



**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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**To:** Konstantin Virnik  
Chair of the Review Committee  
Office of Vaccine Research and Review

**Through:** Kerry Welsh, MD, PhD  
Branch Chief, PB3

Meghna Alimchandani, MD  
Acting Director DPV  
OBPV, CBER, FDA

**Subject:** Review of Pharmacovigilance Plan

**Sponsor:** Bavarian Nordic A/S

**Product:** VIMKUNYA (Chikungunya vaccine,  
Recombinant)\*

**Application Type / Number** BLA / STN 125820/0

**Proposed Indication** Active immunization for the prevention of  
disease caused by Chikungunya virus in  
individuals 12 years and above

**Submission Date:** April 29, 2024

**Action Due Date:** February 15, 2025

\* This product is referred to as CHIKV VLP 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 BLA STN125820/0 based on the safety profile of Vimkunya (Chikungunya Vaccine, Recombinant). 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 Vimkunya, should the indication for this product be approved. Please refer to Appendix 1 for the complete list of materials reviewed for this memorandum.

## **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, there is one live vaccine (IXCHIQ) available to prevent Chikungunya virus disease approved in the United States (US) for individuals 18 years of age and older. Of note, IXCHIQ has been associated with chikungunya-like adverse reactions based on clinical trial data and postmarketing VAERS data.

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.<sup>1</sup>

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.<sup>2</sup>

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 ( $\mu$ PRNT), is provided by a threshold  $\mu$ PRNT titer of  $\geq 150$  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  $\mu$ PRNT titer of  $\geq 150$ .

## **3 PRODUCT INFORMATION**

### 3.1 Product Description

The recombinant vaccine consists of virus-like particles (VLP) from an adjuvanted Chikungunya Senegal strain (CHIKV 37997). A single injection of Vimkunya is administered intramuscularly as a suspension of 40 mcg of CHIKV VLPs with 300 mcg aluminum adjuvant per 0.8 mL dose in a pre-filled syringe. Non-active excipients and buffer components of this are aluminum hydroxide, sucrose, sodium citrate, potassium phosphate dibasic, potassium phosphate monobasic, and water. The package will contain one single-use 1.0 mL prefilled syringe with (b) (4) of filled vaccine to allow for (b) (4) 0.8 mL deliverable.

### 3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125820/0 is:

*VIMKUNYA is a vaccine indicated to prevent disease caused by chikungunya virus infection in individuals 12 years of age and older.*

*This indication is approved under accelerated approval based on serum neutralizing antibody levels considered to be protective. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*

*Reviewer Comment: The Division of Pharmacovigilance (DPV) defers to the 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

There are no approvals outside of the United States for Vimkunya at this time.

The IXCHIQ vaccine, the first vaccine indicated to prevent disease caused by Chikungunya virus, was approved by FDA on November 9, 2023. Safety in pregnancy is a concern for IXCHIQ, given the observed rate of spontaneous abortions during the first three months postvaccination was 25% in clinical trials, which was considered greater than the general population. Chikungunya-like illness was also identified as a safety concern, with 11.7% of clinical trial recipients and only 0.6% of placebo recipients reporting Chikungunya-like illness. Safety in pregnancy and Chikungunya-like illness is being further evaluated by enhanced pharmacovigilance activities and post-marketing studies for IXCHIQ. Please refer to the Division of Pharmacovigilance review memorandum under STN125777/0 for more details.

## 5 DESCRIPTION OF VIMKUNYA CLINICAL TRIAL SAFETY DATABASE

### 5.1 Clinical studies

The clinical study safety data reviewed are from the Sponsor's Clinical Study Report (CSR), Summary of Clinical Safety (SCS), Clinical Overview, and Integrated Summary

of Safety (ISS) submitted to STN 125820/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform 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 125820/0 be approved. Please refer to the package insert for the final clinical safety data.

As described in the Sponsor's SCS, the Sponsor developed five studies toward establishing the efficacy, immunogenicity, tolerability, and/or safety of Vimkunya, as summarized in Table 1. Two additional studies were included in the SCS to provide supportive safety data; however these were conducted using an unadjuvanted CHIKV VLP vaccine formulation, at different dosages, and with different administration schedules not reflective of the final product.

The collective safety information from the five vaccine studies provide data for 4197 participants. There were 3522 participants that were exposed to at least one dose of CHIKV VLP vaccine, 3141 participants that received a single dose of 40/300 mcg CHIKV VLP vaccine, and 675 placebo participants in the pooled analysis. Study EBSI-CV0317-0004 accounts for the largest number of participants (3254 participants) receiving the final formulation and representative of the age group proposed for the current indication.

