Risk Management Plan

for IXCHIQ (Chikungunya vaccine, live)

RMP Version number: final version 3.0

Data lock point for this RMP: 09 July 2025

Rationale for submitting an updated RMP:

- Procedure under Article 20 of Regulation (EC) No 726/2004 from pharmacovigilance data:
  - Addition of the important identified risk “Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions”
  - Addition of the missing information: “Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease”.

Other RMP versions under evaluation: No

Details of the currently approved RMP: Not applicable

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Date of final sign-off: 17 July 2025

QPPV signature

List of Abbreviations

AEs	Adverse events
AESI	Adverse events of special interest
AID50	Animal Infectious Dose
ANC	Absolute Neutrophil Count
ASIA Syndrome	Autoimmune/Inflammatory Syndrome Induced by Adjuvants
CHIKV	Chikungunya virus
CHIKF	Chikungunya fever
EEA	European Economic Area
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EVDAS	EudraVigilance data analysis system
EU-PAS register	The European Union electronic Register of Post-Authorisation Studies Register
FDA	Food and Drug administration
GD	Gestation day
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
HCP	Health care professionals
ICSRs	Individual case safety reports
IOM	Institute of Medicine
ITT population	Intent-to-treat population
LMP	Last menstrual period
LR-CHIKV	Chikungunya virus La Reunion strain
MAH	Marketing Authorisation Holder
n.a.	Not applicable
NHPs	non-human primates
NIP	National Immunisation Program
NSAIDS	nonsteroidal anti-inflammatory drugs
PAHO	Pan American Health Organisation
PL	Package leaflet
PP population	Per-protocol population
PRNT	plaque-reduction neutralisation antibody test
PS-HCPs	Pregnancy-Specific Healthcare Providers
PSUR	Periodic Safety Update Reports
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk management plan
rHA	Recombinant human albumin

SCRI	Self-controlled risk interval analysis
SmPC	Summary of Product Characteristics
TCID50	Tissue culture infection dose 50
VAERS	Vaccine Adverse Event Reporting System
WT	Wild-type
VLA1553	Clinical development name of IXCHIQ

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Part I Product Overview

Table 1: Product(s) Overview

Active substance(s) (INN or common name)	Chikungunya vaccine (live)
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned.
Marketing Authorisation Applicant	Valneva Austria GmbH Campus Vienna Biocenter 3 1030 Vienna Austria
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	IXCHIQ
Marketing authorisation procedure	Centralised
Brief description of the product	Type of product Bio(techno)logical / classical biological / Vaccine
	Summary of mechanism of action IXCHIQ contains live-attenuated CHIKV of the ECSA/IOL genotype. The exact mechanism of protection against CHIKV infection and/or disease has not been determined. IXCHIQ elicits neutralising antibodies against CHIKV.
	Important information about its composition After reconstitution, one dose (0,5 ml) contains: Chikungunya virus (CHIKV) Δ5nsP3 strain (live)* not less than 3.0 log10 $TCID_{50}$** * Produced in Vero cells ** 50% tissue culture infectious dose This product contains genetically modified organisms (GMOs). List of excipients: <u>Powder</u> Sucrose D-Sorbitol L-Methionine Trisodium Citrate Di-Hydrate Magnesium Chloride Di-Potassium- Hydrogen Phosphate Potassium-Di- Hydrogen-Phosphate recombinant Human Albumin (rHA) <u>Solvent</u> Sterile water for injections
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	IXCHIQ is indicated for active immunisation for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 12 years and older.

Dosage in the EEA	IXCHIQ is administered as a single dose of 0.5 ml. The need for re-vaccination has not been established.
Pharmaceutical form(s) and strengths	Powder and solvent for solution for injection. 1 vial of powder 1 prefilled syringe of solvent
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 populations

Indication

IXCHIQ is a vaccine indicated for active immunisation for the prevention of disease caused by chikungunya (CHIKV) virus in individuals 12 years and older.

Incidence

Chikungunya is a viral disease caused by the chikungunya virus (CHIKV) and is primarily transmitted by mosquitos. Several factors contribute to the worldwide spread of chikungunya, including the adaptation of CHIKV to new vectors and the continued expansion of the mosquito vectors into a more temperate climate. Global warming and climate change increase the risk of expansion of chikungunya, as vector habitat continues to expand, posing increased outbreak risk in warmer areas of the US and Europe (1), (2). Globally, there is no real estimate for the number of people affected annually nonetheless, there have been at least five million cases of CHIKV infection over the last 15 years, demonstrating that the virus is an emerging global health threat (3).

Prevalence and incidence of chikungunya

Chikungunya prevalence and incidence have been reported by several studies conducted in Africa, Asia, Oceania, the Americas and Europe. Seroprevalence rates vary largely across countries depending on ongoing outbreaks or endemic situations. Additionally, coinfection by other febrile diseases, such as DENV, might lead to misdiagnoses, contributing to varying rates of reported prevalence and incidence of chikungunya. Despite the variation in climate across Europe, native mosquitoes are present in the whole continent, although the species and seasonal abundance vary dramatically (4). In addition to native mosquitoes, Europe has been colonized by a series of invasive mosquitoes, chief among which is *Aedes albopictus*, a vector for a growing number of viruses. The presence of abundant populations of *Aedes albopictus* increases the risk of autochthonous disease transmission within the human population wherever it is found (4).

In the EU, CHIKV infection is not endemic, even though some outbreaks were reported in France and Italy after the introduction of CHIKV by travellers into receptive areas (areas in which *Aedes albopictus* mosquitoes were established and active). According to the European Centre for Disease Prevention and Control (ECDC), 14 countries reported 160 cases of CHIKV infection in 2018, of which 113 (71%) were laboratory-confirmed (5). All cases were travel related. For the majority of cases, infection probably occurred in Asia (55.8%) and Africa (33.3%). In 2020, 24 European countries reported 59 cases of CHIKV infection, of which 52 (88%) were laboratory-confirmed. All cases were travel related. This number was the lowest reported since 2016, but this was influenced by the COVID-19 restrictions (6).

Reported prevalences and incidences

In the EU/European Economic Area (EEA), the notification rate for CHIKV infection was 0.03/100.000 in the European population during 2014–2018 (5). The United Kingdom reported the highest proportion of the 113 confirmed cases (36.9%), followed by Spain (16.9%) and Germany (16.3%). In England, Wales, and Northern Ireland, there were 501 laboratory-confirmed cases of CHIKV infection in the period 2009–2014 (7).

According to a publication by ECDC in June 2025, since the beginning of 2025 approximately 220,000 CHIKV disease cases and 80 CHIKV disease-related deaths have been reported in 14 countries. The countries reporting the highest number of CHIKV disease cases are Brazil (141,436), Argentina (2,521), Bolivia (605) and Peru (46).

According to an update by the World Health Organisation (WHO) in June 2025, France reported 118 cases of autochthonous chikungunya from the island of La Réunion in August 2024. These cases marked the first detected autochthonous CHIKV transmission on La Réunion since it was last documented in 2014. Transmission persisted into 2025.

In Mayotte, the first locally transmitted cases since 2005–2006 have been raising concern about similar large outbreaks.

According to a publication by the Institut Pasteur in July 2025, several locally acquired cases of chikungunya have been detected in mainland France since the beginning of 2025, mainly in southeastern departments where the mosquito vector is well established.

Demographic characteristics

In Europe, the male-to-female ratio of CHIKV infection was 0.6:1 in 2018 (5). The majority of cases were 25–64 years of age (n=72; 45%). Rates were highest for females aged 25–44 (0.07 cases per 100.000). Rates were higher among females in most age groups, except for those aged 5–14 and those aged 65 years and above. While the ECDC data show the rates in the 0–4 years age group, further breakdown of rates within this band has not been reported in Europe.

Future expansion of habitable areas for CHIKV vectors

Even though CHIKV is not endemic in continental Europe, autochthonous cases were reported in France in 2010, 2014, and 2017, and two large outbreaks occurred in Italy in 2007 and 2017 (13). Hence, Fischer *et al*. assessed the potential risk of transmission of CHIKV in Europe in the future (14). Climatic suitability for CHIKV transmission was based on temperature and precipitation requirement. Large parts of Europe will exceed the lowest observed temperature requirement of 20°C, and the climatic suitability for CHIKV transmission is projected to increase in Northern Italy, western coastal Mediterranean areas of the Balkan States and Greece, and the Pannonian Basin. This is in accordance with an ecological niche model by Tjaden *et al*. that demonstrated that large parts of southern and western Europe and the coastal regions of south-eastern Europe will become suitable for CHIKV transmission (15).

The main existing treatment options

Despite the high burden of the disease, there is no specific therapy approved for chikungunya. Pain relief, supplemented with other palliate options, during the acute, subacute, and chronic phases is the mainstay and the only effective treatment option for disease management (16), (17). Since current treatment only focuses on the relief of symptoms, there is a definitive need for novel treatments, preferably with the ability to cure or fully prevent the disease. The development of curative treatment and/or vaccine for chikungunya is crucial as the disease is characterized by a high morbidity rate and debilitating potential long-term effects. Current, alternative, preventative measures are insufficient, which is demonstrated by the disease's re-emergence and increase in prevalence and vector spread. A vaccine could make a significant contribution to tackling this disease. Returning travellers are sentinels of this rapidly changing epidemiology of chikungunya. Currently, the disease has already spread over 100 countries throughout Africa, Asia, the Americas, and Europe (18). The associated outbreaks are explosive, rapidly spreading, and unpredictable. Although originating in tropical and sub-tropical counties, outbreaks have spread in recent years to the more temperate regions of the world, including Europe.

