# EU RISK MANAGEMENT PLAN

# VIMKUNYA (CHIKUNGUNYA VACCINE; RECOMBINANT, ADSORBED)

**RMP version to be assessed as part of this application:**

| | | | |
|---|---|---|---|
| Data lock point for this RMP | 31-Dec-2023 | Version number | 1.0 |
| Date of final sign off | 29-Jan-2025 | | |

**Rationale for submitting an updated RMP**:

Not applicable for initial marketing authorisation application submission.

**Summary of significant changes in this RMP:**

Not applicable: New document

**Other RMP versions under evaluation:** Not applicable

**Details of the currently approved RMP:** Not applicable

**QPPV name**[1]: Simone Lorenz-Asmus

**Head of GCSP**: [redacted]



[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

1.8.2 Risk-Management System

The QPPV´s actual signature or the evidence that the RMP was reviewed and approved by the QPPV will be included in the finalised approved version of RMP.

**QPPV Signature:** See electronic signature.

**Head of GCSP Signature**: See electronic signature (signed by GCSP Designee).

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| CHIKV | Chikungunya virus |
| CHIKV VLP | Chikungunya virus virus-like particle |
| CHIKV VLP vaccine | Clinical development name of VIMKUNYA |
| CHKVLP059 | Non-adjuvanted CHIKV VLP vaccine |
| CRP | C-reactive Protein |
| CSP | Clinical Study Protocol |
| DCO | Data Cut-Off |
| DLP | Data Lock Point |
| E1 | E1 envelope protein of chikungunya virus Senegal strain 37997 |
| E2 | E2 envelope protein of chikungunya virus Senegal strain 37997 |
| ECDC | European Centre for Disease Prevention and Control |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EU | European Union |
| EVDAS | EudraVigilance Data Analysis System |
| GA | Gestational Age |
| GCSP | Global Clinical Safety and Pharmacovigilance |
| GLP | Good Laboratory Practice |
| GVP | Good Pharmacovigilance Practices |
| HCP | Healthcare Professional |
| HLT | High-Level Term |
| IBD | International Birth Date |
| ICH | International Conference on Harmonisation |
| ICSR | Individual Case Safety Report |
| IIR | Important Identified Risk |
| IM | Intramuscular |
| LMP | Last Menstrual Period |
| MedDRA | Medical Dictionary for Regulatory Activities |

## 1.8.2 Risk-Management System

| | |
|---|---|
| PASS | Post-Authorisation Safety Study(ies) |
| PL | Package Leaflet |
| PT | Preferred Term (MedDRA) |
| QPPV | Qualified Person Responsible for Pharmacovigilance |
| RMP | Risk Management Plan |
| SMC | Safety Monitoring Committee |
| SmPC | Summary of Product Characteristics (EU) |
| SOC | System Organ Class |
| ICSR | Individual Case Safety Report |
| VLP | Virus-like Particle |
| WHO | World Health Organisation |

# PART I: PRODUCT(S) OVERVIEW

**Table 1: Product Overview**

| | |
|---|---|
| **Active substance(s)**<br>**(INN or common name)** | Chikungunya virus (CHIKV) virus-like particle (VLP)<br>Chikungunya vaccine (recombinant, adsorbed) |
| **Pharmacotherapeutic group(s) (ATC Code)** | Other viral vaccines<br>(ATC Code not yet assigned) |
| **Marketing Authorisation Holder** | Bavarian Nordic A/S<br>Philip Heymans Alle 3<br>DK-2900 Hellerup<br>Denmark |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | VIMKUNYA |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product** | Chemical class: Other viral vaccines (J07BX) |
| | Summary of proposed mode of action: It is thought that VIMKUNYA (CHIKV VLP vaccine) can induce protection from CHIKV infection by inducing antibodies against the viral proteins contained in the VLP vaccine resulting in neutralisation of live virus. An adjuvant is added to increase the magnitude of vaccine-mediated immune responses. The proposed mechanism of action of the vaccine is to induce antibodies against the CHIKV proteins C, E1, and E2 contained in the vaccine, resulting in neutralisation of live CHIKV. C is the capsid protein, E1 is a class II fusion protein that mediates membrane fusion during virus infection of cells, E2 is a type I transmembrane glycoprotein responsible for receptor binding to cells during viral replication and has been shown to be the primary target of CHIKV neutralising antibodies produced as a result of natural infection. |
| | Important information about its composition: One dose (0.8 ml) of VIMKUNYA contains 40 µg chikungunya virus (CHIKV) virus-like particles, adsorbed on aluminium hydroxide (corresponding to approximately 300 µg of aluminium). Chikungunya virus VLP refers to the virus-like particle component of the vaccine contains the E1, E2 and C proteins of CHIKV Senegal strain 37997 that self-assemble to form a spherical, highly ordered VLP. It is supplied as |

| | |
|---|---|
| | a 0.8 ml suspension in a single-dose pre-filled syringe for intramuscular (IM) administration in the deltoid muscle. |
| **Hyperlink to the Product Information** | Refer to Module **1.3.1** for Product Information |
| **Indication(s) in the EEA** | Current: Not applicable |
| | Proposed indication: Active immunisation for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 12 years and older. |
| **Dosage in the EEA** | Current: Not applicable |
| | Proposed: VIMKUNYA should be administered intramuscularly as a single dose of 0.8 ml (40 µg CHIKV VLP adsorbed on aluminium hydroxide, hydrated). |
| **Pharmaceutical form(s) and strengths** | Current: Not applicable |
| | Proposed: Suspension for injection in pre-filled syringe.<br>One dose (0.8 ml) contains 40 µg chikungunya virus (CHIKV) virus-like particles[1,2] (VLP) adsorbed on aluminium hydroxide, hydrated.<br><br>[1]produced in human embryonic kidney cells by recombinant DNA technology.<br><br>[2]derived from CHIKV Senegal strain 37997 consisting of CHIKV capsid protein (C) and envelope proteins E1 and E2.<br><br>Aluminium hydroxide, hydrated (approximately 300 µg $Al^{3+}$ per 0.8 ml dose). |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |

# PART II: SAFETY SPECIFICATION

# PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION(S)

The proposed indication for VIMKUNYA is active immunisation for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 12 years and older. The target indication is to prevent disease caused by chikungunya virus infection, in all ages.

The use of this vaccine should be in accordance with official recommendations.

**Incidence, Prevalence, Demographics of the Population in the Proposed Indication:**

The target population of VIMKUNYA (CHIKV VLP vaccine) is considered identical with the general population. In addition, due to the non-replicating properties, VIMKUNYA is expected to be used in individuals not eligible for vaccination with replicating CHIKV vaccines such as immunocompromised individuals. Of note, as described in Table 9 (Part II, SIV.2), immunocompromised individuals and persons with autoimmune disorders (on immunomodulators) were not included in the clinical development programme of VIMKUNYA. However, given that this is a virus-like particle vaccine with a reduced risk of replication, it is expected that the safety profile of the vaccine in immunocompromised or immunodeficient populations will be comparable to the general population.

The epidemiology in the target population is provided in Table 2 below.

