- Assess the incidence of low birth weight, congenital anomalies, and neonatal mortality in infants born to mothers vaccinated with (b) (4)
- Evaluate the incidence of adverse events in women aged 18 to 45 years vaccinated with (b) (4), up to 24 weeks after (b) (4) vaccination

Exploratory Objective:

If feasible, to compare the incidence rate of pregnancy and neonatal outcomes of interest in women vaccinated with (b) (4) with the expected background rate in similar local populations

Reviewer comment: A limitation of this study is the absence of a comparator group. FDA recommended a comparator group be included in this study and the sponsor has stated that adding a comparator group to this study is feasible (response to IR submitted to STN125777/0.63). The potential comparator would include a contemporaneous cohort of pregnant women who have not received (b) (4) vaccine attending the health centers for pregnancy or other routine visits. Vaccinated subjects could be matched with unvaccinated contemporary controls by maternal age at conception (18-19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years, and 40-45 years); gestational age at vaccination; season; and residential area.

Inclusion Criteria:

- Vaccination with (b) (4) at a participating vaccination center in the selected municipalities in Brazil
- Subject is able to understand and follow the study procedures and provide written informed consent prior to any study-related procedures
- Women of child-bearing age (18-45 years) at the time of vaccination

- Women exposed to (b) (4) while pregnant, anytime during their pregnancy, or within 30 days preceding their last menstrual period (i.e., peri-conceptional period). Women who report pregnancy within 24 weeks after receiving the (b) (4) vaccine will also be included.
- Subject can provide valid contact information for remote follow-up

Exclusion Criteria: Subject participating in any interventional clinical trial

Sample Size: 90-130 pregnancies

The sponsor plans to target a total population of 1.5 million individuals, of which the population of women aged 18-45 years is estimated to be 22% or 330,000. If 20% were vaccinated, this is estimated to be 66,000 women. It is estimated that 10% of these vaccinated women may give consent to participated in the study, and this would be approximately 6,600 women. To estimate the number of inadvertent pregnancies, a lower and upper bound was established. For the lower bound, the sponsor took the rate of 1.35% as observed in the clinical trial VLA1553-302 which had three pregnancies out of 223 enrolled women of childbearing age. Based on this, the sponsor expects to have approximately 90 inadvertent pregnancies. To establish an upper bound, the sponsor examined evidence of inadvertent pregnancy in literature and identified a rate of 1.7%. To establish an upper bound a rate of 2% was assumed, which corresponds to approximately 130 inadvertent pregnancies.

Data collection: Women will be followed via either mobile app, email or a call center with pregnancy and birth specific questionnaires up to 12 weeks after the end of the pregnancy, withdrawal, loss to follow-up, or death. Monthly follow up includes pregnancy complications (preeclampsia, eclampsia, ectopic pregnancy, gestational diabetes, placenta previa, placental abruption, hyperemesis gravidarum, intrauterine growth restriction, infections). Record verification will be used where possible.

Pregnancy outcomes are:

- Spontaneous abortion
- Still birth
- Preterm birth
- Live birth
 - o Birth weight
 - o Congenital anomaly
 - o Neonatal death

Study Milestones: The sponsor provided the following study milestones (response to IR submitted to STN125777/0.72):

Final Protocol Submission: November 30, 2023

Study Completion Date: June 30, 2027

Final Report Submission: December 30, 2027

Reviewer Comment: There is a long delay between potential FDA approval and the initiation of the pregnancy study in Brazil given that licensure in Brazil is not expected until late 2024 or 2025. Thus, the sponsor was requested to develop the claims-based study in Puerto Rico, which had the potential to begin sooner following anticipated FDA approval, that was submitted to STN125777/0.46 and STN125777/0.52. However, the sponsor is uncertain if the databases available in Puerto Rico can obtain information on pregnancy and infant outcomes. Future uptake of IXCHIQ in Puerto Rico is also uncertain. The sponsor was thus requested to perform the pregnancy safety study in Brazil as a PMC given that a comparator group is feasible and it was uncertain if the claims-based study in Puerto Rico could be performed.

The sponsor was notified of the request to conduct the pregnancy safety study in Brazil as a PMC in correspondence dated July 23, 2023.

In a response to an IR submitted to STN125777/0.72, the sponsor indicated they would not pursue the claims-based study in Puerto Rico and will only focus on the study option in Brazil.

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

None.