All of this shows that current preventative measures do not outweigh global trends that form the root causes for these increases, such as climate change, globalization, travel, and trade. Existing measures, such as employment of insecticides, wearing long sleeves and pants, mosquito nets, minimising the amount of stagnant water in inhabited areas, and other means to restrict exposure, are mainly focused on vector control. Due to the ineffectiveness of these measures, to limit the burden of this disease and prevent needless suffering of people newly and already at risk of infection, new endeavours must be undertaken to improve the prevention of chikungunya. Therefore, there is an urgent medical need for an integrated prophylactic strategy to control CHIKV, in which the vaccine would play an important role. The development of life-long immunity to natural CHIKV infection suggests that a vaccine containing a live-attenuated virus which mimics natural infection but is unable to cause the disease has the potential to generate life-long protection against it. Given long-term disease-related health impacts and a lack of treatment options, vaccine prevention (developing a vaccine) against CHIKV is a significant unmet need.

Natural history of the indicated condition in the population, including mortality and morbidity

As previously mentioned, there is currently no curative or specific antiviral treatment, nor a vaccine, available to tackle chikungunya. This is especially concerning, given that the morbidity of chikungunya is very high. Chikungunya has an acute phase that affects up to 97% of those infected, with symptoms that include high fever and joint pain. However, it is the chronic phase that is most concerning, as it can last for months or even years, leading to potentially debilitating arthralgia and fatigue. Patients with severe or chronic chikungunya face long-term disability, and suffer from a significant humanistic and economic burden (19), (20), (21). Additionally, mortality is estimated to occur in around 1 in 1000 patients (3.357). Therefore, the disease burden associated with the illness is a serious threat to global public health.

Important co-morbidities

Risk factors for chronic chikungunya are reported in numerous studies. The following groups are at risk for severe disease or progression to chronicity (22): adults >45 years of age, people with chronic medical conditions (e.g., cardiovascular diseases, obesity, diabetes or asthma, high viral load during the acute phase and severe immunologic response in the post-viraemic phase.

Mortality may be higher for atypical cases of chikungunya in patients with underlying co-morbidities such as: respiratory, cardiovascular and neurological disorders and may be higher with increasing age (23).

Part II: Module SII - Non-clinical part of the safety specification

Toxicity

Preclinical toxicology studies to date were limited to a repeat-dose toxicology study.

Repeat Dose Toxicity and Local Tolerance

A repeat dose toxicity study in rabbits (New Zealand White strain) was conducted to determine the potential systemic and local toxicity of VLA1553. Two i.m. injections at a two week interval of VLA1553 ($3.8x10^5$ $TCID_{50}$/dose) were administered. Clinical signs, dermal scoring, body weights, body weight gains, food consumption, ophthalmology, body temperature, and clinical pathology parameters (haematology, coagulation, and clinical chemistry) were evaluated.

In summary, VLA1553 was well tolerated both systemically and locally. VLA1553 was only associated with a transient inflammatory response that was noted by higher circulating C-reactive protein after each injection, and by reactions at the administration sites that, although also present in controls, were graded higher in VLA1553-treated animals and included mixed inflammatory cell infiltration (only present in some animals), haemorrhage and myofiber necrosis (noted in one animal out of 10). The findings were not observed after a 30-day recovery period indicating that reactions had resolved. However, the inflammatory reactions noted at the administration sites should not be regarded as adverse, as they were considered typical and of the nature commonly observed after injection of foreign material.

Hence, the results of the repeat dose toxicity study were supportive for first-in-human clinical use of VLA1553.

Reproductive and Development Toxicity

Macroscopic and microscopic evaluation of male and female reproductive tissues were included in the repeat dose study performed in rabbits. There were no organ weight differences, no pathology findings in the reproductive tissues (ovary, testes etc.) associated with the administration of VLA1553 in the repeat dose toxicity study.

A reproductive and development toxicity study was performed to determine the potential toxicity of VLA1553 when given before (Day 1) and after (Gestation Day [GD] 6) the start of pregnancy via intramuscular injection to female Sprague-Dawley rats and during pre- and post-natal development.

Administration of VLA1553 by intramuscular injection (delivered over two sites) twice before mating and once in early organogenesis was well tolerated in rats at the intended human dose of 1.9×10^4 $TCID_{50}$/0.5 ml. No adverse effects were seen on the dams or the developing foetuses or pups.

Genetic Stability of VLA1553 Attenuation Post-vaccination in Humans

To address the genetic stability of the attenuation and possible genetic changes that may occur during in vivo replication after administration of VLA1553 to volunteers in the Phase 1 clinical trial (VLA1553-101), the sequence conservation of recovered VLA1553 CHIK vaccine virus from subjects in the trial was assessed.

The CHIKV sequence determined from subject samples was analogous to the sequence of VLA1553, which the subjects had received in the Phase 1 trial and thus, maintained the del5nsP3 deletion. Furthermore, no relevant sequence heterogeneities could be detected in this region for any of the tested samples (n=20).

In addition, full genome sequencing identified no mutations in any of the CHIKV genes in isolates derived from human samples neither on Day 3 nor Day 7 after vaccination.

Therefore, this analysis revealed that there is no risk of reversion of CHIKV VLA1553 vaccine to wild-type CHIKV after administration of the VLA1553 vaccine in humans.

Part II: Module SII - Clinical trial exposure

SIII.1 Brief overview of clinical development

One phase 1 clinical trial – VLA1553-101 - and two phase 3 clinical trials – VLA1553-301 and VLA1553-302 - have been conducted to date in the adult population. One follow-up clinical trial VLA1553-303 is currently ongoing. Data are available up to 2 years following immunization with IXCHIQ for participants from clinical trial VLA1553-301.

One phase 3 clinical trial in the adolescent population is currently ongoing – VLA1553-321. From this trial, six-month follow-up data have become available (Part B).

SIII.2 Clinical trial exposure

Overall, 4.643 healthy adult subjects have been enrolled in the VLA1553 clinical programme, of which 3.610 received IXCHIQ.

In addition, 754 adolescents 12-17 years of age have been enrolled in the VLA1553 clinical programme, of which 502 received IXCHIQ.

Overall clinical trial exposure is summarised in the tables below.

Clinical trial exposure in adults:

Table 2: Exposure

Exposure	**Subjects**
Single vaccination	3610
Month 6 re-vaccination	26
Month 12 re-vaccination	68

Table 3: Age group and gender

Age group	**Subjects**	
	male	female
Adults (18 to 45 years)	979	1105
Adults (46 to 64 years)	547	633
Elderly individuals		
65-74 years	141	146
75-84 years	22	32
85 + years	2	3
Total	**1691**	**1919**

Table 4: Dose

Dose of exposure	**Subjects**
3.2x10E3 TCID50	31
3.2x10E4 TCID50	3519
3.2x10E5 TCID50	59
Total	**3609**

Table 5: Ethnic origin

Ethnic origin	Subjects
Hispanic or Latino	608
Not Hispanic or Latino	2961
Not reported	34
Unknown	7
Total	**3610**

Table 6: Body Mass Index (BMI)

BMI	Subjects
BMI < 25 kg/m2	884
BMI ≥ 25 kg/m2 and <30 kg/m2	1126
BMI ≥ 30 kg/m2 and <35 kg/m2	833
BMI ≥ 35 kg/m2	763
Total	**3606**

Clinical trial exposure in adolescents (12-17 years of age):

Table 7: Exposure

Exposure	Subjects
Single vaccination	502

Table 8: Age group

Age Group	Subjects [n(%)]
12 - <15 years	244 (48.6)
15 - <18 years	258 (51.4)
Total	502 (100)

Table 9: Sex

Female [n(%)]	Male [n(%)]	Total [n(%)]
269 (53.6)	233 (46.4)	502 (100)

Table 10: Ethnic origin

Ethnic origin	Subjects [n(%)]
Hispanic or Latino	358 (71.3)
Not Hispanic or Latino	140 (27.9)
Missing	4 (0.8)
Total	**502 (100)**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in clinical trials within the development program

Detailed descriptions of all exclusion criteria for clinical studies VLA1553-101, VLA1553-301 and VLA1553-302 are provided in the individual Clinical Trial Protocols. Exclusion criteria across studies were similar and the majority of these criteria are standard for vaccine studies.

Women who are pregnant

Reason for exclusion: Live vaccines administered to a pregnant woman pose a theoretical risk to the foetus. Therefore, live, attenuated virus vaccines generally are not administered to pregnant women.

Is it considered to be included as missing information? No.

Rationale: Safety in pregnant or breastfeeding women is considered an important potential risk.

Women who are breast-feeding

Reason for exclusion: It is unknown if IXCHIQ is excreted in human milk. A risk to the breastfed child cannot be excluded.

Is it considered to be included as missing information? No.

Rationale: Safety in pregnant or breastfeeding women is considered an important potential risk.

Immunocompromised individuals with known or suspected immunodeficiency, such as subjects with congenital or acquired immunodeficiency, including infection with HIV, status post organ transplantation or immuno-suppressive therapy within 4 weeks prior to vaccination

Reason for exclusion: Individuals who have altered immunocompetence and receive live vaccines might be at increased risk for an adverse reaction because of uninhibited growth of the attenuated live virus or bacteria. Vaccines might be less effective during the period of altered immunocompetence.