**Table 2: Part II: Module SI-1 Epidemiology: General Population (Healthy)**

| Indication/Target Population | CHIKV Vaccination of General Population |
|---|---|
| **Indication** | Proposed indication for VIMKUNYA is to prevent disease caused by chikungunya virus infection in individuals 12 years of age and older. |
| **Incidence of Target Indication** | Chikungunya disease, having emerged as a global public health threat, was first recognised in 1952 during an outbreak in southern Tanzania and has now been identified in over 110 countries in Asia, Africa, Europe, and the Americas. In 2024, and as of 31-Mar-2024, over 160,000 CHIKV cases have been reported worldwide. |
| **Prevalence of Target Indication** | Chikungunya disease occurs in Africa, Asia and Latin America, although imported cases have been recorded in the WHO European Region and the Region of the Americas. Over 2 million cases have been reported since 2005. In 2024, and as of 30-Nov-2024, a total of 23 countries reported 480,000 CHIKV cases and over 200 deaths from the Americas (15), Asia (6), Africa (1) and Europe (1). |

| Indication/Target Population | CHIKV Vaccination of General Population |
|---|---|
| **Mortality in Target Indication** | Chikungunya virus-associated mortality remains low, with patients at extremes of the age spectrum are at higher risk for severe disease. Newborns infected during delivery and older people with underlying medical conditions may become severely ill and CHIKV infection can increase the risk of death. |
| **Potential Health Risk** | Chikungunya disease is characterised by an abrupt onset of fever, frequently accompanied by severe joint pain. The joint pain is often debilitating and usually lasts for a few days but may be prolonged, lasting for weeks, months or even years. Most patients recover fully from the infection; however, occasional cases of eye, heart, joint, and neurological complications have been reported with CHIKV infections. |
| **Demographic Profile of Target Population** | Individuals 12 years of age and older. |

**The Main Existing Treatment Options:**

The treatment for CHIKV disease is supportive, consisting of administration of fluids, antipyretics, and analgesics. There are currently insufficient data to support the efficacy of antivirals and corticosteroids in the treatment of CHIKV disease.

Prevention of CHIKV infection is mostly restricted to protection against mosquito bites. Currently, there is no approved vaccine to prevent CHIKV infection or disease in the EU. The protection against subsequent infection has been shown to correlate with the presence of CHIKV serum antibodies that neutralise the virus *in vitro* (7, 34).

**Natural History of the Indicated Condition in the Untreated Population, including Morbidity and Mortality:**

Chikungunya virus is an arthropod-borne alphavirus of the family *Togaviridae*. The virion contains a positive-sense single-strand RNA genome with a long open reading frame coding for capsid (C), envelope (E1, E2, E3) and 6K structural proteins, together with four nonstructural proteins (nsP1, nsP2, nsP3, and nsP4). Envelope 1 protein is a class II fusion protein that mediates membrane fusion during virus infection of cells. Envelope 2 protein is a type I transmembrane glycoprotein responsible for receptor binding to cells during viral replication and was shown to be the primary target of CHIKV neutralising antibodies produced as a result of natural infection.

Since the 1952-1953 outbreak in Tanzania (26) this disease has been endemic in Africa and parts of Asia with transmission occurring through *Aedes aegypti* and, more recently, via *Aedes albopictus* mosquitoes (22). Recent notable outbreaks of CHIKV in non-endemic areas include those in the Indian Ocean islands, including La Réunion in 2005-2006 (23), and Guangdong, China in 2010 (33). Beginning in 2014, cases of CHIKV disease were reported among United States of America (US) travellers returning from affected areas in the Americas and local transmission was identified in the state of Florida, US territory of Puerto Rico, and the US Virgin Islands (18). According to the World Health Organisation (WHO), CHIKV has now been identified in 118 countries in Asia, Africa, the Americas, and Europe

(13). Transmission has been interrupted on islands where a high proportion of the population is infected and then immune; however, transmission often persists in countries where large parts of the population have not yet been infected. All regions with established populations of *Ae. aegypti* or *Ae. albopictus* mosquitoes have now experienced local mosquito-borne transmission (13). Although mosquitoes are the primary mode of transmission of CHIKV, blood-borne transmission via needle stick is possible and maternal-foetal transmission has been documented during pregnancy (5).

Following an incubation period of 2 to 12 days, acute clinical manifestations include high fever, rash, gastrointestinal complications, headache, muscle pain, nausea, fatigue, myalgia, and joint pain (2,21,31). The most classic symptom of chikungunya disease is a debilitating polyarthralgia that is present in greater than 90% of cases (29). This acute phase resolves within several weeks, but joint pain and arthritis may persist for months or years. Chronic symptoms lasting >3 months, including joint pain and other nonspecific symptoms, affect 43% (95% CI, 35–52%) of patients on average, with East/Central/South African (ECSA)-derived strains causing more chronic disease than Asian strains (19).

Although CHIKV has circulated more regularly over the last two decades than in the past its transmission remains enigmatic, with long interepidemic intervals (10–15 years) (28), even in regions with high arbovirus burden and especially at the local scale where studies would be executed. Like the other arboviruses, CHIKV transmission is characterise by sporadic, short-lived, spatially heterogenous transmission dynamics (27). Although the disease and pathogen are well studied, epidemiological (especially longitudinal) data are limited and confounded by other febrile illnesses, especially dengue. Few locations describe recurrent CHIKV transmission, and no prospective study has provided a reliable estimate of incidence rates. The areas that have reported possible endemic transmission of CHIKV include Indonesia (15), Northern Thailand (16), Southern Thailand (Armed Forces Research Institute of Medical Sciences [AFRIMS] unpublished data) and possibly Kenya (11) and Cambodia (Naval Medical Research Unit-2 unpublished data). The level of transmission (i.e., average annual attack rates) and the mechanism of persistence are not well known (a sylvatic transmission cycle is one possibility). Analysis of published serological survey data predicts that sites are only capable of supporting high numbers of endpoint events in a vaccine study if the site has an outbreak with at least a moderately high basic reproductive number and, critically, has not experienced a large CHIKV disease outbreak in a decade or more due to population immunity (20).

These observations indicate that there may be two types of epidemiological context for CHIKV transmission: 1) populations where transmission is highly episodic with long interepidemic periods without transmission, and 2) populations where there may be low levels of sustained interepidemic transmission. In the former, there is high uncertainty in the timing of an outbreak because transmission depends on the (re)introduction of CHIKV, but attack rates are expected to be high. In the latter, episodic transmission may be more likely because the virus is maintained locally, but outbreaks are expected to be highly localised with low average attack rates. In both cases, uncertainty in the timing, location, and magnitude of CHIKV transmission is the core challenge of conducting a clinical efficacy study for a CHIKV vaccine.

1.8.2 Risk-Management System

According to European Centre for Disease Prevention and Control, in 2023 and as of 26-Jul-2023, approximately 300,000 cases and over 300 deaths have been reported worldwide. The majority of cases have been reported in the Americas from Brazil (192,822), Paraguay (101,963), Argentina (1593), Bolivia (1,311), and in Asia from Thailand (598). Deaths have been reported from Brazil (60) and Paraguay (256).

In 2024, and as of 30-Nov-2024, over 480,000 CHIKV cases and over 200 deaths have been reported worldwide. A total of 23 countries reported CHIKV cases from the Americas (15), Asia (6), Africa (1) and Europe (1) (12).

Chikungunya is not endemic in mainland European Union/European Economic Area (EU/EEA) and the majority of the cases are travellers infected outside of mainland EU/EEA (12). When the environmental conditions are favourable, in areas where *Ae. albopictus* is established, viraemic travel-related cases may generate a local transmission of the virus as demonstrated by the sporadic events of CHIKV transmission since 2007. However, no events of autochthonous transmission were reported in the EU/EEA since 2017 [Table 3; adapted from (12)].