**Table 1: Summary of clinical studies supporting the safety of Vimkunya**

Study	N	Description
PXCX-CV-317-001 (Referred to as Study 001)	445 participants 18-45 years of age; 441 received CHIKV VLP vaccine	Phase 2 parallel group, randomized, double-blind dose- and schedule finding clinical study. Enrolled participants aged 18-45 to evaluate dosing and scheduling safety at seven and up to 28, 57, 182, 365 or 760 days after a single or double immunization depending on the treatment arm (10 treatment groups).
EBSI-CV-317-002 (Referred to as Study 002)	60 participants 18-45 years of age; 60 received CHIKV VLP vaccine	Phase 2 parallel group, open-label clinical study. Half of participants received investigational heterologous alphavirus vaccine 60 days prior to injection of CHIKV VLP vaccine; Enrolled participants aged 18-65 to evaluate safety at 28 and 182 days after a single immunization.
EBSI-CV-317-010 (Referred to as Study 010)	25 participants 18-45 years of age; 25 received CHIKV VLP vaccine	Phase 2 open-label, single arm clinical study; Enrolled participants aged 18-45 to evaluate safety at 28, 64, and 183 days after a single immunization.

EBSI-CV-317-004 (Referred to as Study 004)	3254 participants aged 12-65 years of age; 2790 received CHIKV VLP vaccine	Phase 3 pivotal randomized, placebo-controlled, double-blind, parallel-group design; Enrolled participants aged 12-64 to evaluate safety at 28, 92, and 183 days after a single immunization.
EBSI-CV-317-005 (Referred to as Study 005)	413 participants 65 years of age or older; 206 received CHIKV VLP vaccine	Phase 3 pivotal randomized, placebo-controlled, double-blind parallel-group design; Enrolled participants 65 and older to evaluate safety at 28, 92, and 183 days after a single immunization.

\*Adapted from Table 1, Summary of Clinical Safety, STN 125820/0, Module 2.7.4

## 5.2 Adverse events

### 5.2.1 Solicited and Unsolicited Adverse Events

The most common solicited systemic adverse events (AEs) (Incidence 37.1% for any event among single dose 40/300 mcg CHIKV VLP recipients) in the pooled analysis of clinical studies (Studies 001, 002, 010, 004, 005) with 3114 vaccinees<sup>1</sup> were fatigue (18.7%, n= 582), headache (17.0%, n=530), and myalgia (16.8%, n=523). The most common solicited injection site adverse event (incidence 23.3%, n=725, among single dose 40/300 mcg CHIKV VLP recipients) was pain. Solicited systemic AEs reported up to seven days after vaccination with CHIKV VLP include fever, chills, fatigue, headache, myalgia, arthralgia/joint pain, nausea, and malaise. For all symptoms, the CHIKV VLP vaccine group experienced a higher rate of events than the placebo group.

In the pooled analysis, unsolicited AEs (for any event) occurred in 15.7% (n=492/3141) of 40/300 mcg CHIKV VLP recipients and 14.4% (n=97/675) of placebo recipients. The most common System Organ Class (SOC) occurring up to seven days post-vaccination in the 40/300 mcg CHIKV VLP group were infections and infestations (5.8%), the most common of which were COVID-19 (2.0%) and upper respiratory infection (0.5%). In the pooled analysis, the top 10 unsolicited AEs occurring in the 40/300 mcg CHIKV VLP group were headache, arthralgia, dizziness, fatigue, rash, injection site pain, and myalgia. Grade ≥3 unsolicited AEs that were considered treatment-related by the investigator included a grade 3 dehydration, which resolved without medical intervention, and a grade 3 fatigue, both occurring in the 40/300 mcg CHIKV VLP vaccine group.

*Reviewer comment: Adverse events with arthralgia/arthritis were of particular interest given prolonged arthralgia was a concern with the IXCHIQ vaccine. No imbalance was observed between the treatment arms with arthralgia/arthritis with use of CHIKV VLP. Adverse events with arthralgia/arthritis are further discussed below.*

Arthralgia/Arthritis:

<sup>1</sup> The denominator for solicited adverse events is based on the number of participants who completed a diary.

The solicited adverse event of arthralgia/joint pain occurred at 7.4% (n=230/3114) compared to 6.2% (n=41/661)<sup>1</sup> in those that received placebo in the pooled data analysis. Most cases were mild or moderate in severity. Three patients experienced new onset or worsening prolonged arthralgia that was medically attended greater than seven days in duration.