Is it considered to be included as missing information? No.

Rationale: IXCHIQ is contraindicated in immunodeficient or immunosuppressed individuals due to disease or medical therapy (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised).

History of immune-mediated or clinically relevant arthritis/arthralgia

Reason for exclusion: Individuals with a history of immune-mediated or clinically relevant arthritis/arthralgia were excluded to allow differentiation from post-vaccination arthritis/arthralgia (i.e. solicited systemic adverse events and adverse events of special interest) in study participants.

Is it considered to be included as missing information? No.

Rationale: Vaccine-associated arthritis is considered an important potential risk.

History of allergy to any component of the vaccine

Reason for exclusion: Patients with known allergy/hypersensitivity to the active ingredient or comparator were excluded from the clinical studies as these individuals may have a higher risk of hypersensitivity reactions, including anaphylaxis.

Is it considered to be included as missing information? No.

Rationale: Hypersensitivity and anaphylaxis are covered in section 4.4. “Warnings and precautions for use” of the IXCHIQ SmPC.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

Clinical trials are limited in size and, therefore, unlikely to detect very rare adverse reactions, or adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

The following table shows exposure of special populations.

Table 11: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Pregnancy was an exclusion criterion in clinical trials with IXCHIQ. However, exposure during pregnancy was reported in 16 adult women and 3 adolescents.
Breastfeeding women	There were no clinical trial cases indicative of exposure during breastfeeding.
Frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions	Not included in the clinical development program.
Population with relevant different ethnic origin	Please refer to Table 5 for exposure information by ethnic origin from clinical trials with VLA1553.
Adolescent population	Data have become available from 502 adolescents 12-17 years of age exposed to IXCHIQ in phase 3 clinical trial VLA1553-321.

Part II: Module SV - Post-authorisation experienceT

SV.1. Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Exposure from marketing experience worldwide (status 14 May 2025)

It is important to emphasize that the figures on doses [redacted] administered are based on estimates derived from commercial data sources. These estimates are subject to inherent limitations, including reporting delays, inconsistencies between distributed and actually administered doses, and variability in data collection practices across different healthcare systems. [redacted]

Worldwide distribution overview on IXCHIQ doses* - 14th May 2025	US	CA	EU w/o Fr	France ML & Overseas	La Réunion	**Total**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total estimated doses in arms	19,350	5,800	250	6,099	6,418	**37,917**
[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]

Part II: Module SVI – Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Vaccines in general are not considered to present a risk for abuse. The potential for misuse of IXCHIQ is considered negligible as it is available via prescription only, to be administered by a healthcare professional, and primary immunisation is one dose only.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The safety concerns for IXCHIQ are listed in Table 12 below.

Table 12: Summary of Safety Concerns

Important Identified Risks	Chikungunya-like adverse reactions
Important Potential Risks	Vaccine-associated arthritis
	Cardiac events
	Safety in pregnant or breastfeeding women
Missing Information	Safety in patients with autoimmune or inflammatory disorders
	Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions
	Long-term safety
	Co-administration with other vaccines

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated), and covered in SmPC section 4.8:

Reactogenicity events are common and known to occur for the investigational product being studied. Solicited systemic and local events were collected in clinical trials with IXCHIQ in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction.

In clinical trials VLA1553-101, VLA1553-301 and VLA1553-302 (pooled analysis) the most common solicited systemic adverse reactions (≥20%) were headache (28.6%), fatigue (27.0%), fatigue (27.0%) and myalgia (22.0%). Solicited systemic adverse reactions are provided in Table 13.

Table 13: Solicited Systemic Adverse Reactions by PT (Pooled Safety Population)

Category	IXCHIQ (N=3082) % of subjects	Placebo (N=1033) % of subjects
Any Solicited Systemic Adverse Reaction	47.0	23.6
Headache	28.6	12.4
Fatigue	27.0	11.2
Myalgia	22.0	6.8
Arthralgia	15.0	4.5
Fever	12.4	0.6
Nausea	9.9	4.9
Rash	1.8	0.3

Category	IXCHIQ (N=3082) % of subjects	Placebo (N=1033) % of subjects
Vomiting	1.5	0.8

PT=preferred term

The most common (≥10%) solicited injection site reaction was tenderness (10.6%). Table 14 summarises the frequency of solicited injection site reactions reported in clinical trials with IXCHIQ.

Table 14: Solicited Injection Site Adverse Reactions (Pooled Safety Population)

Category	IXCHIQ (N=3,082) % of subjects	Placebo (N=1,033) % of subjects
Any Solicited Injection Site Adverse Reactions	14.8	11.1
Tenderness	10.6	8.0
Pain	5.9	3.6
Erythema/Redness	1.5	1.5
Induration	1.4	0.8
Swelling	0.7	0.8

PT=preferred term

Laboratory parameters:

The most common abnormal laboratory parameters were neutropenia (41.8%), leukopenia (31.2%), lymphopenia (22.3%), Alanine aminotransferase increased (ALT: 15.5%), and Aspartate aminotransferase increased (AST: 11.7%) (based on an immunogenicity subset of 372 IXCHIQ recipients).

An analysis of clinical laboratory data of the pooled dataset (VLA1553-101, -301, and -302) showed that the majority of subjects had neutrophil, lymphocyte and leukocyte counts and ALT/AST levels within normal ranges both at baseline and after VLA1553 vaccination. Most of the cases with a decrease in neutrophil, lymphocyte or leukocyte counts and/or increase in ALT/AST were classified as mild or moderate; severe abnormalities were reported by low percentages of subjects (2.3% or less), and the most frequent one was decreased neutropenia. These laboratory parameter abnormalities were only transient and normalised up to Day 29.

There is currently no evidence from clinical trials with VLA1553 to suspect undesirable clinical outcomes because of transient, mostly mild or moderate abnormal laboratory findings in white blood cell counts or liver function tests after vaccination with IXCHIQ.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

Anaphylaxis:

Anaphylaxis is included in section 4.4 of the SmPC “Special warnings and precautions for use”. Healthcare providers are aware of the risk of anaphylactic reactions and have the appropriate measures in place as part of clinical practice.

Seizure:

Seizure is included in section 4.4 of the SmPC “Special warnings and precautions for use” as an anxiety-related reaction. Healthcare providers are aware of the risk of injury from fainting and have the appropriate measures in place as part of clinical practice.

Other reasons for considering the risks not important:

Adverse Events of Special Interest (AESIs) as defined for IXCHIQ are adverse events based on the AESI lists developed by ACCESS and SPEAC/Brighton Collaboration, a revision of AEs from live-attenuated yellow fever vaccine studies, as well as safety results from clinical trials VLA1553-301 and VLA1553-302. The AESI list contains events previously identified with immunisation in general (e.g., Guillain-Barré-Syndrome), or with theoretical concerns based on immunopathogenesis or viral replication during infection (e.g. rheumatoid arthritis, spondyloarthritis).

Of these events, the following were reported in clinical trials with IXCHIQ in the VLA1553 group:

- Venous thrombosis: one non-serious case
- Diverticulitis: one serious case
- Guillain-Barré-Syndrome: one serious case
- Syndrome of inappropriate antidiuretic hormone secretion: one serious case.

AESIs are listed in Table 15 below.

Table 15: Adverse Events of Special Interest

Infection	Laboratory-confirmed Chikungunya virus infection
Musculoskeletal and connective tissue disorders	Spondyloarthropathy Rheumatoid arthritis, polyarthritis Fibromyalgia Polyarthralgia
Systemic	Convulsion Disseminated intravascular coagulation Venous thromboembolism Haemorrhagic stroke Syndrome of inappropriate antidiuretic hormone secretion Colonic diverticulitis
Neurologic	Aseptic meningitis Bell's Palsy Myelitis transverse Encephalitis Encephalomyelitis Acute Disseminated Encephalomyelitis Guillain-Barré-Syndrome Optic neuritis Central Nervous System Inflammation
Others	Sudden Death

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Chikungunya-like adverse reactions

Risk-benefit impact

The occurrence of certain adverse event combinations, referred to as "Chikungunya-like adverse reactions", was retrospectively evaluated in the pooled safety data from phase 1 and 3 clinical trials with VLA1553 (N=3.610).

Chikungunya-like adverse reactions (related and unrelated) were broadly defined, i.e. occurrence of fever (≥38°C or 37.8°C depending on the clinical trial)

AND

any single symptom (from the list initially defined in each clinical trial protocol) including arthralgia / arthritis (not only in extremities), fatigue, chills, pain, peripheral oedema, headache, dizziness, paraesthesia, myalgia, back pain, rash, hyperhidrosis, eye disorders

[e.g. conjunctivitis, retinitis, uveitis, optic neuritis,…] and cardiac events [e.g., tachycardia, arrythmia, myocarditis and other cardiac complications])

AND

occurring within 30 days post vaccination (regardless of the order of their onset and duration).

Adverse event combinations qualifying as Chikungunya-like adverse reactions were reported in 12.1% of participants. Among those, combinations of fever with headache, fatigue, myalgia or arthralgia were the most common, all other symptoms were reported in fewer than 10% of Chikungunya-like adverse reactions.