**Table 3: Part II: Module SI-2 Autochthonous Transmission of CHIKV in Mainland EU/EEA (2007–Present)**

| Year | Country, region, municipalities | Number of autochthonous cases | Period of circulation (probable) | Origin of the primary travel-related case (probable) | Virus | Ref.[2] |
|---|---|---|---|---|---|---|
| 2007 | Italy, region of Emilia Romagna, (main transmission areas in Castiglione di Cervia and Castiglione di Ravenna) | ≈ 330 suspected, probable and confirmed | July–September | India | CHIKV ECSA | [1,24] |
| 2010 | France, Var department, Fréjus | 2 | September | India | CHIKV ECSA | [10, 32,8] |
| 2014 | France, Hérault department, Montpellier | 12 | September–October | Cameroon | CHIKV ECSA | [8,6] |
| 2017 | France, Var department, Le Cannet-les-Maures and Taradeau | 17 (11 in Cannet-des-Maures and 6 in Taradeau) | July–September | Central Africa | CHIKV ECSA | [8,3,4] |
| 2017 | Italy, Lazio region (Anzio, Latina and Roma) and Calabria region (Guardavalle marina) | 270 confirmed and 219 probable | August–November | Asia (India/ Pakistan) | CHIKV ECSA[1] | [9,19, 25,14] |

Ref = Reference; CHIKV ECSA= Chikungunya virus East/Central/South African lineage

[1]CHIKV ECSA belonging to a branch of Indian Ocean Lineage (IOL) reported from Indian subcontinent (India, Pakistan)
[2]The table combines information published in official reports and in the scientific literature plus information that was provided by the public health institutes and/or the ministries of health in the affected Member States.

1.8.2 Risk-Management System

**Table 4: Important Co-morbidities in Different Target Populations**

| Indication/Target Population | Important Co-morbidities |
|---|---|
| **General Population** | As per general population, co-morbidities may include cardiovascular, malignancies, and diabetes. |
| **Older Adults ≥ 65 years** | In addition to the co-morbidities in the general population: dementia, arthritis, hyperlipidaemia, chronic obstructive pulmonary disease, and ischaemic heart disease. |

# PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

## SII.1 Toxicity Studies

No risks have been identified in the non-clinical testing programme, and the available nonclinical toxicology and pharmacology data support the safety, dose, dosing regimen, route and formulation proposed for the human use, i.e. a single intramuscular (IM) adjuvanted dose containing 40 μg CHIKV VLP.

The CHIKV VLP vaccine has been shown to be safe and well-tolerated in the toxicity programme conducted in rats and rabbits, investigating acute and repeated dose toxicity, local tolerance, as well as developmental toxicity.

The clinical dose of 40 μg was administered IM in all studies, adding an additional safety margin by administering the vaccine up to 5-times as opposed to the single administration intended for human use. None of the studies raised any concerns in relation to human safety.

- **Single-dose Toxicity Study**

No single dose toxicology studies with CHIKV VLP vaccine have been performed. Instead, exposure obtained in the repeat-dose toxicity studies covers in excess the clinical posology for using CHIKV VLP as a single dose vaccine.

- **Repeat-Dose Toxicity Study**

At the initial stage of the development, a non-adjuvanted CHIKV VLP vaccine (CHKVLP059) was tested. CHKVLP059 was administered IM 4-times in three-week intervals to rabbits with each dose containing 40 μg CHIKV VLP.

All animals survived to the scheduled necropsies. There were no treatment-related effects on in-life parameters including clinical observations, dermal (Draize) scoring, ophthalmology, body temperatures, body weights and body weight changes, or food consumption. Because of the clinical sequelae of natural chikungunya, additional parameters monitored in this study included clinical observations of range-of-motion of joints and the ability to move in a free field, as well as particular attention to macroscopic post-mortem observations and histopathology of joints. Post-infection arthritis symptoms are believed to be a direct result of infection of joints, rather than an immunological phenomenon. While it was not expected that CHKVLP059 would recapitulate these symptoms, to be conservative, the specified signs of arthritis were monitored in the rabbits, but none were observed.

CHKVLP059 treated animals had statistically significant increases in fibrinogen and CRP at some time points postvaccination, suggesting an inflammatory response indicative of an immune reaction, which is supported by the fact that all vaccinated animals developed antibodies.

In conclusion, CHKVLP059 was well-tolerated locally and systemically following four IM administrations of the clinical dose of 40 mg each. There are no demonstrated product-related safety concerns.

- **Reproductive/Developmental Toxicity**

CHIKV VLP vaccine (adjuvanted) was evaluated in two developmental and reproductive toxicology (DART) studies in the standard rabbit and rat models.

In the first study, female New Zealand White (NZW) rabbits were administered five IM injections of 40 μg CHIKV VLP vaccine 28 and 14 days prior to the initiation of the mating phase, on Gestation Days 7 and 21 and again on Lactation Day 7.

The vaccine was well tolerated with no maternal systemic toxicity. It induced an antibody response in all vaccinated animals with antibody transfer to the offspring.

In-utero exposure of litters did not affect embryo-foetal viability or foetal body weights. Additionally, exposure to CHIKV VLP vaccine did not cause any external, visceral, or skeletal malformations or variations in the females that were Caesarean-sectioned prior to delivery. These females, administered 4 doses of CHIKV VLP vaccine, had a reduced number of corpora lutea and implantation sites; however, the overall significance of this finding was unable to be established since the opposite (i.e. an increase in implantation sites) was observed in the females allowed for natural delivery (administered 5 doses of CHIKV VLP vaccine). Similarly, an apparent reduction in viability (63.18% in the CHIKV VLP vaccine dose group compared with 77.28% in controls) and increased clinical signs (reduced activity, splayed limbs) in the offspring from females administered CHIKV VLP vaccine compared to the control values reflected normal variation in offspring viability when compared to historical control values (viability as low as 57.4%) from two strains of rabbits used for these studies at this Testing Facility.

Therefore, CHIKV VLP vaccine was considered well tolerated and safe in this study.

In the second study, female rats were administered five IM injections of 40 μg CHIKV VLP vaccine 28 and 14 days prior to mating, on Gestation Days 0 and 14, and on Lactation Day 7 (Group 2), or three IM injections of 40 μg CHIKV VLP vaccine 14 days prior to mating and on Gestation Days 0 and 14 (Group 3).

CHIKV VLP vaccine did not induce any maternal toxicity, nor did it affect parturition parameters (gestation length, gestation index, live newborn pups/litter, live birth index, and uterine implantation sites).

No vaccine-related effects on female reproductive performance (mating, fertility, and pregnancy indices) were observed in Group 3 females. In Group 2 females, the mating index was statistically lower (77.3% vs 100% in controls) in comparison to concurrent controls. The pregnancy index in this group of females was also statistically lower (68.2%) in comparison to controls (100%), but this was attributed to the low number of mated females as the fertility index was comparable to concurrent controls (88.2% vs 95.5% in controls).

No vaccine-related effects were observed on offspring survival, sex ratios, clinical findings, body weights, reflex and physical development, or macroscopic findings in the two treated groups.

Vaccination yielded a robust antibody response in female rats and conferred passive immunity to their offspring.

In conclusion, IM administration of rats with CHIKV VLP vaccine at a dose level of 40 µg/dose was well-tolerated and safe, with potential effects limited to a low mating index. This was however only seen in one of two groups of female rats and there were no CHIKV VLP-related effects on mating indices in the previous study in NZW rabbits.

- **Genotoxicity**

Not applicable.

- **Carcinogenicity**

Not applicable.

## SII.2 Safety Pharmacology

No specific safety pharmacology studies have been performed and no adverse pharmacodynamic effect has been observed in toxicology or clinical studies that would warrant further studies.

- **Other Toxicity-related Information or Data**

Not applicable.

## SII.3 Safety concerns that have not been adequately addressed by clinical data or which are of unknown significance

There are no safety concerns from nonclinical studies.

**Need for additional non-clinical data if the product is to be used in special populations**

There is no targeted special population requiring specific nonclinical data.