The prolonged arthralgia cases are summarized below:

1. Subject (b) (6) (Study 004). 37-year-old female with a medical history of seasonal allergies, bilateral tubal ligation, gallbladder excision, idiopathic recurrent episodes of syncope/collapse, and cannabis use, received the vaccine study drug in her left deltoid on (b) (6). She experienced Grade 2 (moderate) left shoulder pain radiating to the left neck from April 24, 2022. She went to the ER on (b) (6) and was prescribed buprenorphine and ibuprofen. Patient was lost to follow-up on May 24, 2022 and the outcome was listed as not recovered/not resolved given the loss to follow-up and inability to collect data on the end date of her arthralgia as described in a response to an Information Request (IR) submitted to STN125820/0.22.
2. Subject (b) (6) (Study 004). 58-year-old male with a medical history of hypertension, right elbow pain, and erectile dysfunction received the vaccine study drug on (b) (6). He was involved in an automobile accident on (b) (6) and later developed Grade 2 (moderate) bilateral glenohumeral pain and lumbago. He was treated by a chiropractor and prescribed diclofenac sodium (oral and cream) and tizanidine. All symptoms were resolved by May 15, 2022 (81 days).
3. Subject (b) (6) (Study 004). 24-year-old male with medical history of anxiety, depression, and hyperlipidemia received the vaccine study drug on (b) (6). He experienced grade 1 arthralgia from March 23, 2022 to July 1, 2022 (101 days duration). Patient experienced a concomitant symptomatic gonococcal pharyngitis and genital HSV infection with resultant, ongoing penile lesion and associated intermittent neuromuscular/joint pain flare symptoms. Patient received multiple treatments for the concomitant infections, including antibiotic and antiviral medications, and symptoms resolved.

*Reviewer comment: Narratives of the patients with prolonged arthralgia were reviewed. No concerns were identified with the cases of prolonged arthralgia, given that other documented issues, such as a motor vehicle accident and infection, unrelated to vaccination with Vimkunya, are more likely the cause of the prolonged arthralgia. In an IR response submitted to STN125820/0.22, the Sponsor stated that the median and mean duration of arthralgia among unsolicited arthralgia events was 25.0 days and 63.6 days, respectively, among the single dose 40/300 mcg CHIKV VLP vaccine recipients with arthralgia (n=17) as compared to a mean and median duration of 4.0 days and 4.0 days, respectively, among the pooled placebo recipients with arthralgia (n=4). Review of the unsolicited arthralgia case narratives of individuals with arthralgia durations exceeding 30 days submitted to STN125820/0.26 and STN125820/0.43 did not reveal any new concerns, given that other issues such as a motor vehicle accident,*

*trauma/falls, and pre-existing chronic joint pain were more likely the cause of the prolonged arthralgia.*

### **5.2.2 Withdrawals Due to AEs**

A total of 5/4197 (0.12%) withdrawals were due to unsolicited AEs in the pooled analysis. There were four adverse events (Worsening nephrocalcinosis, Hit and Run Road Traffic Accident, Fronto-ethmoid encephalocele, and Respiratory failure) leading to withdrawal in the CHIKV VLP arm and one adverse event (Lung cancer) in the placebo arm leading to withdrawal. Three of these events are deaths and one is a pregnancy outcome, all of which are further described below under the 5.2.4 Deaths and 5.2.6 Safety in Pregnancy. The patient experiencing worsening nephrocalcinosis is described below.

1. Subject (b) (6) (Study 001). 40-year-old female with a medical history of nephrocalcinosis s/p lithotripsy, migraines, restless leg syndrome, dysmenorrhea, seasonal allergies, obesity, gastric bypass, uterine ablation, hysterectomy, recurrent pancreatitis, anxiety and depression received the vaccine on (b) (6) (b) (6). She experienced worsening nephrocalcinosis on (b) (6). She continued oxybutynin and started Urocit-K on (b) (6) to treat the worsening calcinosis. The worsening nephrocalcinosis was reported as resolved on May 28, 2018, however the patient withdrew from the study as a result of the adverse event.

*Reviewer Comment: Narratives of the patients who withdrew were reviewed. No common factors were identified with the cases of withdrawals due to adverse events.*

### **5.2.3 Serious Adverse Events (SAEs)**

There were 1.1% (n= 37/3522) of subjects in the pooled CHIKV VLP arm and 0.6% (n= 4/675) of subjects in the placebo arm that reported 41 and four SAEs, respectively. SAEs occurred most frequently in the System Organ Class Infections and Infestations. This class included preferred terms pneumonia, gastroenteritis, appendicitis, cellulitis, pyelonephritis, tubo-ovarian abscess, influenza B, infection of chemotherapy port site, clostridium difficile infection, COVID-19, Methicillin-resistant staphylococcus aureus infection, urosepsis, and cellulitis. There was one SAE of retinal detachment that was considered possibly treatment-related by the study investigator discussed below.

1. Subject (b) (6) (Study 004). 57-year-old female with medical history of depression, insomnia, and strabismus surgery of the right eye (1967) received the study drug on (b) (6). On January 19, 2022 patient experienced loss of vision in right eye. She underwent surgical revision on a retinal detachment on (b) (6). Patient informed study group on February 7, 2022 that she had experienced black spots in her vision for about one month prior to the vision loss on January 19, 2022.