Important Potential Risk: Vaccine-associated arthritis

Risk-benefit impact

In the Pooled Dataset (VLA1553-101, VLA1553-301, VLA1553-302), the proportion of subjects who experienced musculoskeletal stiffness, joint stiffness, joint swelling, arthritis, or osteoarthritis was comparable between the VLA1553 and placebo group (1.1% and 1.2%). All events were reported with low frequency (≤0.5% in the VLA1553 group).

While arthritis will have an impact on the individual's activity, post-vaccination arthritis is expected to be transient in nature.

Rubella-containing vaccines (e.g., MMR) can cause mild, acute, transient arthralgia or arthritis, rarely in children but very commonly in adult women (between 10-25% of adult female vaccinees without preexisting rubella immunity), usually beginning 1-3 weeks after vaccination and then persisting up to 3 weeks. Other vaccines currently routinely recommended to the general population in the U.S. have not been shown to cause chronic arthralgia or arthritis (24).

A limited number of case studies after COVID-19 vaccine administration have been published. Overall, evidence for a causal relationship between arthritis and vaccines in general from scientific literature appears limited.

Important Potential Risk: Cardiac events

Risk-benefit impact

Cardiac events, including atrial fibrillation, are frequently observed in the general population (e.g., US incidence of atrial fibrillation was estimated at 1,2 million new cases in 2010, increasing (25). In addition, they are also reported as atypical complication of Chikungunya infection (26) , (27).

Cardiac events have also been observed as rare events following vaccination such as influenza vaccination, COVID-19 vaccination, or smallpox vaccination (28).

A limited number of cardiac events have been reported in IXCHIQ clinical trials. For 5 participants in the VLA1553 group the following SAEs from the SOC Cardiac Disorders were

reported: atrial fibrillation (2), cardiac arrest (1), cardiomyopathy (1), coronary artery disease (1). All these SAEs were assessed as unrelated by the investigator.

There is currently limited evidence to attribute the possibility of a causal relationship between the occurrence of serious cardiac disorders and vaccination with IXCHIQ.

Important Potential Risk: Safety in pregnant and breastfeeding women

Risk-benefit impact

Live vaccines tend not to be administered during pregnancy as a precaution because of the theoretical risk of foetal infection. There has been no evidence to date of direct foetal injury after the administration of live viral vaccines to pregnant women (29). However, since the theoretical possibility of foetal infection exists, live vaccines should generally be delayed until after delivery.

On the other hand, pregnant women are at increased risk of complications associated with CHIKV infection compared to non-pregnant women. Pregnant women with CHIKV infection may be at increased risk for adverse pregnancy outcomes, including preterm labour and delivery. Vertical transmission of CHIKV from mothers with viraemia at delivery to their infants has been reported and can cause severe, potentially fatal neurological disease in neonates.

There is limited amount of data from the use of IXCHIQ in pregnant women. These data are not sufficient to conclude on the absence of potential effects of IXCHIQ on pregnancy, embryo-foetal development, parturition and post-natal development.

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Animal studies did not indicate any direct or indirect harmful effects with respect to lactation. It is unknown if IXCHIQ is excreted in human milk. A risk to the breastfed child cannot be excluded.

Missing Information

Use in patients with autoimmune or inflammatory disorders

Risk-benefit impact

There is no information on the safety of IXCHIQ in individuals with autoimmune or inflammatory disorders. It is a theoretical concern that the vaccine may exacerbate their underlying disease.

Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions

Risk-benefit impact

IXCHIQ has been studied in individuals with stable chronic diseases, e.g. hypertension or obesity. However, it has not been studied in frail individuals with severe co-morbidities. The immune function may be compromised due to the condition or treatment of the condition.

Long-term safety data

Risk-benefit impact

The understanding of the long-term safety of IXCHIQ is currently limited. Safety data are being collected in the ongoing follow-up clinical trial VLA1553-303 for up to 2 years following immunisation with IXCHIQ. Further long-term safety data will be collected from the Randomized Controlled Trial VLA1553-404.

Co-administration of IXCHIQ with other vaccines

Risk-benefit impact

IXCHIQ is not recommended to be co-administered with other vaccines because there are no data on the safety and immunogenicity following concomitant administration of IXCHIQ with other vaccines. Data of co-administration of IXCHIQ with other vaccines will be collected in Post-Authorisation Safety Study VLA1553-401, in the Randomized Controlled Trial VLA1553-404, as well as through routine pharmacovigilance.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The following new safety concerns have been added to the RMP:

- The new important identified risk “Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions.

- The missing information: “Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease”.

No reclassification of safety concerns has been performed.

Important Identified Risk: increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions

Risk-benefit impact

Serious adverse events have been reported with the use of IXCHIQ, particularly in individuals aged 65 years and older and in individuals with multiple underlying chronic and/or uncontrolled medical conditions. 77% of SAEs were reported in individuals aged 65 years and older. Of these, 92% reported underlying medical conditions.

Severe reactogenicity or chikungunya-like adverse reactions may lead to deterioration of general condition including malaise and decreased appetite, exacerbation of pre-existing diseases, confusional state, encephalopathy, or encephalitis, leading to falls, hospitalisation and death. Vaccinees should be instructed to promptly seek medical attention if they experience, after vaccination, symptoms suggestive of severe reactogenicity or severe chikungunya-like adverse reactions.

While most serious side effects occurred in older people, Ixchiq is effective at triggering the production of antibodies against the chikungunya virus, which may be of particular benefit for older people at increased risk of severe chikungunya disease and of death due to chikungunya infection.

IXCHIQ should only be given when there is a significant risk of acquiring chikungunya infection, and after careful consideration of the potential risks and benefits.

Further data in this population will be collected in Post-Authorisation Safety Study VLA1553-401 and in the Prospective Safety Cohort Study VLA1553-406.

Missing information: Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease

Risk-benefit impact

While an increased risk for serious adverse events has been identified in individuals ≥65 years of age with chronic medical conditions, only limited data are available to evaluate if individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses are also at increased risk for serious adverse events. Further data will be collected in Post-Authorisation Safety Study VLA1553-401 and in the Prospective Safety Cohort Study VLA1553-406.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII 3.1 Important Identified Risk: Chikungunya-like adverse reactions

Table 16: Chikungunya-like adverse reactions

Potential mechanism, evidence source and strength of evidence	The occurrence of certain adverse event combinations, referred to as Chikungunya-like adverse reactions, was retrospectively evaluated in the pooled safety data from phase 1 and 3 clinical trials (N=3.610). Chikungunya-like adverse reactions were broadly defined as follows: a) Fever (≥38 °C or 37.8°C depending on the clinical trial) AND b) any single symptom (from the list initially defined in each protocol) including arthralgia/arthritis (not only in extremities), fatigue, chills, pain, oedema peripheral, headache, dizziness, paraesthesia, myalgia, back pain, rash, hyperhidrosis, eye disorders [e.g., conjunctivitis, retinitis, uveitis, optic neuritis,…] and cardiac events [e.g., tachycardia, arrhythmia, myocarditis and other cardiac complications]) AND c) occurring within 30 days post vaccination (regardless of the order of their onset and duration). Adverse event combinations qualifying as Chikungunya-like adverse reactions were reported in 12.1% of participants. Among those, combinations of fever with headache, fatigue, myalgia or arthralgia were the most common, all other symptoms were reported in fewer than 10% of Chikungunya-like adverse reactions. The reported symptoms were mostly mild. 1.8% of participants reported at least one severe symptom, most commonly fever or arthralgia. Median onset of Chikungunya-like adverse reactions was 3 days after vaccination, and median time to resolution was 4 days. Longer-lasting symptoms ≥30 days occurred in 0.4% of participants.”
Characterization of the risk	The vast majority of Chikungunya-like adverse reactions were unspecific symptoms consistent with a strong innate immune response, which are also seen after vaccination with other licensed, highly immunogenic vaccines and do not appear to reflect chikungunya-associated events. Clinically, the hallmark of chikungunya infection is high-grade fever and severe joint pain, while the AESI analysis used a very broad definition that factually allows any individual with fever and (among others) one of the solicited systemic AEs of joint pain, muscle pain, headache, and fatigue to qualify. In a typical presentation of chikungunya, it would be expected to see about 40% of individuals with acute disease to progress to chronic symptoms. If the approx. 12% of individuals with Chikungunya-like adverse reactions really were representing chikungunya-associated disease, the resulting rate of chronic disease would be a hypothetical 4%. This has, however, not been observed with VLA1553 at all: the overall rate of longer-lasting arthralgia was not different between VLA1553 and placebo.
Risk factors and risk groups	Unknown.
Preventability	Prevention may not be possible, particularly as only one dose of IXCHIQ is given.

Impact on the risk-benefit of the biologic product	Unknown.
Public health impact	The frequency of Chikungunya-like adverse reactions in the post-marketing setting is unknown.