## SII.4 Conclusions on non-clinical data

Repeated dose toxicity revealed that CHKVLP059 was well-tolerated locally and systemically following four IM administrations of the clinical dose of 40 mg each. There are no demonstrated product-related safety concerns. Reproduction and developmental toxicity studies showed that CHIKV VLP vaccine was well-tolerated with no maternal systemic toxicity. It induced an antibody response in all vaccinated animals with antibody transfer to the offspring. No vaccine-related effects were observed in offsprings.

There are no safety concerns from nonclinical studies.

# PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

## SIII.1 Brief Overview of Clinical Development

The CHIKV VLP vaccine was in-licensed by PaxVax Inc. from the US National Institutes of Health (NIH) Vaccine Research Center (VRC), which initiated the development of an unadjuvanted formulation of CHIKV VLP vaccine (designated CHKVLP059 at that time). PaxVax, Inc. was acquired by Emergent BioSolutions, Inc. in October 2018, and the vaccine (designated PXVX0317 at that time) was further developed under a fully owned subsidiary,

Emergent Travel Health, Inc. On 15-May-2023, Bavarian Nordic A/S acquired the CHIKV VLP vaccine development programme from Emergent Travel Health, Inc. As the new sponsor, Bavarian Nordic, A/S assumed responsibility for the completion of the phase 3 studies and for all planned CHIKV VLP vaccine clinical studies.

## SIII.2 Clinical Trial Exposure

The cumulative number of exposed subjects from completed clinical trials is 3522.

Five clinical studies have been completed utilising CHIKV VLP vaccine, these studies include:

- PXVX-CV-317-001: a phase 2 randomised, placebo-controlled, double-blind study to evaluate the safety, tolerability, and immunogenicity of eight formulation/schedule combinations of CHIKV VLP vaccine with and without aluminum hydroxide adjuvant, to identify the optimal IM dose and select the dosing regimen for further development. This study enrolled 445 healthy adults 18 to 45 years of age in the US.
- EBSI-CV-317-002: a phase 2 open-label study to evaluate the safety of a single adjuvanted dose of CHIKV VLP vaccine (40 µg CHIKV VLP) in subjects who had been previously vaccinated with other alphavirus vaccines. This study enrolled 60 healthy adults 18 to 65 years of age in the US.
- EBSI-CV-317-010: a phase 2 open-label study to assess the safety and immunogenicity of a single adjuvanted dose of CHIKV VLP vaccine (40 µg CHIKV VLP) in healthy adults 18 to 45 years of age in the US. The study enrolled 25 subjects who received a single adjuvanted dose of CHIKV VLP vaccine, and subjects were followed for 182 days to assess neutralising antibody responses and safety.
- EBSI-CV-317-004: a phase 3 randomised, placebo-controlled, double-blind study to determine safety, immunogenicity, and lot consistency of a single adjuvanted dose of CHIKV VLP vaccine (40 µg CHIKV VLP). The study enrolled 3258 healthy adults and adolescents 12 to 65 years of age in the US; healthy male and nonpregnant female adults and adolescents were stratified by age group (12 to <18, 18 to <46, and 46 to <65 years of age). A total of 3254 of the 3258 randomised subjects received either CHIKV VLP vaccine or placebo.
- EBSI-CV-317-005: a phase 3 randomised, placebo-controlled, double-blind, parallel-group study to determine safety and immunogenicity of a single adjuvanted dose of CHIKV VLP vaccine (40 µg CHIKV VLP). The study enrolled 413 healthy adults ≥65 years of age in the US; subjects were stratified by age group (65 to <75 and ≥75 years of age). A total of 413 subjects were randomised to receive either CHIKV VLP vaccine or placebo.

Safety assessments of 3522 participants who were exposed to at least a single dose of CHIKV VLP vaccine supported that vaccination with VIMKUNYA has a favourable safety profile. No trends for unexpected and/or serious adverse reactions were identified and no difference in the safety profile has been observed among the age groups.

1.8.2 Risk-Management System

Based on currently available clinical data, vaccination with VIMKUNYA is safe and well-tolerated. The majority of the adverse drug reactions were local adverse reactions, mild to moderate in intensity, and were non-serious.

Tables below provide a breakdown of exposure to CHIKV VLP vaccine in Phase 2 and 3 clinical trials by duration, age group, gender, dose and ethnic origin.

**Table 5: Duration of Exposure to CHIKV VLP Vaccine, Phase 2 and 3 Studies, Safety Population**

| **Cumulative for all Indications (Person Time)** | | |
|---|---|---|
| **Duration of Exposure*** | **Study Participants** | **Persons** |
| e.g. <1 m | 3522 | 3522 |
| 1 to <3 m | 0 | 0 |
| 3 to <6 m | 0 | 0 |
| ≥6 m etc. | 0 | 0 |
| **Total Persons** | **3522** | |

***Duration of exposure" is not applicable for a vaccine, as there is no administration over a time period.**

**Table 6: Exposure by Age Group and Gender**

| | **Study Participants** | | | **Person Time** | | |
|---|---|---|---|---|---|---|
| **Age Group** | **M** | **F** | **Total** | **M** | **F** | **Total** |
| Preterm Newborn Infants | 0 | 0 | 0 | 0 | 0 | 0 |
| Term Newborn Infants (0 to 27 days) | 0 | 0 | 0 | 0 | 0 | 0 |
| Infants and Toddlers (28 days to 23 months) | 0 | 0 | 0 | 0 | 0 | 0 |
| Children (2 to e.g. 11 years) | 0 | 0 | 0 | 0 | 0 | 0 |
| Adolescents (e.g. 12 to 17 years) | 119 | 98 | 217 | 119 | 98 | 217 |
| Adults (e.g. 18 to 64 years) | 1472 | 1627 | 3099 | 1472 | 1627 | 3099 |
| Elderly: 65-74 years | 66 | 93 | 159 | 66 | 93 | 159 |
| Elderly: 75-84 years | 14 | 27 | 41 | 14 | 27 | 41 |
| Elderly: 85 + years | 1 | 5 | 6 | 1 | 5 | 6 |
| **Total** | **1672** | **1850** | **3522** | **1672** | **1850** | **3522** |

1.8.2 Risk-Management System

**Table 7: Exposure by Dose**

| Dose of Exposure | Study Participants | Person time |
|---|---|---|
| CHIKV VLP Single Dose 40/300 µg | 3141 | 3141 |
| CHIKV VLP Other Dose | 381 | 381 |
| **Total** | **3522** | **3522** |

**Table 8: Exposure by Ethnic Origin**

| Ethnic Origin | Study Participants | Person time |
|---|---|---|
| Not Hispanic or Latino | 2824 | 2824 |
| Hispanic or Latino | 635 | 635 |
| Unknown/Not Reported | 63 | 63 |
| **Total** | **3522** | **3522** |

# PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## SIV.1 Limitations of ADR detection common to clinical trial development programmes

| Ability to Detect Adverse Reactions | Limitation of Clinical Trial Programme | Discussion of Implications for Target Population |
|---|---|---|
| Which are rare (≥1/10000) and very rare (<1/10000) | A total number of 3522 participants with specific inclusion/exclusion criteria (i.e., healthy volunteers) received CHIKV VLP vaccine in the clinical development programme which is limited in terms of populations studied compared to post-marketing exposure. | This sample size is limited to allow for the detection of rare and very rare adverse events. A larger population exposure from post-approval use would allow for more expansive safety exposure and monitoring. |
| Due to prolonged exposure | VIMKUNYA was not studied as an investigation product for prolonged exposure. | No safety issues were identified in the CHIKV VLP clinical studies, and no new safety concern is expected in the target population over time.<br>A long-term follow-up study to evaluate safety and immunogenicity post-single or a booster vaccination is ongoing. No study participant has received a booster dose. |
| Due to cumulative effects | Cumulative exposure was not studied as this is a single dose vaccine. | The effects of cumulative exposure are unknown given that the vaccine is administered as a single dose. A booster dose study is currently ongoing. No study participant has received a booster dose. |
| Which have a long latency | Clinical study subjects have been followed-up from 183 and up to 760 days. | New and unknown AEs due to long latency seem to be unlikely. Long-term safety monitoring study is ongoing. |

## SIV.2 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 9 summarizes important exclusion criteria regarding the population that were excluded from the pivotal clinical studies utilising CHIKV VLP vaccine.