*Reviewer comment: The Preferred Terms for SAEs were reviewed. No imbalances were noted.*

#### 5.2.4 Deaths

A total of three deaths occurred: one death in Study 004 and two deaths in Study 005. There were two deaths among the 40/300 mcg CHIKV VLP group and one in the placebo group, none of which were assessed as related to study IP by the Sponsor. A summary of the deaths are as follows:

1. 32-year-old male (Subject (b) (6) from Study 004) experienced a road traffic hit and run accident on day<sup>(b) (6)</sup> which was fatal at the site of the accident. He was not taken to a hospital and pronounced dead at the site. No autopsy was performed. Medical history included herniated disc L4-L5 and methadone use.
2. 71-year-old female (Subject (b) (6) from Study 005) experienced lung cancer (placebo) on day<sup>(b) (6)</sup> which was fatal that day. Medical history included hypertension, emphysema, umbilical hernia, and lung cancer.
3. 77-year-old female (Subject (b) (6) from Study 005) experienced respiratory failure on day<sup>(b) (6)</sup> due to worsening community acquired pneumonia, which was fatal on Day 87. She was initially admitted to the hospital for difficulty breathing secondary to pneumonia. Due to her worsening overall health, she was discharged to hospice. Medical history included arthritis of bilateral shoulders, myocardial infarction (2018), high cholesterol, hypertension, insomnia, bronchial congestion, intestinal spasms, back pain, bilateral shoulder and knee pain, basal cell carcinoma, and constipation.

*Reviewer comment: All deaths occurred several months after vaccination. There were no common factors among the cases of death and all had other conditions or circumstances that likely led to death (road traffic accident, lung cancer, and community acquired pneumonia). We agree with the sponsor assessment that the deaths were not attributed to vaccination.*

#### 5.2.5 Adverse Events of Special Interest (AESIs)

AESIs include arthralgia, spinal osteoarthritis, and joint dislocation. AESIs were reported in 6/3522 subjects (0.2%) in the pooled CHIKV VLP arm and 2/675 (0.3%) in the placebo arm. The cases of prolonged arthralgia were discussed under 5.2.1.

*Reviewer comment: The cases of arthralgia are discussed under 5.2.1 Solicited and Unsolicited Adverse events. No other imbalances or common factors were identified with the cases of AESI.*

#### 5.2.6 Safety in Pregnancy

There were 11 pregnancies (with 12 pregnancy outcomes) that were recorded for female participants: nine pregnancies in Study 001 (eight in CHIKV VL arm and one in placebo arm) and two in Study 004 (both CHIKV VL arm). There were no reports of pregnancy in the other three studies. Pregnancy outcomes were reported for eight subjects vaccinated with CHIKV VLP. There were seven live births in six of the ten pregnant study participants that received CHIKV VLP. Among the vaccine arm, there was one ectopic pregnancy, one spontaneous abortion that led to an incomplete induced abortion complicated by hemorrhage, one early term cesarean delivery with major congenital anomaly (fronto-ethmoid encephalocele), two preterm infants (33 week twin set) that required a neonatal intensive care unit (NICU) admission for preterm birth



and low birth weight, three early term normal births, one full term normal birth, and two unknown outcomes (due to loss to follow-up). The one pregnancy that occurred in the placebo arm resulted in a full term normal birth.

In Study 001, three pregnancies were complicated by SAEs. There was one patient that experienced an incomplete spontaneous abortion. In Study 004, one pregnancy was complicated by an SAE. Narratives of the SAEs are included below.