Table 17: Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions

Potential mechanism, evidence source and strength of evidence	A clustering of SAEs, thereof one with fatal outcome, has been noted in individuals ≥65 years of age with chronic medical conditions from post-marketing use of IXCHIQ. Of the total of 31SAEs reported between 09 November 2023 and 30 June 2025, 24 (77%) occurred in individuals aged ≥65, highlighting a significant increase in frequency beginning at this threshold. For the majority of individuals aged ≥65, underlying medical conditions were reported. Epidemiological data show that approximately 40–50% of adults aged 65–69 have two or more chronic conditions; this rises to over 60% in those aged 70–74 and exceeds 75% in adults aged ≥75. A higher risk of serious adverse reactions in older adults may be related to poorer vaccine-virus replication control due to immunosenescence (reduced function of the immune system at an advanced age) and pre-existing immunocompromising conditions.
Characterization of the risk	Through post-marketing use of IXCHIQ, an increased risk for serious adverse events was identified in individuals ≥65 years of age with comorbidities. The comorbidities reported overall reflected common conditions such as hypertension, hyperlipidaemia, hypercholestaerinaemia, diabetes mellitus, coronary artery disease and chronic obstructive pulmonary disease. Only for 8.3% of individuals in this age group no underlying medical condition was reported. 58% of individuals in this age group reporting serious adverse events were hospitalised.
Risk factors and risk groups	Individuals ≥65 years of age with chronic medical conditions
Preventability	A precautionary approach in this subgroup is needed. IXCHIQ should only be given when there is a significant risk of acquiring chikungunya infection, and after careful consideration of the potential risks and benefits by the HCP.

Impact on the risk-benefit of the biologic product	While most serious side effects occurred in older people, Ixchiq is effective at triggering the production of antibodies against the chikungunya virus, which may be of particular benefit for older people at increased risk of severe chikungunya disease.
Public health impact	The incidence of SAEs, including hospitalisation and death, in individuals ≥ 65 years of age is currently unknown.

SVII.3.2 Important Potential Risk: Vaccine-associated arthritis

Table 18: Vaccine-associated arthritis

Potential mechanism, evidence source and strength of evidence	While the pathophysiology of vaccine associated joint-related side effects, which have been less commonly reported, is poorly understood, it is hypothesised that vaccines which contain inactivated viral pathogens or attenuated pathogens may function as agents that trigger autoimmune disease (30) (31). While this has been discussed in recent times, specifically in the context of COVID-19 vaccine administration, only a limited number of case reports have been published. Some evidence in support of a causal relationship between rubella vaccine in women and arthralgia has been shown; however, there was less evidence for a relationship between rubella vaccine in women and chronic arthralgia (32) (33) or arthritis (34). In a report published in 2012 by the Institute of Medicine (IOM), there was little evidence for a relationship between influenza vaccine and onset or exacerbation of arthropathy, or for hepatitis B vaccine and onset or exacerbation of arthritis. The IOM concluded that there was no mechanistic evidence for an association between all other vaccines and arthralgia, arthritis and arthropathy (35). Studies in patients with autoimmune inflammatory arthritis showed no change in disease severity or relapse rates after influenza vaccination (36) (37). Two main theories have been proposed to elucidate the development of autoimmunity: one is antigen-specific, an example of which is molecular mimicry. Another one is known as “bystander activation” induced by adjuvants (38). The latter is also called “Autoimmune/Inflammatory Syndrome Induced by Adjuvants” (ASIA syndrome). Molecular mimicry occurs when sequence similarities between self and foreign peptides lead to the cross-activation of auto-reactive T or B cells by pathogen-derived antigens in a susceptible individual (39). Bystander activation refers to autoreactive T or B cells that activate independently of the presence of an antigen (40).

Characterization of the risk

In the Pooled Dataset (VLA1553-101, VLA1553-301, VLA1553-302), the proportion of subjects who experienced musculoskeletal stiffness, joint stiffness, joint swelling, arthritis, or osteoarthritis was comparable between the VLA1553 and placebo group (1.1% and 1.2%). All events were reported with low frequency (≤0.5% in the VLA1553 group).

Frequency of selected PTs per treatment group for the pooled dataset

	Statistic	VLA1553 (N=3610)	Placebo (N=1033)	Overall (N=4643)
Any Selected PTs	n (%) Obs [95% CI]	41 (1.1) 48 [0.8, 1.5]	12 (1.2) 12 [0.7, 2.0]	53 (1.1) 60 [0.9, 1.5]
Musculoskeletal and connective tissue disorders	n (%) Obs [95% CI]	41 (1.1) 48 [0.8, 1.5]	12 (1.2) 12 [0.7, 2.0]	53 (1.1) 60 [0.9, 1.5]
Musculoskeletal stiffness	n (%) Obs [95% CI]	17 (0.5) 20 [0.3, 0.8]	5 (0.5) 5 [0.2, 1.1]	22 (0.5) 25 [0.3, 0.7]
Osteoarthritis	n (%) Obs [95% CI]	11 (0.3) 11 [0.2, 0.5]	2 (0.2) 2 [0.1, 0.7]	13 (0.3) 13 [0.2, 0.5]
Joint stiffness	n (%) Obs [95% CI]	9 (0.2) 10 [0.1, 0.5]	2 (0.2) 2 [0.1, 0.7]	11 (0.2) 12 [0.1, 0.4]
Joint swelling	n (%) Obs [95% CI]	5 (0.1) 5 [0.1, 0.3]	2 (0.2) 2 [0.1, 0.7]	7 (0.2) 7 [0.1, 0.3]
Arthritis	n (%) Obs [95% CI]	2 (0.1) 2 [0.0, 0.2]	1 (0.1) 1 [0.0, 0.5]	3 (0.1) 3 [0.0, 0.2]

Note. n = number of participants experiencing an event; Obs = number of events.

All events of arthritis and osteoarthritis were assessed as not related to study vaccination by the investigator.

In the pivotal clinical trial VLA1553-301, a total of 514/3082 subjects (16.7%) reported solicited arthralgia in the VLA1553 arm, and 50/1033 (4.8%) in the placebo arm. Of the cases reported in the VLA1553 arm, 425 cases (13.8%) were mild, 80 (2.6%) were moderate, and 9 cases (0.3%) were severe. Of the total number of solicited arthralgia cases, 468 (15.2%) were considered related in the VLA1553 group compared to 46 (4.5%) in the placebo group.

In the VLA1553 arm, most solicited systemic AEs occurred at lower frequency in the elderly study population. Mild arthralgia was reported in 14.3% of subjects aged 18 to 64 years compared to 10.1% of subjects ages ≥65 years.

The most frequently observed AESIs were a combination of pyrexia and arthralgia. Twenty-one of 28 AESI symptoms were captured as solicited AEs and 6 of 11 subjects qualified as AESI based on solicited AEs only. Laboratory investigations for standard diagnostic work-up (RF, ACPA, ferritin and CRP) were not clinically significant for all samples taken in the study and did not reveal any safety concern. The DSMB reviewed and assessed all AESIs and considered 10 of 11 of these cases as vaccine-related with symptoms typically reported after administration of a live-attenuated vaccine.

	The majority of AESIs were self-limiting and resolved after 2-4 days.
Risk factors and risk groups	Unknown.
Preventability	Prevention may not be possible, particularly as only one dose of IXCHIQ is given.
Impact on the risk-benefit of the biologic product	While arthritis will have an impact on the individual's activity, post-vaccination arthritis is expected to be transient in nature.
Public health impact	The frequency of vaccine-associated arthritis in the post-marketing setting is unknown.

SVII.3.2 Important Potential Risk: Cardiac events

Table 19: Cardiac events

Potential mechanism, evidence source and strength of evidence	Cardiac events have been reported as atypical complication of Chikungunya infection, including myocarditis and different rhythm disturbances (25), (26) (27), though its mechanisms are not being fully understood currently. Cardiac events have also been observed as rare events following vaccination such as influenza vaccination, COVID-19 vaccination, or smallpox vaccination (41). A limited number of cardiac events have been reported in IXCHIQ clinical trials. There were 5 participants in the VLA1553 group for whom SAEs from the System Organ Class “Cardiac Disorders” were reported (atrial fibrillation [2], cardiac arrest [1], cardiomyopathy [1], coronary artery disease [1]). All these SAEs were assessed as unrelated by the investigator. There is currently limited evidence to attribute the possibility of a causal relationship between the occurrence of serious cardiac disorders and vaccination with IXCHIQ. In addition, occurrence of cardiac events is rather frequent in the general population (25).
Characterization of the risk	Given the range of possible cardiac events, the limited number of case reports received in clinical trials, and the significant bias due to the high background rate, it is currently not possible to describe vaccine-associated frequency or risk (relative or absolute). Cardiac events can be life-threatening or fatal, though some are reversible (e.g., palpitations).
Risk factors and risk groups	E.g., age, positive family history, tobacco use, obesity (25).
Preventability	Prevention may not be possible, particularly as only one dose of IXCHIQ is given.
Impact on the risk-benefit of the biologic product	As there is currently limited evidence to attribute the possibility of a causal relationship between the occurrence of serious cardiac disorders and vaccination with IXCHIQ, the impact on the benefit-risk ratio appears limited.
Public health impact	Only a rather limited, if any, impact on public health is foreseen. Cases of cardiac events in the post-marketing setting will be followed up via a dedicated questionnaire if reporter information is available (see Annex IV).