**Table 9: Exclusion Criteria in Pivotal Clinical Studies within the Development Programme**

| Exclusion Criterion | Reason for Exclusion | Is it considered to be included as missing information (Yes/No) | Rationale |
|---|---|---|---|
| History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine. | VIMKUNYA should not be administered to subjects with known hypersensitivity to any component of the vaccine in order to limit the risk of such reaction upon vaccination. | No | Allergic and anaphylactic reactions have the potential to be life-threatening or even result in death in the absence of appropriate intervention. Exclusionary statement regarding hypersensitivity reaction was included in clinical study protocols. VIMKUNYA is contraindicated in patients with known hypersensitivity to the active substance and to any of its excipients; therefore. use in this patient population is not recommended for the approved indication. Additionally, statement regarding appropriate medical treatment must be immediately available to manage anaphylactic reactions following administration of the vaccine is included in the contraindications section of the SmPC for VIMKUNYA. |
| Any medical condition that in the judgement of the investigator would make vaccine administration unsafe. | The administration of a vaccine to individuals with clinically significant medical conditions which in the Investigator's opinion may jeopardise the safe administration of the study vaccine were precautionarily excluded. | No | Although safety of VIMKUNYA when administered to individuals with clinically significant medical conditions has not been studied, it is not considered as a missing information given the common medical practice of not administering vaccines to individuals |

| | | | |
|---|---|---|---|
| | | | with diseases or conditions that may put them at increased risk. |
| Use of any investigational or non-registered product (drug, vaccine or medical device) including licensed vaccines, other than the study vaccine during the period beginning 30 days before the first dose of study (Receipt or anticipated receipt of any vaccine from 30 days prior to Day 1 through Day 22). | These products could influence the individual's immune response to the vaccine and could affect the accuracy of the immune response and safety data. | No | Although co-administration of VIMKUNYA with other vaccines commonly used in the target population is yet to be studied, no specific vaccine has been identified, that may pose a potential safety issue when co-administered with VIMKUNYA. |
| Individuals with hepatitis B and C | Individuals with active viral inflammation of the liver (e.g. Hepatitis B and C) may be at an increased risk of liver cirrhosis and liver cancer which may confound proper safety assessment during study participation as well as potentially negatively affect their immune response to vaccination. | No | The safety profile and immune response could be affected in participants with active hepatitis B and C; however, the safety profile of VIMKUNYA is not expected to be different in these categories of individuals if their liver function is within normal limits. |
| Pregnancy and breastfeeding individuals. | There is limited reproductive or developmental toxicology data available for CHIKV VLP vaccine. Clinical trial data regarding use of VIMKUNYA use in pregnant or breastfeeding individuals is limited. | Yes | There were no adequate and well-controlled clinical studies utilising VIMKUNYA in pregnant and breastfeeding women. As stated in the SmPC, VIMKUNYA administration during pregnancy and breastfeeding should be considered when the potential benefits outweigh any potential risk for the mother and foetus/baby. |
| Paediatric population <12 years of age. | No data regarding safe use of VIMKUNYA in children <12 years of age. | No | No dedicated clinical trial was conducted in this population and the proposed indication of the planned marketing authorisation application will not include paediatric population <12 years of age; therefore, this is not considered missing information. |

| | | | |
|---|---|---|---|
| Any confirmed or suspected immunodeficient or immunocompromised state. | Immunocompromised or immunodeficient (whether congenitally acquired, acquired via HIV infection or due to concomitant medication such as chemotherapy etc.) participants may have impaired immune responses to vaccines and would therefore limit the ability to demonstrate immunogenicity, which is the primary pivotal endpoint. | No | Given that VIMKUNYA is a virus-like particle vaccine with a reduced risk of replication, and that there are no indications that the safety profile in immunocompromised or immunodeficient subpopulations is expected to be different, this does not represent a safety issue. |
| Individuals with clinically significant cardiovascular, pulmonary, rheumatologic or other chronic disease. | Conditions in individuals with clinically significant co-morbidities or chronic conditions including cardiac, pulmonary or rheumatologic may be aggravated during participation in clinical trials. | No | There is no evidence that the safety profile of this population receiving VIMKUNYA will be different to that of the general population; hence, not considered a missing information. |
| Individuals with bleeding disorder and/or are receiving anticoagulants. | The intramuscular administration of a vaccine could increase the risk of bleeding in individuals with bleeding disorder and/or are on anticoagulants. | No | Although minimal, the risk of bleeding may not be completely eliminated. Prevention and management of injection site bleeding and/or bruising after IM injection in patients with bleeding disorders or prior history of significant bleeding is fully integrated into standard immunisation practice. Use in this patient population does not require further characterisation and is therefore not considered as missing information. |
| CHIKV seropositive (prior exposure, diagnosis with Chikungunya, prior vaccination against Chikungunya virus infection or receipt of any CHIKV product). | Previous exposure to VIMKUNYA may limit the assessment of immunogenicity due to prior immune response. | No | Prior exposure to VIMKUNYA may confound the assessment of immunogenicity. Minimal immune response may not provide protection against CHIKV infection. Use in this category of individuals does not require further characterisation and is therefore not considered as missing information. |
| Body Mass Index (BMI) $\geq$35 kg/m$^2$ | Obesity is believed to impair immune function, which may compromise immunogenicity. | No | The inclusion of morbidly obese participants may confound the immune response and may have obesity-related co-morbidities which may have impact |

1.8.2 Risk-management System

| | | | |
|---|---|---|---|
| | | | on safety. However, there is no evidence that the safety profile of these individuals receiving VIMKUNYA will be different to that of the general population and is therefore, not considered a missing information. |

## SIV.3 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare and very rare adverse reactions based on the cumulative number of exposed subjects, or those caused by prolonged or cumulative exposure. Since VIMKUNYA is a single dose vaccine, there are no adverse reactions expected from prolonged or cumulative exposure.

## SIV.4 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

The clinical development programme focused on healthy population aged 12 years and older. The exclusion criteria from the controlled clinical studies included medical conditions that are contraindicated when vaccinating with VIMKUNYA and those which are not contraindicated but for which caution must be exercised.