### **Adverse Events Among Pregnant Women**

1. Subject (b) (6) (Study 001). 34-year-old female with medical history of eczema, headaches, tubal pregnancy resulting in miscarriage and laparoscopic tubal excision (b) (6) ectopic pregnancy resulting in right salpingostomy (2011), endometriosis, asthma, low back pain, and right ankle pain received the vaccine on (b) (6). Patient experienced abdominal pain and vaginal bleeding on (b) (6) and was diagnosed with ectopic pregnancy. She received methotrexate on (b) (6) and (b) (6). Patient did not receive repeat vaccination on day 29 (b) (6) secondary to positive pregnancy test. She recovered fully by June 30, 2018.
2. Subject (b) (6) (Study 001). 31-year-old female with no significant medical history received the vaccine on (b) (6) and (b) (6). Date of pregnancy was not identified. Patient experienced threatened preterm labor from (b) (6) followed by vaginal bleeding from May 21, 2019 to June 3, 2019 and placental abruption on (b) (6) which resolved (b) (6). Patient delivered by cesarean section preterm twin males at 33 weeks gestation on (b) (6). Infants required NICU stay due to preterm birth and low birth weight. Patient was lost to follow up on August 9, 2019.
3. Subject (b) (6) (Study 001). 34-year-old female with medical history of anemia, intermittent headaches, seasonal allergies, and cesarean section (x2) received the vaccine on (b) (6). Patient experienced a urinary tract infection from (b) (6) which was successfully treated with antibiotics. Patient had a ParaGard IUD which was removed in (b) (6). Date of pregnancy was not identified. Patient experienced incomplete spontaneous abortion from (b) (6) to (b) (6). She was treated with misoprostol on (b) (6). She experienced hemorrhage from incomplete induced abortion from (b) (6) to (b) (6) which led to worsening of anemia from October 1, 2018 to April 30, 2019. She was treated with Cytotec, methergine, morphine, IV fluids, and packed red blood cells.
4. Subject (b) (6) (Study 004). 28-year-old female with medical history of anxiety, polycystic ovarian syndrome, vitamin d deficiency, and ADHD received the vaccine on (b) (6). Patient was identified on July 28, 2022 and reported on August 16, 2022. Pregnancy was complicated by gestational hypertension and Class A2 Diabetes Mellitus. The fetus developed fronto-ethmoid encephalocele, diagnosed prenatally. Patient delivered infant by cesarean section on (b) (6) at 37 weeks gestation. The infant required blow-by oxygen due to grunting and retractions at delivery and was admitted into the NICU and discharged home on (b) (6).

*Reviewer comment: Due to the small number of pregnancy study participants, the safety of CHIKV VLP vaccine in pregnant participants and neonates is limited. There was one ectopic pregnancy in a woman with a prior history of ectopic pregnancy and likely predisposition to subsequent ectopic pregnancies. The preterm birth outcomes were associated with a twin pregnancy, and while it is not possible to attribute causation of the preterm birth (followed threatened preterm labor, vaginal bleeding, and placental abruption) to the twin pregnancy, it is a common complication of twin pregnancies due to the increased stress on the uterus in pregnancies involving multiple infants. There was one outcome of front-ethmoid encephalocele, a neurologic congenital anomaly. The etiology of birth defects is often multifactorial and can be caused by genetic factors, infection, and exposure to certain substances during pregnancy. Major congenital anomalies are fairly common, occurring in 3% or about one in every 33 infants in the U.S. and therefore, with the limited data and no pattern of this anomaly seen in the other infants, there are multiple factors that could be attributed to this pregnancy outcome outside of vaccination.<sup>3</sup> A specific safety signal concerning spontaneous abortion is not present (n=1 and in line with the typical frequency observed in the general population), which was a concern in the IXCHIQ vaccine.*

*No effects on pregnancy were observed in animal studies. Decreased postnatal viability in the kits of vaccine-treated pregnant rabbits (63.18% vs. 77.28% among the control group at day 4 postpartum) was observed in “A Fertility and Postnatal Development Toxicity Study of PXVX0317 Vaccine by Intramuscular Injection in Female Rabbits.” FDA calculated the percent survival in the vaccine group as compared to the control group at 28 days postnatally to be 42.2% vs. 69.0% respectively. Decreased activity was also noted in the kits of vaccinated females compared to controls. Please see the Pharmacology-Toxicology review memorandum for more details. The clinical significance of these animal study findings for humans is unknown.*

*A pregnancy safety study is recommended as a post-marketing commitment to assess safety in pregnancy, lactation, neonates, and infants to one year of age given the animal study findings and limited safety information in humans (please see Section 6.2.1 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 2. Sponsor’s Pharmacovigilance Plan**

<b>Type of Concern</b>	<b>Safety Concern</b>	<b>Proposed Action</b>
Identified	No risks have been identified by the sponsor	

Potential	Chikungunya-like illness including vaccine associated arthralgia	Routine pharmacovigilance with labeling statements and close safety monitoring, including 1) submission of any spontaneous report of Chikungunya-like illness including vaccine associated arthralgia regardless of seriousness or label status to VAERS as an expedited report for three years post-licensure, 2) summary and analysis of Chikungunya-like illness including vaccine associated arthralgia in periodic safety reports, using cumulative and interval data, and 3) dedicated follow-up questionnaire for spontaneous reports of potential Chikungunya-like illness including vaccine associated arthralgia to ensure structured follow-up.
Missing	Safety in pregnant women or breastfeeding women	Routine pharmacovigilance with labeling statements summarizing the animal study findings included in Prescribing Information and consideration of developmental and health benefits of breastfeeding along with the mother's clinical need for CHIKV VLP vaccine. Safety monitoring and reporting of exposures in pregnancy and lactation will include: 1) a pregnancy registry protocol open for five years, 2) summary and analysis of safety in pregnancy in periodic safety reports, using cumulative and interval data, and 3) a dedicated follow-up questionnaire for

		spontaneous reports of exposure in pregnancy to ensure structured follow-up.
Missing	Use in immunocompromised individuals and persons on immunomodulators (persons with autoimmune disorders)	Routine pharmacovigilance with labeling statement regarding the possibility of diminished immune response in immunocompromised persons and individuals receiving immunosuppressive therapy.
Missing	Interaction with other vaccines	Routine pharmacovigilance