SVII.3.2 Important Potential Risk: Safety in pregnant or breastfeeding women

Table 20: Safety in pregnant or breastfeeding women

Potential mechanism, evidence source and strength of evidence	Live vaccines tend not to be administered during pregnancy as a precaution because of the theoretical risk of foetal infection. There has been no evidence to date of direct foetal injury after the administration of live viral vaccines to pregnant women (42). Animal studies with IXCHIQ did not indicate direct or indirect harmful effects with respect to reproductive toxicity. Pregnant and lactating women were excluded from clinical trials so far. Nevertheless, 18 pregnancies were recorded in adult women: 15 pregnancies in clinical trial VLA1553-301 (13 in the VLA1553 arm and two in the placebo arm), and 3 in clinical trial VLA1553-302. One participant was lost to follow-up. For 15 participants who were vaccinated with IXCHIQ during pregnancy outcomes were reported as follows: live birth with no congenital anomalies (10/15), spontaneous abortions (5/15, thereof one foetal death, i.e. foetus with Turner syndrome, 45 X genetic disorder). None of these outcomes were assessed as related to the vaccine by the investigator. An independent Data Safety Monitoring Board conducted a detailed review of all available data on the reported miscarriages and did not identify any safety concerns. The observed rate of spontaneous abortion (31.3%) is higher than those which typically occurs in the general population (about 12-16%) (43) (44) or in women vaccinated with mRNA COVID-19 vaccine (14.1%) (45). However, these data should be interpretated with caution due to the small sample size compared to the general population. Furthermore, 3 pregnancies were reported in the adolescent population. Thereof, for two pregnancies both the mother and child were reported as being healthy. For the third pregnancy, the outcome is pending.
Characterization of the risk	On the other hand, pregnant women are at increased risk of complications associated with CHIKV infection compared to non-pregnant women. Pregnant women with CHIKV infection may be at increased risk for adverse pregnancy outcomes, including preterm labour and delivery. Vertical transmission of CHIKV from mothers with viraemia at delivery to their infants has been reported and can cause severe, potentially fatal neurological disease in neonates. There is limited amount of data from the use of IXCHIQ in pregnant women. These data are not sufficient to conclude on the absence of potential effects of IXCHIQ on pregnancy, embryo-foetal development, parturition and post-natal development. It is unknown if IXCHIQ is excreted in human milk. A risk to the breastfed child cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IXCHIQ and any potential adverse effects on the breastfed child from IXCHIQ.
Risk factors and risk groups	Risk of exposure to wild-type CHIKV, gestational age, risks to the foetus or neonate from vertical transmission of wild-type CHIKV.

Preventability	While live vaccines should generally be delayed until after delivery, the risk to the mother and foetus or infant through infection with CHIKV also needs to be taken into consideration.
Impact on the risk-benefit of the biologic product	The effect of IXCHIQ on mother, foetus and breastfed infant is currently unknown, as data are currently insufficient to inform on any vaccine-associated risk.
Public health impact	Unknown at this point in time. The observed rate of spontaneous abortion (31.3%) in clinical trials with IXCHIQ is higher than those which typically occur in the general population (about 12-16%) (43) (44) or in women vaccinated with mRNA COVID-19 vaccine (14.1%) (45). However, these data should be interpretated with caution due to the small sample size compared to the general population.

SVII.3.2 Missing Information

Table 21: Missing information

Missing Information	**Evidence source**	**Risk anticipated in the population not studied**	**Population in need of further characterisation**
Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions	IXCHIQ has been studied in individuals with stable chronic diseases (e.g. hypertension, obesity). However, it has not been studied in frail patients with acute or progressive, unstable or uncontrolled clinical conditions.	The immune function may be compromised due to the condition or treatment of the condition.	Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions will be investigated in the Post-Authorisation Safety Study VLA1553-401, in the Prospective Safety Cohort Study VLA1553-406, and through routine pharmacovigilance.
Use in patients with autoimmune or inflammatory disorders	There are no data on the safety of the vaccine in patients with autoimmune or inflammatory disorders. IXCHIQ is contraindicated in immunodeficient or immunosuppressed individuals due to disease or medical therapy (e.g., from haematologic or solid tumours, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised).	It is a theoretical concern that the vaccine may exacerbate their underlying disease.	Use in patients with autoimmune or inflammatory disorders will be investigated in Post-Authorisation Safety Study VLA1553-401 and in the Prospective Safety Cohort Study VLA1553-406and through routine pharmacovigilance.
Co-administration with other vaccines	There are no data on the interaction of IXCHIQ with other vaccines at this point in time.	Theoretically, vaccines may interact with each other and change the immune response to either vaccine or induce safety concerns.	Data in individuals who will receive other vaccines concomitantly will be collected in the Post-Authorization Safety Study VLA1553-401, in the Prospective Safety Cohort Study VLA1553-406and through routine pharmacovigilance.

Missing Information	Evidence source	Risk anticipated in the population not studied	Population in need of further characterisation
Long-term safety data	Understanding of the long-term safety profile of IXCHIQ is currently limited. At this point in time, safety data up to 1 year after vaccination are available for subjects who received IXCHIQ in clinical trial VLA1553-101, while safety data up to 6 months after vaccination are available for subjects who received IXCHIQ in clinical trials VLA1553-301 and VLA1553-302.	While there is currently no evidence to suspect an adverse long-term safety profile, given the lack of data the possibility cannot be excluded.	Long-term safety data are / will be collected in clinical trial VLA1553-303, in the adolescent clinical trial VLA1553-321, in the Randomized Controlled Trial VLA1553-404, as well as through routine pharmacovigilance.
Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease	Between 09 November 2023 and 30 June 2025, only few serious ICSRs were reported in the age group 18-64. Extension of the indications to adolescents has been approved since 28 March 2025.	While an increased risk for serious adverse events has been identified in the elderly population (≥65 years) post-marketing, only limited data are available to evaluate if individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses are also at increased risk for serious adverse events.	Data in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses will be collected in Post-Authorization Safety Study VLA1553-401 and in the Prospective Safety Cohort Study VLA1553-406.

Part II: Module SVIII - Summary of the safety concerns

Table 22: Summary of safety concerns

Important Identified Risks	Chikungunya-like adverse reactions
	Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions
Important Potential Risks	Vaccine-associated arthritis
	Cardiac events
	Safety in pregnant or breastfeeding women
Missing Information	Safety in patients with autoimmune or inflammatory disorders
	Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions
	Long-term safety
	Co-administration with other vaccines
	Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance for the lifecycle of a product is a critical component to the detection, assessment, understanding and mitigation of individual case safety reports (ICSRs). Objectives of routine pharmacovigilance include having processes in place to ensure the ongoing and timely collection, processing, follow-up, and analysis of ICSRs and aggregate data globally, following regulatory guidance and global Standard Operating Procedures. Valneva monitors the safety profile of its products, evaluates issues potentially impacting the product benefit-risk profile in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations.

III.1.1 ICSR Reporting

All ICSRs received for IXCHIQ will be processed and reported in accordance with the requirements specified in the EU Guideline on good pharmacovigilance practices (GVP) Module VI - “Collection, management and submission of reports of suspected adverse reactions to medicinal products”, as well as US Guidance for Industry – Postmarketing Safety Reporting for Human Drugs and Biological Products including Vaccines.

Spontaneous cases of confirmed vaccination failure will be reported within the required 15 days of receipt.

Routine pharmacovigilance activities beyond the receipt and review of individual ICSRs

Signal detection

Routine signal detection activities for IXCHIQ will be performed on a two-weekly basis.

Signal detection will be performed over all spontaneous and solicited ICSRs in the global post-authorisation database that are received from all sources, including cases from EVDAS or other regulatory databases. Overall, sources of data will include all scientific information concerning the use of IXCHIQ and the outcome of the use, i.e. quality, non-clinical and clinical data, in accordance with EU GVP Module IX Signal Management, section IX.B.1 “Sources of data and information”, as well as Guidance for Industry “E2E Pharmacovigilance Planning”. Batch-specific analysis in accordance with the principles in section P.I.B.5 of the EU GVP module on “Vaccines for Prophylaxis against Infectious Diseases”.

Signal detection activities will include routine as well as specific review of ICSRs consistent with the AESI list provided in PART II. SVII.1.1 – Risks not considered important for inclusion in the list of safety concerns in the RMP.

Specific attention will be set on the analysis of reports of symptoms similar to CHIKV disease, i.e., Chikungunya-like adverse reactions, vaccine-associated arthritis, atypical presentations with cardiac involvement, and cases requiring hospitalization.

Summary table of data sources and frequencies for signal detection activities

Table 23: Summary table of data sources and frequencies for signal detection activities

Data source	Frequency of review
IXCHIQ ICSRs	Weekly
Literature (PubMed)	Weekly
Regulatory Authorities' websites (e.g. EudraVigilance, VAERS, Canada Vigilance Adverse Reaction Online Database, and further databases as applicable)	Weekly
Valneva's global post-authorisation safety database, including all spontaneous and solicited ICSRs, reports downloaded from EudraVigilance and EVDAS, and other regulatory databases	Two-weekly
Product quality complaint data	Monthly
PRAC recommendations on signals	Monthly
Monthly signal detection report analysing data from the two-weekly signal detections, extended with data from sales, batch specific analysis, PRAC recommendations on signals and, if applicable, clinical data	Monthly
Aggregate review of the Clinical Trial Databases	As per study milestones / interim or final analyses

Periodic Safety Update Reports (PSURs)

PSURs will be submitted as required by applicable local regulation.

A summary and analysis of all cases of Chikungunya-like adverse reactions, vaccine-associated arthritis, cardiac events, and reports of pregnancies will be included for both interval and cumulative data. Furthermore, separate safety analyses will be done for the elderly population (≥65 years) as well as for the age group 12-64 years.

Cases indicative of antibody-dependent enhancement (ADE) will be closely monitored with special analyses in the PSURs, including review of relevant literature and or any other source (e.g. PRAC minutes) available.

Putative sexual transmission of CHIKV or vaccine virus will be closely monitored in the PSURs through analysis of cases, review of literature and any source of data.