7.2 Important Potential Risks

7.2.1 Potential Risk: Vaccine-associated arthritis

An imbalance was observed in the clinical studies for arthritis and arthralgia, including prolonged cases following vaccination with IXCHIQ. Post-vaccination arthritis is expected to be transient in nature. The risk of vaccine-associated arthritis will be listed in the US Prescribing Information Section 6 (Adverse Reactions). Cases of arthralgia and arthritis will be followed-up via a dedicated Questionnaire. DPV recommends enhanced pharmacovigilance for arthritis/arthralgia for three years post-approval, i.e., expedited reports (i.e., submission of 15-day reports) to VAERS, regardless of label status or seriousness, and a summary and analysis of all reports of arthritis and arthralgia (including prolonged cases) in Periodic Adverse Experience Report for interval and cumulative data.

Reviewer comment: The proposed PVP to monitor the potential risk of vaccine-associated arthritis is appropriate with the addition of enhanced PVP activities.

7.2.2 Potential Risk: Neutropenia, Leukopenia

An imbalance in neutropenia and leukopenia was observed in the clinical studies. The risk of leukopenia and neutropenia will be listed in the US Prescribing Information Section 6 (Adverse Reactions). Cases of leukopenia, especially neutropenia, will be followed-up via a dedicated Questionnaire.

Reviewer comment: The proposed PVP to monitor the potential risk of leukopenia and neutropenia is appropriate.

7.2.3 Potential Risk: Cardiac events

The sponsor added cardiac events to their PVP as an Important Potential Risk due to an imbalance in serious cardiac adverse events (five serious adverse events in the vaccine group compared to none in the placebo group) in the clinical trials for IXCHIQ (response to IR submitted to STN125777/0.55). The sponsor will use a dedicated adverse event questionnaire to facilitate collection of structured data for cardiac adverse events, including atrial fibrillation. The sponsor will also perform enhanced pharmacovigilance activities that includes submission of all spontaneous reports of cardiac adverse events, including atrial fibrillation, as expedited reports (i.e., submission of 15-day reports) to VAERS, regardless of label status or seriousness, for three years post-licensure, and analysis of all reports of spontaneous cardiac adverse events (including atrial fibrillation) in periodic safety reports for interval and cumulative data.

Reviewer comment: The proposed PVP to monitor the potential risk of cardiac events with the addition of enhanced PV reporting is appropriate.

7.2.4 Missing Information: Pregnant or breastfeeding women

Pregnant subjects were excluded in the clinical pivotal studies since live vaccines administered to a pregnant woman pose a theoretical risk to the fetus, and therefore, are generally not administered to pregnant women. There is a risk of transmission of virus between mother and fetus that may have adverse effects on the fetuses and nursing babies. The effect of the Chikungunya vaccine in pregnant patients is not known.

The sponsor will perform both routine and enhanced pharmacovigilance activities to further evaluate safety in pregnancy. The sponsor will submit all spontaneous reports of spontaneous abortion to VAERS as expedited reports, regardless of label status or seriousness, for three years post-licensure should IXCHIQ be approved, and submit an assessment (based on interval and cumulative data) including a summary and analysis of safety in pregnancy in periodic safety reports. The sponsor will also use a dedicated pregnancy questionnaire to facilitate structure data collection.

The sponsor is performing a voluntary study of safety outcomes in U.S. travel clinics, including outcomes in pregnant women; however, this study will likely not have a sufficient number of pregnant women to meaningfully evaluate safety. The sponsor was thus requested to perform a pregnancy safety study in a population in which IXCHIQ exposure will likely be routine. The sponsor submitted proposals for a study in Brazil and a study in Puerto Rico using claims data. The study in Brazil will be a PMC and the sponsor will not pursue the study in Puerto Rico due to feasibility concerns (response to IR submitted to STN125777/0.72).

Reviewer Comment: The sponsor's PVP to evaluate safety in pregnancy is adequate with updated information regarding the dedicated pregnancy studies.

7.2.5 Missing Information: Autoimmune or inflammatory disorders

There is no information on the safety of the vaccine in autoimmune or inflammatory disorders. The theoretical concern is that the vaccine may exacerbate underlying disease. It is hypothesized that vaccines which contain inactivated viral pathogens or attenuated pathogens may function as agents that trigger autoimmune disease. Individuals with autoimmune or chronic inflammatory diseases, including those who may be on immunosuppressants, will be monitored in the voluntary post-marketing safety study and through routine pharmacovigilance.