\*Adapted from Tables 7, 8, 9, 10, 11 Risk Management Plan, STN125820/0.32, Module 1.16.1

*Reviewer Comment: The pharmacovigilance plan submitted to STN125820/0.1 does not include the pregnancy safety study. On October 18, 2024, DPV sent an information request to the sponsor requesting they add the pregnancy safety study to their PVP. The sponsor updated their PVP in the IR response submitted to 125820/0.32.*

### **6.1 Enhanced Pharmacovigilance**

The sponsor will perform expedited reporting to VAERS regardless of seriousness or label status for chikungunya-like illness including vaccine associated arthralgias. The sponsor will also include summaries of both interval and cumulative data in the periodic safety reports and follow-up questionnaires to facilitate collection of structured data for chikungunya-like illness including vaccine associated arthralgia and safety in pregnancy. The sponsor will establish a post-marketing pregnancy study for five years to further evaluate safety in pregnancy, lactation, neonates, and infants up to age one.

*Reviewer comment: FDA requested the above enhanced pharmacovigilance activities in order to obtain further characterization of the Important Potential Risk and Missing Information in the postmarket period. The Sponsor agreed to these requests in the IR response submitted to STN125820/0.32. FDA clarified that the duration of expedited reporting was limited to three years post-licensure, which was acknowledged by the Sponsor in the response submitted to STN125820/0.52.*

### **6.2 Safety-related Post-marketing Study**

The sponsor proposes a post-marketing pregnancy study, and has agreed to conduct it as a PMC, to evaluate safety in pregnancy, lactation, neonates, and infants up to age one.

### **6.2.1 “VIMKUNYA Pregnancy Registry: An Observational Prospective Study of the Safety of VIMKUNYA Vaccine Exposure in Pregnant Women and their Offspring”**

This is a prospective, observational, non-interventional, post-marketing study to evaluate the safety of the CHIKV VLP vaccine. This study plans to enroll 50 pregnant women from the U.S. and European Union planning to travel to endemic areas. Women will be followed until completion of data collection on pregnancy outcome and offspring will be followed until one year of age. Vaccine administration will occur as part of standard preventive care before identification for study eligibility. Vaccine dosage and administration should be according to the Prescribing Information and standard clinical practice.

#### **Primary objective:**

- To evaluate pregnancy outcomes in women immunized with Vimkunya up to 28 days before conception or at any time during pregnancy.
- To evaluate outcomes until one year of age in offspring of women immunized with Vimkunya 28 days prior to conception or at any time during pregnancy.

**Study duration:** The study duration is estimated at five years. Women will be enrolled for up to 10 months, offspring will be enrolled for one year, and data collection will occur until the last enrolled subject is followed through pregnancy outcome and the first year of life of the infant.

**Inclusion criteria:** Self-identification or identification by a healthcare provider of pregnant women exposed to Vimkunya within 28 days of conception or at any time during pregnancy.

**Sample Size:** 50 pregnancies

**Data collection:** Data will be collected through questionnaires at three timepoints. An initial pregnancy questionnaire will be used as soon as possible following enrollment. An outcome pregnancy questionnaire will be used after the estimated date of delivery. An infant outcome questionnaire will be used at 28 days of life, six-months, and one year of age.

Pregnancy endpoints are:

- Preterm birth
- Spontaneous abortion
- Fetal death/stillbirth
- Major congenital anomalies

Neonatal/infant endpoints are:

- Small for gestational age (SGA)
- Large for gestational age (LGA)
- Low birth weight (LBW)
- Admission to a neonatal intensive care unit

- NICU duration of stay
- Mechanical ventilation in neonatal period
- Neonatal death
- Postnatal growth at one year of age (may use weight-for-age <5%)
- Neonatal/infant seizures
- Neurodevelopmental delay
- Infant mortality through 12 months of age

**Study Milestones:** The sponsor provided the following study milestones (response to IR submitted to STN125820/0.32):

Final Protocol Submission: May 30, 2025  
 Study Completion Date: August 31, 2030  
 Final Report Submission: February 28, 2031