Additionally, in future PSURs, the following safety issues will be discussed with detailed assessment if causality, temporal relationship, and potential underlying risk factors:

- Thrombotic microangiopathy,
- Thrombocytopenia
- Neurotropic adverse events, including encephalopathy, encephalitis, aseptic meningitis, and other central nervous system manifestations

- Renal impairment including acute kidney injury.

In future PSURs, monitoring of off-label use and medication errors will include a description and discussion of vaccine administration to immunocompromised individuals (including the condition leading to contraindication). Separate vaccine exposure estimates and SAE incidence rates will be provided for travellers and residents of endemic areas, stratified by age and gender when available.

In future PSURs, a new modelling exercise by age group and in various settings (travellers versus living in outbreak or endemic setting) will be provided, using appropriate assumptions and sensitivity analyses.

Specific adverse reaction follow-up questionnaires

Follow-up questionnaires will be used to collect targeted information as follows:

- Arthralgia / arthritis
- Cardiac events
- Pregnancies
- Chikungunya-like adverse reactions

For details, please see Annex IV “Specific adverse drug reaction follow-up forms”.

III.2 Additional pharmacovigilance activities

Clinical Trial VLA1553-303:

Category 3 - Required additional pharmacovigilance activities

Study title:

An open-label, Single arm trial to evaluate antibody persistence and long-term safety of a live-attenuated chikungunya virus vaccine candidate (VLA1553) in adults aged 18 years and above.

Rationale and study objectives:

To evaluate the long-term safety i.e. SAEs and persistence of antibodies in participants, the VLA1553-303 trial builds on the data from VLA1553-301 and is designed to evaluate the persistence of antibodies and long-term safety i.e. SAEs in up to 375 subjects who participated in the VLA1553-301 trial.

Primary objective:

To evaluate persistence of antibodies annually from 1 to 10 years after single immunization with VLA1553.

Secondary objectives:

To evaluate long-term safety (i.e., SAEs) 6 months to 2 years after the single immunization with VLA1553.

Trial design:

This is a prospective, multicentre, open-label Phase 3b, single arm clinical trial evaluating the persistence of antibodies and long-term safety, i.e.. In the precursor trial VLA1553-301 a total of 4,128 participants were allocated in a 3.1 ratio to VLA1553 (n=3,093) or control group (n=1,035). The 4,115 vaccinated participants in this trial were stratified into 2 age strata of participant aged 18 to 64 years (Stratum A: 3,652 participants) and participants of 65 years of age or above (Stratum B: 463 participants). The first enrolled and randomized approximately 500 participants constituted the initial group of participants (i.e., the

immunogenicity subset of trial VLA1553-301) that were approached to join VLA1553-303. Thereafter, additional participants were approached in a predefined manner to achieve a more robust number of participants in trial VLA1553-303.

All participants are asked to return to the trial site at Month 6 VLA1553-301 (Visit of VLA1553-303), followed by Year 1 (Visit 1), and annual visits up to Year 10 (Visit 10) for immunogenicity sampling. If the individual titre drops to a $\mu PRNT_{50}$ ≤40 during immunogenicity sampling, the respective participant will have an end of trial visit at the next scheduled visit. SAEs were also to be assessed up until Year 2 in all participants. Moreover, any AESIs reported to be ongoing at the point in time the participant rolls over to trial VLA1553-303 will be monitored.

Study population:

In this open-label Phase 3b, single arm trial, persistence of long-term safety i.e. SAEs (there were no ongoing AESIs from precursor trial VLA1553-301) are evaluated in participants recruited from the VLA1553-301 trial. Of the 393 participants from trial VLA1553-301 invited to participate in the trial, 363 (including 310 participants of Stratum A [18 to 64 years] and 53 participants of Stratum B [≥65 years]) constituted the whole sample population. All 363 participants completed the Year 1 Visit (Part A of the trial), and 317 [76.3%) completed the Year 2 Visit (Part B of the trial).

Milestones:

First Participant In: 02 April 2021

The overall trial duration (First Participant In – Last Participant Out) is estimated to be approximately 122 months.

Completion:

CSR Part A (Visit 1, Year 1): 01 Mar 2023

CSR Part B (Visit 2, Year 2): 17 Jan 2024

CSR Part C (Visit 3, Year 3): planned Q4/2024

CSR Part D (Visit 4, Year 4): planned Q4/2025

CSR Part E (Visit 5, Year 5): planned Q4/2026 and accordingly up to CSR Part J (Visit 10, Year 10): planned Q4/2031.

Clinical Trial VLA1553-321:

Category 3 – Required additional pharmacovigilance activities

Trial title:

A multicentre, randomised, controlled, double-blinded pivotal trial to evaluate safety and immunogenicity of a live-attenuated chikungunya virus vaccine candidate (VLA1553) in adolescents aged 12 years to <18 years.

Rationale and trial objectives:

In this pivotal Phase 3 trial, VLA1553 at the dose level tested previously in Phase 3 trials in adults, are evaluated for immunogenicity and safety in adolescents aged 12 to <18 years in multiple sites in a CHIKV endemic country (i.e., Brazil), and therefore in a population with pre-existing immunity against CHIKV. VLA1553 or placebo was administered intramuscularly into the deltoid muscle as a single-dose immunisation on Day 1. Participants are followed up for safety, immunogenicity, and antibody persistence up to 12 months. A first statistical analysis (Part A analysis, Day 29) was triggered as soon as all participants completed Day 29. Once all participants completed Visit 6/Day 180, a second interim analysis (Part B analysis) was performed.

Primary objective:

The primary objective is to evaluate the immunogenicity and safety of the full dose of the live-attenuated CHIKV vaccine candidate (VLA1553) 28 days following vaccination in adolescents aged 12 years to <18 years after a single immunisation.

Secondary objectives:

The secondary objectives are to assess the immunogenicity and safety of the full dose of VLA1553 following vaccination in adolescents aged 12 years to <18 years up to Month 12 after a single immunisation.

In addition, the immunogenicity and safety of VLA1553 in participants previously exposed to CHIKV are assessed.

Trial design:

VLA1553-321 was a multicentre, prospective, randomised, double-blinded, pivotal clinical trial evaluating the full dose (4.0 log_{10} $TCID_{50}$ per 0.5 mL, 1x10E4) of VLA1553 in comparison to a placebo control randomized at a 2:1 ratio in adolescents aged 12 years to <18 years in a CHIKV endemic country (i.e., Brazil).

Trial population:

It was anticipated that 750 participants would be enrolled and randomised 2:1 to VLA1553 or placebo (VLA1553: 500; placebo: 250) at approximately 5 to 10 investigative sites in Brazil. The actual number of participants randomized was 765, thereof 11 participants were randomized but not dosed. Those participants randomized and dosed in 10 investigative sites in Brazil were distributed between the trial arms VLA1553 (502) and placebo (252).

Milestones:

Milestone	**Date**
First Participant In	14 Feb 2022
Last Participant Out	16 Feb 2024
CSR Part A (Visit 3, Day 29)	21 Dec 2023
CSR Part B (Visit 5, Month 6)	24 May 2024
CSR Part C (Visit 6, Month 12)	planned Q1 2025

Post-marketing Safety Studies

Post-Authorisation Safety Study:

Category 3 – Required additional pharmacovigilance activities

Study title:

A Post-marketing Safety study of live-attenuated chikungunya virus vaccine (VLA1553) routinely administered in adults aged 18 years and above in the US planning to travel to endemic areas.

(Study Identifier: VLA1553-401)

Rationale and study objectives:

Chikungunya disease is a mosquito-borne disease caused by the chikungunya virus (CHIKV), which has re-emerged and is highly likely to spread globally within the next decade (46, 47). CHIKV infections are characterized by an acute febrile illness accompanied by headache, muscle pain, and skin rash, resulting in chronic and incapacitating arthralgia in up to 60% of patients (48-50). Some patients may suffer from severe and often debilitating joint pain which can persist for years, especially in adults (21, 51). The disease is difficult to eradicate because the virus is maintained in nature by spread among arthropod vectors and their hosts, without the need of human-to-human contact for transmission (52, 53). Currently,

CHIKV is responsible for significant outbreaks worldwide, and treatment is limited to relieving symptoms. The control and prevention of CHIKV is currently limited to interventions such as the use of insecticides, wearing long sleeves and trousers, and other means to restrict exposure to vector mosquitos (54). As mosquito control programs are not highly efficient in controlling outbreaks, vaccines are essential to reduce the burden of disease (55).

One single injection of VLA1553, given as a suspension after reconstitution of targeted $1x10^4$ $TCID_{50}$ per 0,5 ml dose in a pre-filled syringe, is the first vaccine indicated for active immunisation for the prevention of disease caused by Chikungunya virus, with approval received by the by the Food and Drug Administration (FDA) on 9 November 2023 and by the European Medicines Agency (EMA) on 28 June 2024. IXCHIQ was launched in the US early 2024. There is a need to further characterise the vaccine's safety profile and to evaluate the effectiveness of risk-management measures. This study will be a post-licensure prospective observational study to monitor the safety of the live-attenuated chikungunya virus vaccine (VLA1553) routinely administered in adults aged 18 years and above, residing in the U.S. planning to travel to endemic areas.

Primary objective:

To estimate the incidence of medically attended AESIs, including infection with chikungunya virus, Chikungunya-like adverse reactions, vaccine-associated arthralgia, and cardiac events following the administration of live-attenuated chikungunya virus vaccine (VLA1553) in adults aged 18 years and above in the US planning to travel to endemic areas.