Reviewer comment: The proposed PVP to monitor the risk of missing information for autoimmune and inflammatory disorders is appropriate.

7.2.6 Missing Information: Frail adults with acute or progressive, unstable, or uncontrolled clinical conditions e.g., cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions

There is limited use in a population ≥ 65 years and older. The vaccine has not been studied in frail individuals with severe co-morbidities, and only has been studied in healthy adults. The immune function may be compromised due to the condition or treatment of the condition. Individuals who are frail with acute or progressive, unstable, or uncontrolled clinical conditions will be monitored in the voluntary post-marketing safety study and through routine pharmacovigilance.

Reviewer comment: The proposed PVP to monitor the risk of missing information for individuals who are frail with severe co-morbidities is appropriate.

7.2.7 Missing Information: Long-term safety

The long-term safety of the Chikungunya vaccine is not known. Data will be monitored in clinical studies and the voluntary post-marketing safety study and through routine pharmacovigilance.

Reviewer comment: The proposed PVP to monitor the risk of missing information for long-term safety is appropriate.

7.2.8 Missing Information: Interaction with other vaccines

The vaccine will be used in individuals who may also receive other vaccines. Data of coadministration with other vaccines will be collected in a voluntary post-marketing safety study as well as through routine pharmacovigilance.

Reviewer comment: The proposed PVP to monitor the risk of missing information for individuals who have received other vaccinations is appropriate.

8 DPV ASSESSMENT

Review of the clinical trial data identified potential imbalances in arthritis/arthralgia, neutropenia and leukopenia, cardiac events, and spontaneous abortion. In addition to routine pharmacovigilance, the safety concerns of arthritis/arthralgia, cardiac events, and spontaneous abortion will be further evaluated in the post-market setting with enhanced pharmacovigilance activities, which include expedited reporting, a summary

and analysis in periodic safety reports, and dedicated adverse event questionnaires. The sponsor will further evaluate neutropenia and leukopenia with a dedicated adverse event questionnaire and will be included in the 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 sponsor will conduct a voluntary post-marketing safety study of 5,000 U.S. travelers for medically attended adverse events of special interest, including pregnancy outcomes. The sponsor's PVP is acceptable.

9 DPV RECOMMENDATIONS

Should IXCHIQ be approved for the active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years and above, the sponsor's PVP (version 0.6, dated July 31, 2023), which includes two post-market studies (one PMC and one voluntary safety study), enhanced pharmacovigilance activities for the Important Potential Risks and safety in pregnancy, and routine surveillance in accordance with 21 CFR 600.80 is acceptable. The PMC will further evaluate safety in pregnancy in the post-market setting. DPV will review the final protocol of the PMC study upon submission. The available safety data do not substantiate a need for a REMS. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

APPENDIX

1. Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Documents Reviewed
12/22/2022	Sponsor	STN125777/0.3	Summary of Clinical Safety
12/22/2022	Sponsor	STN125777/0.3	Risk Management Plan
12/22/2022	Sponsor	STN125777/0.3	Clinical Overview
12/22/2022	Sponsor	STN125777/0.3	VLA1553-301 Clinical Study Report
12/22/2022	Sponsor	STN125777/0.3	VLA1553-101 Clinical Study Report
12/22/2022	Sponsor	STN125777/0.3	VLA 1553-PASS Clinical Post Marketing Protocol
2/10/2023	Sponsor	STN125777/0.7	VLA1553-302 Clinical Study Report
3/14/2023	Sponsor	STN125777/0.19	Information Request Response #18, Clinical
4/28/2023	Sponsor	STN125777/0.32	Information Request Response #32, PVP
5/19/2023	Sponsor	STN125777/0.42	Information Request Response #37, Brazil Pregnancy Study (b) (4) -403
6/16/2023	Sponsor	STN125777/0.52	Information Request Response #46, Puerto Rico Pregnancy Study VLA1553-40X PR
6/21/2023	Sponsor	STN125777/0.55	Information Request Response #52, Updated Risk Management Plan
7/14/2023	Sponsor	STN125777/0.63	Information Request Response #63, Post-marketing Studies (b) (4) PASS Pregnancy and VLA1553-40X PR
7/20/2023	Sponsor	STN125777/0.68	Information Request Response #66, Clinical AE Causality Assessment
7/26/2023	Sponsor	STN125777/0.72	Information Request Response #68, Post-marketing Safety Studies and PVP

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