**Table 10: SIV.4: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes**

| Type of Special Population | Exposure |
|---|---|
| Pregnant women | Pregnant and breastfeeding women were excluded from the clinical development programme. Limited pre-pregnancy exposure data to CHIKV VLP vaccine are available from 10 pregnant study participants, refer to Part II: Module SVII.1.2, for their pregnancy outcomes.<br>Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, VIMKUNYA should only be administered during pregnancy and breast feeding if the benefits of immunisation outweigh the risks for the mother and foetus/baby. |
| Breastfeeding women | |
| Paediatric population (<12 years of age) | Not included in the clinical development programme. |
| Paediatric population (12 to <18 years of age) | The overall clinical development of CHIKV VLP vaccine comprised a population aged 12 years and older. Two hundred and seventeen (217) adolescents have been exposed to CHIKV VLP vaccine in clinical trials (Refer to Part II: Module SIII) |

1.8.2 Risk-management System

| Type of Special Population | Exposure |
|---|---|
| Study Participants with relevant comorbidities:<br>• Individuals with active hepatitis B and C<br>• Individuals with clinically significant cardiovascular, pulmonary, rheumatologic or other chronic disease<br>• Elderly population with dementia<br>• Individuals with bleeding disorder and/or on anticoagulant therapy<br>• Individuals with Body Mass Index ≥35 kg/$m^2$ | Not included in the clinical development programme |
| Elderly (≥65 years of age) | The overall clinical development of CHIKV VLP vaccine comprised a population aged 12 years of age and older with a study conducted in adults ≥65 years of age.<br><br>Two hundred and six (206) elderly participants have been exposed to CHIKV VLP vaccine in clinical trials (Refer to Part II: Module SIII) |
| Other Category:<br>• Individuals with seropositivity to VIMKUNYA (prior exposure, prior diagnosis with Chikungunya, prior vaccination against Chikungunya virus infection)<br>• Immunocompromised/immunodeficient Individuals (e.g., HIV) | Not included in the clinical development programme |

1.8.2 Risk-management System

# PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

There is no data for this section as VIMKUNYA has not been marketed in any country.

## SV.1 Post-Authorisation Exposure

Not applicable for initial marketing authorisation application submission.

### SV.1.1 Method Used to Calculate Exposure

Not applicable for initial marketing authorisation application submission.

### SV.1.2 Exposure

Not applicable for initial marketing authorisation application submission.

**Table 11: Exposure Table by Indication, Gender, Age Group, and Region**

Not applicable for initial marketing authorisation application submission.

# PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

## Potential for misuse for illegal purposes:

No potential for illegal use of the vaccine has been identified. VIMKUNYA does not have potential for use as a recreational drug.

# PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

## SVII.1 Identification of Safety Concerns in the Initial RMP Submission

All safety data available from the CHIKV VLP vaccine clinical development programme were evaluated in order to characterise the risks (potential/identified) associated with administration of VIMKUNYA.

### SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following topics were not considered relevant for inclusion in the list of safety concerns for initial EU RMP approval:

Known risks that do not impact the risk-benefit profile:

- Local injections site reactions (including injection site tenderness/pain, redness/erythema, and swelling): Injection-site reactions are commonly observed following intramuscular (IM) injections and have been reported reactogenicity events on Days 1-8 in CHIKV VLP vaccine clinical studies as very common (injection site pain) and uncommon (Injection site redness, Injection site swelling) ADRs, which were generally mild or moderate in severity and self-limiting. Specific guidance on the administration of VIMKUNYA for Health Care Professionals (HCPs) will be provided in the SmPC, and this is fully aligned with standard clinical practice for the management of injection site reactions following immunisation.
- Joint pain (Arthralgia), a symptom of CHIKV infection, has also been reported following vaccination with CHIKV VLP vaccine during the clinical development programme (all non-serious), and would not be categorised as an important risk as it can be otherwise explained by inflammation. Chikungunya virus-induced arthropathy arises from infection of multiple cell types in the joint and the infiltration of mainly mononuclear cells. Innate responses (primarily involving type I interferon responses and natural killer cells) and cognate responses (primarily involving CD4 T helper 1 cells), alongside activation of macrophages and monocytes, mediate CHIKV-induced arthritic immunopathology (30).

1.8.2 Risk-management System

Adverse reactions were mostly mild to moderate in severity. A tabulated summary of the adverse reactions observed with VIMKUNYA from the five pooled clinical studies in 3522 individuals 12 years of age and older is presented in Table 12.

**Table 12: Frequency of Adverse Reactions Reported Following Administration of VIMKUNYA (Overall Safety Population N=3522)**

| **System Organ Class**<br>**Adverse Reaction** | **VIMKUNYA (CHIKV VLP Vaccine)**<br>**N=3522**<br>**%** |
|---|---|
| **General disorders and administration site conditions** | |
| Injection site pain | 23.96% |
| Fatigue | 17.84% |
| Chills | 7.39% |
| Malaise* | 7.01% |
| Injection site redness | 0.40% |
| Injection site swelling | 0.31% |
| Pyrexia | 0.77% |
| Injection site bruising | 0.26% |
| **Nervous system disorders** | |
| Headache | 16.71% |
| Dizziness | 0.20% |
| Paraesthesia | 0.14% |
| **Musculoskeletal and connective tissue disorders** | |
| Myalgia | 16.51% |
| Arthralgia | 7.30% |
| Pain in extremity | 0.06% |
| **Gastrointestinal disorders** | |
| Nausea | 6.87% |
| Diarrhoea | 0.09% |
| Lip swelling | 0.06% |
| **Blood and lymphatic system disorders** | |
| Lymphadenopathy | 0.06% |

| System Organ Class<br>Adverse Reaction | VIMKUNYA (CHIKV VLP Vaccine)<br>N=3522<br>% |
|---|---|
| **Infections and infestations** | |
| Gastroenteritis | 0.06% |
| **Respiratory, thoracic and mediastinal disorders** | |
| Nasal congestion | 0.11% |
| Oropharyngeal pain | 0.09% |
| Rhinorrhoea | 0.06% |
| **Skin and subcutaneous tissue disorders** | |
| Rash | 0.14% |

No serious treatment-related adverse events and no serious adverse events of special interest (defined as the occurrence of new onset or worsening of arthralgia that was medically attended) have occurred in clinical trials with VIMKUNYA. No treatment-related deaths have been reported in clinical trials with VIMKUNYA.

Based on available information, no unexpected adverse reaction trends have been identified following the administration of VIMKUNYA.

Please note that the information provided above is included to enable an overview of the clinical safety profile of VIMKUNYA. As no safety concerns have emerged from these data, upcoming revisions of the Risk Management Plan may no longer detail clinical data, unless any safety signals or safety concerns are found.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance; through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised): very rare potential risks for any medicinal treatment, including vaccines, which are well known to healthcare professionals are not included in the list of safety concerns.

### SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

**Important identified risks**

There are no important identified risks classified for VIMKUNYA at the time of initial EU RMP submission.

**Important potential risk:**

There are no important potential risks classified for VIMKUNYA at the time of initial EU RMP submission.

**Missing information**

The following topics are classified as missing information for VIMKUNYA at the time of initial EU RMP submission:

- **Use during Pregnancy and while Breastfeeding:**

There were no adequate and well-controlled studies of CHIKV VLP vaccine in pregnant and breastfeeding women. Due to limited safety information regarding VIMKUNYA administration in pregnant and breastfeeding women, these special populations were not enrolled in clinical trials and female of childbearing potential were required to use contraceptive methods per clinical study protocol specification.

Clinical studies were not conducted in pregnant and breastfeeding women, although there is some experience from clinical trials.

Based on the updated information received and as of 18-Oct-2024, 12 pregnancies (11 participants received CHIKV VLP vaccine, 1 received placebo) have occurred during clinical trials with CHIKV VLP vaccine.

One pregnant study participant who received placebo (pregnancy confirmed 57 days post-last vaccination with placebo) delivered a healthy infant.

The outcomes for the 11 pregnancies following CHIK VLP vaccine exposure are as summarised:

- 3 full term normal pregnancies [redacted]
- 5 early-term pregnancies and 1 pre-term pregnancy.
  - 3 early-term pregnancies [redacted]
  - 1 pregnancy (LMP 143 days post-last vaccination) [redacted] Prior history of preterm labour.
  - 1 pregnancy in a [redacted] study participant with history of polycystic ovary became pregnant 163 days after CHIKV VLP vaccine administration. Prenatal care was complicated by gestational hypertension and diabetes which were managed by a high-risk Maternal Foetal Medicine Physician. [redacted]
  - 1 pregnancy [redacted] (pregnancy 623 days postvaccination) with medical event of [redacted].
- 2 terminated pregnancies:
  - 1 [redacted] pregnancy in a study participant with prior history of [redacted]. The pregnancy was confirmed 24 days post-first vaccination. The pregnancy was terminated medically.