*Reviewer Comment: The sponsor initially planned a three-year study without a targeted enrollment number to occur only in the U.S. submitted to STN125820/0.29. DPV recommended establishing a study site in an area where Chikungunya is endemic to obtain enough patients for a clinically meaningful evaluation, as well as to use a prespecified internal comparison population. The sponsor agreed to extend the study to five years with a targeted enrollment of 50 women in the U.S. and the European Union submitted to STN125820/0.47. Given the sponsor does not intend to license Vimkungya in a Chikungunya-endemic area at this time, it declined establishing a study site in a Chikungunya-endemic area with an internal comparator group as submitted to STN125820/0.40.*

*The original registry synopsis did not include infant or neonatal outcomes. As a result of the decreased postnatal viability of kits of vaccine-treated pregnant rabbits observed in the animal studies, the FDA recommended the addition of neonatal and infant outcomes to the pregnancy registry study. The Sponsor updated their pregnancy registry to include neonatal and infant outcomes submitted to STN 125820/0.40.*

*The Sponsor planned for three timepoints of data collection to include following enrollment, following the estimated date of delivery, and following one year of age for the infant. The FDA recommended two additional timepoints of data collection for the infant: at one-month of age and at six months of age. The one-month follow-up would allow for adequate capture and/or recall of neonatal outcomes. Neonatal death is typically defined as death in first 28 days of life, hence one month follow-up would allow for capture of neonatal death, as well as other proposed infant outcomes such as NICU admissions and durations and any mechanical ventilation required in the neonatal period. The six-month follow-up would provide important data on growth, seizures, and neurodevelopmental delay in early infancy. The Sponsor acknowledged these timepoints and updated the registry protocol submitted to STN 125820/0.52.*

*OBPV/DPV and OVRP discussed this study proposal and agreed that this would be a postmarketing commitment. A PMC notification was issued to the Sponsor on January 3, 2025.*

## **7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN**

### **7.1 Important Identified Risks**

None.

### **7.2 Important Potential Risks**

#### **7.2.1 Important Potential Risks: Chikungunya-like illness including vaccine associated arthralgia**

Safety concern for chikungunya-like illness including vaccine associated arthralgia was not seen in clinical trials as was observed for the IXCHIQ vaccine. Given that it is not understood whether symptoms in natural chikungunya infection are secondary to the viral particles or the body's immune response to those particles, it is theoretically possible for virus-like particles to cause chikungunya-like symptoms without viremia. Thus, FDA requested the Sponsor include chikungunya-like illness including vaccine associated arthralgia as an Important Potential Risks in the PVP with enhanced pharmacovigilance activities. The Sponsor will submit spontaneous reports as expedited reports with dedicated structured follow-up, and a summary and analysis in periodic reports for cumulative and interval data.

*Reviewer Comment: The proposed PVP to monitor the potential risk of Chikungunya-like illness including vaccine associated arthralgia is appropriate with the addition of enhanced PVP activities.*

### **7.3 Important Missing Information**

#### **7.3.1 Missing Information: Pregnant or breastfeeding women**

Pregnant subjects were excluded in the clinical pivotal studies since there was limited reproductive or developmental toxicology data available for the CHIKV VLP vaccine. The effect of CHIKV VLP vaccine in pregnant patients is not known. Data from a pregnancy study in rabbits suggested reduced viability and activity in the kits of vaccinated pregnant females, although the clinical relevance to humans is unknown.

The sponsor will perform both routine and enhanced pharmacovigilance activities to further evaluate safety in pregnancy. The sponsor will include a labeling statement summarizing the animal study findings and encouraging consideration of developmental and health benefits of breastfeeding along with the mother's clinical need for CHIKV VLP vaccine and any potential adverse effects of the breastfed child from the vaccine or the underlying maternal condition. We defer to OVRP on the final approved labeling language. The sponsor has agreed to establish a pregnancy registry as a PMC for at least 50 pregnant women for five years with one year of infant follow-up, dedicated follow-up questionnaires for spontaneous reports regarding safety in pregnancy, and

submit a summary and analysis in periodic reports based on cumulative and interval data.

*Reviewer comment: The proposed PVP to monitor the risk of missing information for pregnancy is adequate. Infant outcomes in the pregnancy PMC registry were requested based on rabbit data suggesting reduced offspring viability.*

### **7.3.2 Missing Information: Immunocompromised Individuals and persons on immunomodulators (autoimmune disorders)**

There is no information on the safety of the vaccine in autoimmune or inflammatory disorders. The theoretical concern is that those who are immunocompromised may have reduced immune response leading to reduced vaccine effectiveness or that the vaccine may exacerbate underlying disease. It is hypothesized that vaccines which contain viral-like particles may function as agents that trigger autoimmune disease. Individuals with immunocompromise or those on immunomodulators will be monitored through routine pharmacovigilance.