- 1 Pregnancy (pregnancy confirmed 102 days post-last vaccination) that resulted in [redacted]. Prior history of [redacted].

Risk-benefit impact: Based on the above-described pregnancy exposures and the corresponding causality assessments, there is no evidence of an increased risk associated to maternal exposure with VIMKUNYA. However, the amount of data is limited. Therefore, VIMKUNYA should be used during pregnancy only if the benefit of administration of VIMKUNYA during pregnancy and while breastfeeding outweighs any potential risk to the mother and foetus/baby.

## SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable for the initial marketing authorisation application submission.

## SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

### SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

No events or risks are categorised as important identified or potential risk at the time of initial RMP submission.

### SVII.3.2 Presentation of the Missing Information

**Table 13: Anticipated Risk/Consequence of the Missing Information**

| **Use during Pregnancy and Breastfeeding** | |
|---|---|
| **Evidence Source** | There were no adequate and well-controlled studies of VIMKUNYA in pregnant and breastfeeding women. Due to the limited safety information regarding the use of VIMKUNYA in pregnant and breastfeeding women, these special populations were not enrolled in clinical trials and females of childbearing potential were required to use effective contraception methods per clinical study protocol specification.<br>Animal studies do not indicate direct or indirect harmful effects to pregnant females or their offspring in developmental and reproductive toxicity studies. These animal studies have shown that antibodies induced by the vaccine transfer through the placenta to the foetus; however, there are no adequate controlled trials of VIMKUNYA in pregnant women. Animal studies have shown that antibodies induced by the vaccine have been found to transfer in the milk to offspring; however, it is not known whether VIMKUNYA is excreted in human milk.<br>Population in need of further characterisation: Pregnant and Breastfeeding Women<br>Anticipated risk/consequence: Based on the nonclinical and limited clinical safety data regarding CHIKV VLP vaccine exposure prior to pregnancy and breastfeeding, it is not expected that VIMKUNYA administration will pose increased risk; however, there is the consideration of use in this special situation only if the potential benefits outweigh any potential risk for the mother and foetus/baby. Administration of VIMKUNYA during pregnancy and breast feeding should be considered when the potential benefits outweigh any potential risk for the mother and foetus/baby. |

# PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

**Table 14: SVIII.1: Summary of Safety Concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | • Use during pregnancy and breastfeeding |

# PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

## III.1 Routine Pharmacovigilance Activities

Bavarian Nordic undertakes routine pharmacovigilance activities consistent with the International Conference on Harmonisation (ICH) E2E Pharmacovigilance Planning Guideline.

Routine pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to rapidly assess the ongoing safety profile of VIMKUNYA throughout clinical development and in the post-authorisation period in order to characterise and communicate pertinent safety data appropriately.

In addition to ICH requirements, Bavarian Nordic's routine pharmacovigilance activities in relation to VIMKUNYA are also aligned with the measures described in Good Pharmacovigilance Practice (GVP) Module IX for vaccine surveillance and signalling methods, as well as all other GVP modules for maintaining and managing a pharmacovigilance system, ensuring single case and aggregate reporting and providing timely and accurate product information.

Routine safety reporting and monitoring including the collection, follow-up assessment, and reporting of individual case safety reports (ICSRs) from any source; signal detection and evaluation; and preparation and submission of aggregate reports will be performed according to GVP and other globally applicable guidelines and regulations.

In specific populations such as immunocompromised individuals or those receiving other vaccines concomitantly, the following routine pharmacovigilance activities will be undertaken:

- Routine pharmacovigilance activities, including ongoing review and evaluation of spontaneous ICSRs, signal detection activities, annual safety analysis in periodic aggregate safety reports of potential use in immunocompromised individuals and in case of co-administration with other vaccines.
- Review of ICSRs and interval review of aggregate safety data to determine increased frequency of reporting in these categories of individuals.
- Expedited adverse drug reaction reports and periodic aggregate safety reporting.

Routine pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to rapidly assess the ongoing safety profile of VIMKUNYA throughout clinical development and in the post-authorisation period in order to characterise and communicate pertinent safety data appropriately.

No other forms of routine pharmacovigilance activities are required at this time.

**Traceability:**

The SmPC includes instructions for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability (section 4.4) and to report any suspected adverse reactions including batch/Lot number if available (section 4.8).

In addition, the vaccine carton labelling also contains a 2-D barcode encoding brand name and batch/lot number that will be made available to support documentation of the batch/lot traceability.

## III.2 Additional Pharmacovigilance Activities

Bavarian Nordic will conduct additional pharmacovigilance activities to further evaluate the missing information for 'Use during pregnancy'.

**VIMKUNYA Pregnancy Registry summary**

Study short name and title:

VIMKUNYA Pregnancy Registry: An Observational Prospective Study of the Safety of VIMKUNYA Vaccine Exposure in Pregnant Women and their Offspring

Rationale and study objectives:

This is an observational prospective registry study to evaluate pregnancy outcomes in women immunised with VIMKUNYA up to 28 days before conception or at any time during pregnancy.

Study design:

Pregnant women will be enrolled in the registry prospectively, after exposure to VIMKUNYA in routine clinical settings but before knowledge of the pregnancy outcome. This registry is strictly observational. The decision to vaccinate a pregnant individual is made by the patient and the health care provider. No vaccine products will be provided by the manufacturer as part of this registry protocol.

Study population:

To enrol in the registry, participants must have been exposed to VIMKUNYA up to 28 days before conception or during pregnancy and have received VIMKUNYA in a healthcare setting.

The number of participants is not defined; enrolment will be determined by passive reporting of pregnancy exposures to VIMKUNYA and consent to the collection of follow-up data. There is no limit to participation during the 3-year enrolment period.

Milestones:

Protocol available: 30-May-2025

Registry period (years): 5 years

Estimated registry start date: 31-Aug-2025

Final report submission: 28-Feb-2031

## III.3 Summary Table of Additional Pharmacovigilance Activities

**Category 1** – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation.

Not applicable

**Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances.

Not applicable

**Category 3 -** Required additional pharmacovigilance activities.

VIMKUNYA Pregnancy Registry, see Table 15.

**Table 15: Part III.1: On-going and planned additional pharmacovigilance activities**

| Study / Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1 -** Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| Not applicable | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| Not applicable | | | | |
| **Category 3 -** Required additional pharmacovigilance activities | | | | |
| VIMKUNYA Pregnancy Registry: An Observational Prospective Study of the Safety of VIMKUNYA Vaccine Exposure in Pregnant Women and their Offspring<br>Planned | To evaluate pregnancy outcomes in women immunised with VIMKUNYA up to 28 days before conception or at any time during pregnancy. | Use during pregnancy and breastfeeding | Protocol submission | 30-May-2025 |
| | | | Annual updates | Progress reports on enrolment and intermediate analysis results will be provided yearly. |
| | | | Final report | 28-Feb-2031 |

# PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

To date, the determination of the VIMKUNYA efficacy was based on vaccine induced anti-CHIKV serum neutralising antibody titres as an immunological surrogate endpoint, as it is widely accepted that immunity against CHIKV infection and disease is conferred by neutralising antibodies. To further characterise the efficacy profile of VIMKUNYA, Bavarian Nordic plans to conduct the following post-authorisation study, which is an event-driven study to evaluate the efficacy, safety, and immunogenicity of a single dose of VIMKUNYA in healthy adults and adolescents 12 years of age and older who reside in areas with high risk for CHIKV transmission (EBSI-CV-317-007).