*Reviewer comment: The proposed PVP to monitor the risk of missing information in immunocompromised individuals and persons on immunomodulators is adequate.*

### **7.3.3 Missing Information: Interaction with other vaccines**

The vaccine will be used in individuals who may also receive other vaccines. Data for coadministration with other vaccines will be collected 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 did not identify any significant safety concerns. Though there were no cases of chikungunya-like illness in the VIMKUNYA clinical safety database, it remains a theoretical concern based on observations from a different chikungunya vaccine, IXCHIQ (and is labeled under *Warnings and Precautions* and *Clinical Trials Experience* sections of the IXCHIQ USPI). There is limited human data on safety in pregnancy, representing a population with missing information, and rabbit studies demonstrated decreased viability among kits in the early postnatal period.

In addition to routine pharmacovigilance, chikungunya-like illness, and vaccine exposure during pregnancy, lactation, and the neonatal/infant period, will be further evaluated in the post-market setting with enhanced pharmacovigilance activities. Enhanced pharmacovigilance for chikungunya-like illness will include expedited (15-day) reporting to VAERS, sponsor follow up with questionnaire, and sponsor summary and analysis in periodic safety reports. Enhanced pharmacovigilance for safety in pregnancy will include follow up of spontaneous reports with a targeted questionnaire, and sponsor summary and analysis in periodic safety reports. Safety in pregnancy will be further evaluated in a pregnancy registry study, which will be a PMC, and the study



will be conducted in the U.S. and the European Union. The sponsor's PVP is acceptable.

## 9 DPV RECOMMENDATIONS

Should Vimkunya be approved, the sponsor's PVP (version 3.0, dated October 24, 2024) is acceptable. Safety monitoring for Vimkunya will include the following:

- Routine surveillance and adverse event reporting in accordance with 21 CFR 600.80.
- Enhanced pharmacovigilance for chikungunya-like illness: The sponsor will submit expedited (15-day) reports to VAERS for 3 years following licensure, follow up spontaneous reports of chikungunya-like illness with a targeted questionnaire, and include a safety assessment in periodic safety reports.
- Enhanced pharmacovigilance for safety in pregnancy: The sponsor will follow up spontaneous reports of pregnancy exposure with a targeted questionnaire, and include a safety assessment in periodic safety reports.
- A postmarketing commitment for a pregnancy registry study to further evaluate safety in pregnancy. DPV will review the final study protocol upon submission. The available safety data do not substantiate a need for a safety study as a PMR under 505(o) of FDCA or a REMS. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

## REFERENCES

<sup>1</sup>European Centre for Disease Prevention and Control. Chikungunya worldwide overview. <https://www.ecdc.europa.eu/en/chikungunya-monthly>

<sup>2</sup>World Health Organization. <https://www.who.int/news-room/fact-sheets/detail/chikungunya>

<sup>3</sup>Centers for Disease Control and Prevention. (2008). Update on overall prevalence of major birth defects—Atlanta, Georgia, 1978–2005. *MMWR Weekly Report*, 57(1), 1–5. Retrieved December 13, 2024, from <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm>

**APPENDIX**  
**Materials Reviewed**

**Table A1: Materials reviewed in support of this assessment**

<b>Date</b>	<b>Source</b>	<b>Document Type</b>	<b>Document(s) Reviewed</b>
6/10/2024	Sponsor	STN125820/0.1	Summary of Clinical Safety
6/10/2024	Sponsor	STN125820/0.1	Risk Management Plan
6/10/2024	Sponsor	STN125820/0.1	Clinical Overview
6/10/2024	Sponsor	STN125820/0.1	Clinical Study Report
6/10/2024	Sponsor	STN125820/0.1	CRFs for Deaths, Other SAEs, and Withdrawals for AEs
6/10/2024	Sponsor	STN125820/0.1	CHIKV VLP Integrated Summary of Safety
6/10/2024	Sponsor	STN125820/0.1	Other CRFs Submitted
9/27/2024	Sponsor	STN125820/0.22	Information Request Response #22, Arthralgia Duration Clarifications
10/07/2024	Sponsor	STN125820/0.26	Information Request Response #24, Arthralgia Case Narratives
10/15/2024	Sponsor	STN125820/0.29	Information Request Response #24, Pregnancy Registry Protocol Synopsis
10/25/2024	Sponsor	STN125820/0.32	Information Request Response #27, Updated Pregnancy Registry Protocol and Revised Pharmacovigilance Plan
11/15/2024	Sponsor	STN125820/0.40	Information Request Response #34, Updated Pregnancy Registry Protocol
11/25/2024	Sponsor	STN125820/0.43	Information Request Response #24, Arthralgia Case Narrative Correction
12/3/2024	Sponsor	STN125820/0.47	Information Request Response #39, Updated Pregnancy Registry Protocol
12/18/2024	Sponsor	STN125820/0.52	Information Request Response #45, Updated Pregnancy Registry Protocol and Revised Pharmacovigilance Plan