**Study Short Name and Title**: A Phase 3b Randomised, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of an Adjuvanted Chikungunya Virus Virus-like Particle (CHIKV VLP) Vaccine for the Prevention of Chikungunya Disease in Adolescents (12 to <18 Years) and Adults (≥18 Years).

**Study Objectives**: The primary efficacy objective of the study is to evaluate the vaccine efficacy (VE) of VIMKUNYA compared to placebo in the prevention of laboratory confirmed acute CHIKV disease in adolescents and adults (12 years of age and older). The safety objective is to evaluate the safety of VIMKUNYA in adolescents and adults (12 years of age and older).

**Study Design/Study Population**:

The study will enrol up to 6144 participants to be stratified (for balance) by age group (12 to <18, 18 to <46, 46 to <65, 65 to <75, and (≥75 Years old) and site and randomised 1:1 to VIMKUNYA or placebo. Provided consent is not withdrawn, all participants will be followed after investigational product administration for a minimum duration of 6 months and maximum of 3 years to identify cases of CHIKV disease and to monitor the safety of the vaccine.

**Milestones:** The protocol of the study EBSI-CV-317-007 (**link to protocol**) has been submitted to the CHMP for Scientific Advice previously. The study will be initiated in Q3 2025 dependent on the declaration of CHIKV outbreak. Study enrolment is event driven. Up to 6144 participants is the projected number to enrol to achieve the target number of confirmed cases given the transmission and efficacy assumptions. If the event target of 64 acute CHIKV cases (or updated event target number) is achieved with lower enrolment or if futility or success are declared by the Data Monitoring Committee (DMC), then study enrolment may be stopped earlier, subject to considerations about incidence of chronic CHIKV disease. If the event target of 64 acute CHIKV cases is not achieved with 6144 participants, then study feasibility will be evaluated, and additional participants may be enrolled. A final study report is tentatively planned depending on enrolment, for submission by August 2030.

**Table 16: Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations**

| **Study Status** | **Summary of objectives** | **Efficacy uncertainties addressed** | **Milestones** | **Due Date** |
|---|---|---|---|---|
| Efficacy studies which are conditions of the marketing authorisation | | | | |
| Study EBSI-CV-317-007 (A Phase 3b Randomised, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of an Adjuvanted Chikungunya Virus Virus-like Particle (CHIKV VLP) Vaccine for the Prevention of Chikungunya Disease in Adolescents (12 to <18 Years) and Adults (≥18 Years)<br><br>(planned) | To evaluate the vaccine efficacy (VE) of VIMKUNYA compared to placebo in the prevention of laboratory confirmed acute CHIKV disease in adolescents and adults (12 years of age and older). | Efficacy of VIMKUNYA to prevent CHIKV disease. | Submission of final protocol<br><br>Final report | March 2025<br><br>August 2030 |

# PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

## Risk Minimisation Plan

VIMKUNYA has been shown to be safe and well-tolerated, revealing no risks requiring risk minimisation activities beyond routine measures.

## V.1 Routine Risk Minimisation Measures

**Table 17: Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety concern | Routine risk minimisation activities |
|---|---|
| **Important identified risks** | |
| None | |
| **Important potential risks** | |
| None | |
| **Missing information** | |
| Use during pregnancy and breastfeeding | **Routine risk communication:**<br>Specific statement in SmPC regarding use of VIMKUNYA during pregnancy and breastfeeding if the potential benefits outweigh any potential risk to the mother and foetus/baby.<br>• SmPC Section 4.6<br>• PL Section 2 |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>None. |

## V.2 Additional Risk Minimisation Measures

Part V.2: Routine risk minimisation activities as described in Part V Section V.1 are sufficient to manage the safety concerns of the medicinal product. Additional risk minimisation measures are not currently indicated.

# V.3 Summary of Risk Minimisation Measures

**Table 18: Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| **Important identified risks** | | |
| None | | |
| **Important potential risks** | | |
| None | | |
| **Missing information** | | |
| Use during pregnancy and breastfeeding | **Routine risk minimisation measures:**<br>• Specific statement in SmPC regarding use of VIMKUNYA during pregnancy and breastfeeding if the potential benefits outweigh any potential risk to the mother and foetus/baby:<br>• SmPC Section 4.6<br>• PL Section 2<br>• Vaccine product subject to medical prescription and administration by a licensed HCP.<br>**Additional risk minimisation measures:**<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>Annual safety analysis in periodic aggregate safety reports of exposures to VIMKUNYA during pregnancy and breastfeeding, and adverse reactions that may be associated with exposure to VIMKUNYA.<br>**Additional pharmacovigilance activities**: VIMKUNYA Pregnancy Registry; final study report: 28-Feb-2031. |

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## SUMMARY OF RISK MANAGEMENT PLAN FOR VIMKUNYA (CHIKV VLP VACCINE)

This is a summary of the risk management plan for VIMKUNYA, which details the population not studied or excluded from clinical study, risks not considered important for inclusion in the list of safety concerns, missing information and how this risk can be minimised, and how more information will be obtained about the uncertainties regarding VIMKUNYA administration (missing information) as applicable.

The summary of product characteristics (SmPC) and its package leaflet provide essential information to healthcare professionals and patients on how VIMKUNYA should be used.

This summary of the RMP for VIMKUNYA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of VIMKUNYA RMP.

## I THE MEDICINE AND WHAT IT IS USED FOR

VIMKUNYA is a recombinant virus-like particle vaccine, adjuvanted with aluminium hydroxide, non-replicating vaccine for the prevention of disease caused by chikungunya virus infection in individuals 12 years of age and older. It is administered by intramuscular injection.

Further information about the evaluation of VIMKUNYA benefits can be found in VIMKUNYA EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/medicines-human-use-under-evaluation

## II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of VIMKUNYA, together with measures to minimise such risks and the proposed studies for learning more about VIMKUNYA risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging

- The authorised pack size- the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status- the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously, monitored and regularly evaluated, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of VIMKUNYA is not yet available, it is listed under 'missing information' below.

## II.A List of Important Risks and Missing Information

Important risks of VIMKUNYA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VIMKUNYA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

**List of important risks and missing information**

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | • Use during pregnancy and breastfeeding |

## II.B Summary of Important Risks

No risks are categorised as important for VIMKUNYA at the time of the initial RMP submission.

## II.C Post-Authorisation Development Plan

### II.C.1 Studies which are Conditions of the Marketing Authorisation

**Study title:** A Phase 3b Randomised, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of an Adjuvanted Chikungunya Virus Virus-like

Particle (CHIKV VLP) Vaccine for the Prevention of Chikungunya Disease in Adolescents (12 to <18 Years) and Adults (≥18 Years) (EBSI-CV-317-007).

Purpose of the study: The primary efficacy objective of the study is to evaluate the vaccine efficacy (VE) of VIMKUNYA compared to placebo in the prevention of laboratory confirmed acute CHIKV disease in adolescents and adults (12 years of age and older). The safety objective is to evaluate the safety of VIMKUNYA in adolescents and adults (12 years of age and older). This study is planned.

### II.C.2 Other Studies in Post-Authorisation Development Plan

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

Purpose of the study: This is an observational prospective registry study to evaluate pregnancy outcomes in women immunised with VIMKUNYA up to 28 days before conception or at any time during pregnancy. This study is planned.

# ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

# ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable, as there are no additional risk minimisation measures proposed.