Secondary objectives:

- To quantify the relative risk associated with VLA1553 and each medically attended AESI for which a risk window after vaccination can be defined using a self-controlled risk interval (SCRI) analysis.
- To compare the observed incidence rate with the expected rate in the population for each medically attended AESI.
- To describe the risk of medically attended AESIs following live-attenuated CHIKV vaccine (VLA1553) administration and co-administration with other vaccines.
- To describe the use of the live-attenuated CHIKV vaccine (VLA1553) and the risk of medically attended AESIs in individuals aged ≥ 65 years, HIV positive participants, patients with autoimmune or inflammatory disorders, patients with acute or progressive, unstable, or uncontrolled clinical conditions, individuals with an infection in the past 3 days from the index date or with known or suspected defect of the immune system.

Study design:

A prospective observational descriptive cohort study of approximately 5.000 adults (age ≥18 years) who receive VLA1553 in the US and who will be followed up for 6 months will be conducted. The study population will be identified in a representative sample of vaccination centres that administer vaccines to travellers in the US.

The primary comparative analysis will be a self-controlled risk interval analysis (SCRI) for safety outcomes. To triangulate the findings an indirect comparison with age-sex adjusted rates of AESI in relevant populations will also be performed.

Enrolment in the study will occur on the day of administration of VLA1553 in the vaccination centre. Additionally, participants can be enrolled within 5 days after receiving a single shot of the CHIKV vaccine (VLA1553). After enrolment, vaccinees will be followed up via mobile app, email and call centres with targeted questionnaires periodically at weeks 1, 2, 4, 6, 8, 12 and 24 following the index date, or until the earlier of: occurrence of death, withdrawal of consent, loss to follow-up, or end of study period, whichever occurs first. During those contacts, information on targeted AESIs that are medically attended, as well as on laboratory confirmed CHIKV infection as well as Chikungunya-like adverse reactions, vaccine-associated arthralgia, and cardiac events, and other vaccinations will be established. Occurrence of medically attended AESIs, as reported by participants, will trigger a validation of the diagnosis by a health care professional (HCP) through a review of medical charts and/or interview, where available. Laboratory-confirmed infection with CHIKV during follow-up will be investigated and documented.

Study population:

Study participants will be enrolled after they receive a single shot of VLA1553 at a participating US travel clinic.

Milestones:

Study is expected to end 42 months after the start of enrolment, with the delivery of the final study report (36 months for data collection and 6 months after the last participant enrolled for follow-up and database lock).

Post-Authorisation Pregnancy Study:

Category 3 – Required additional pharmacovigilance activities

Study title:

Observational study to evaluate the safety of live-attenuated chikungunya virus vaccine (VLA1553) in pregnant women exposed to the vaccine in Brazil.

(Study Identifier: VLA1553-403)

Rationale and study objectives:

Live-attenuated vaccines are typically contraindicated in pregnancy as the live-attenuated virus could potentially cross the placenta and result in viral infection in the foetus (28). However, because CHIKV infection shortly before delivery may have serious consequences, vaccination of pregnant women might be reasonable during an outbreak context following stringent individual risk benefit assessment. In addition, inadvertent exposure to the vaccine can occur during pregnancy, necessitating a comprehensive evaluation of its safety profile for pregnant women and their offspring. Although clinical trials of VLA1553 included 19 pregnant individuals (13 in VLA1553-301, 3 in VLA1553-302 and 3 in clinical trial VLA1553-321 in adolescents), the limited number of cases reported is insufficient to

establish the safety of maternal vaccination. Notably, among those women who became pregnant within 3 months after VLA1553 vaccination, there were 4 documented cases of spontaneous abortions at <20 weeks gestation (i.e., one foetus with Turner syndrome 45 X, one female participant with morbid obesity (BMI=60 kg/m2) coupled with two previous miscarriages, one anembryonic pregnancy, one female for whom no other reasons could be identified). One miscarriage was reported at 8 weeks gestation in a female participant who became pregnant more than 3 months after vaccination. No spontaneous abortion was considered to be related to VLA1553 vaccination by the investigators and no safety concern was identified by the Data and Safety Monitoring Board. Pregnancy losses in early pregnancy are very common even without identified causes, and there were underlying factors for three of five miscarriages reported.

This study will be a post-licensure prospective observational study to monitor pregnancy outcomes in the mother and infant (i.e., live birth, preterm birth, spontaneous abortion, still birth) in women of child-bearing age (18-45 years) and able to provide informed consent residing in Brazil who have been exposed to the live-attenuated CHIKV vaccine (IXCHIQ) up to 30 days before their last menstrual period (LMP) or, at any point during pregnancy. Also, these women and their offspring will be followed up until end of pregnancy and, if applicable, 12 weeks after delivery (live birth). This study is primarily descriptive and designed to detect potential safety signals rather than test hypotheses.

Primary objective:

To evaluate pregnancy outcomes and infant health up to 12 weeks post-delivery among pregnant women who received IXCHIQ within 30 days before their last menstrual period (LMP) or anytime during their pregnancy.

Secondary objective:

To describe the frequency of adverse events among pregnant women exposed to IXCHIQ within 30 days before their last menstrual period or anytime during their pregnancy.

Study design:

This is an observational, non-interventional study to evaluate the safety of the live-attenuated CHIKV vaccine (IXCHIQ) in pregnant women and their offspring. The study includes women who were exposed to the vaccine up to 30 days before their last menstrual period (LMP) (i.e., peri-conceptional period) or women exposed at any time during pregnancy. Pregnancy and offspring data will be collected up to 12 weeks after delivery (live birth). This study is part of a pilot vaccination initiative conducted in selected municipalities in Brazil following licensure of the vaccine. Participation is voluntary. The study will collect information including vaccine exposure, demographic information, pregnancy data, and medical history while compiling additional data on medication usage and pregnancy outcomes, including infant health up to 12 weeks post-expected delivery date. This approach involves collecting reports Both by the participating women and, if possible, confirmed and expanded by their pregnancy-specific healthcare providers. Additionally, with consent, medical records and relevant databases may be accessed by study staff to further verify and supplement the information.

Study population:

The participants in this study consist of pregnant women who have been exposed to IXCHIQ within 30 days before their last menstrual period or at any time during pregnancy from specific municipalities in Brazil where the pilot vaccination initiative was conducted following the vaccine's licensure.

Milestones:

Milestone	**Planned date**
Protocol submission to FDA	05 Mar 2024
Start of data collection	01 Oct 2025
Last participant in	30 Jun 2026
Study completion	30 Sep 2027
Final report submission	31 Dec 2027

Post-Authorisation Pregnancy Study:

Category 3 – Required additional pharmacovigilance activities

Study title:

Live-Attenuated Chikungunya Vaccine (IXCHIQ) Safety in Pregnant Women: A US Observational Study on Pregnancy Outcomes.

(Study Identifier: VLA1553-405)

Rationale and study objectives:

The Chikungunya virus (CHIKV) is causing a global rise in mosquito-borne illness, with current treatments limited to symptom relief. The live-attenuated vaccine IXCHIQ is the first vaccine for CHIKV, but its safety in pregnant women is limited from current clinical trials along which takes into account the exclusion from clinical studies. Concerns about foetal infection from vaccine viremia exists, although animal studies suggest no adverse effects on animal foetal development. A proposed post-marketing observational trial in the US aims to monitor pregnancy outcomes in women who became pregnant before or after receiving IXCHIQ, to assess the vaccine's safety implications for both the mother and the infant up to 12 weeks post-delivery.

Primary objective:

The primary objective of this study is to monitor and evaluate the outcomes of pregnancy and infant health up to 12-weeks among in the United States who received IXCHIQ while pregnant, utilizing a web-based pregnancy registry.

Study design:

This post-marketing, non-interventional, web-based pregnancy registry study focusing on pregnancy safety outcomes for women in the US who receive IXCHIQ from 30 days before their last menstrual period (LMP) up to 12-weeks post expected delivery date. Participation

is voluntary and relies on self-reported exposure during pregnancy. Data will be collected from both participating women and, where available, confirmed and expanded by their pregnancy-specific healthcare providers (PS-HCPs) and travel clinic staff. The study is observational and aims to provide safety data in this population for the vaccine. The intent of the registry is to prospectively collect data describing exposure to IXCHIQ immediately before or during pregnancy, potential confounding factors (such as exposure to other medications and vaccines), and information related to the outcome of the pregnancy.

Study population:

The participants in this study consist of women aged 18 years or older in the United States. To be eligible, individuals must have provided consent to participate and have been exposed to IXCHIQ within 30 days before their LMP or at any time during pregnancy.

Milestones:

Milestone	**Planned date**
Protocol update submission	31 Jan 2025
Start of data collection	31 Mar 2025
Interim Study Report	31 May 2027
Last participant in	31 May 2028
End of data collection	30 Nov 2028
Final report submission	31 May 2029

Prospective Safety Cohort Study

Category 3 – Required additional pharmacovigilance activities

(Study Identifier: VLA1553-406)

This prospective safety cohort study will focus on a representative sample of the target population that received the Chikungunya vaccine VLA1553 during the pilot vaccination programme conducted in selected Chikungunya-endemic Brazilian municipalities. While clinical trials with VLA1553 provided valuable safety data in non-endemic areas, this prospective safety cohort study aims to assess the VLA1553 vaccine's safety under real-world conditions in endemic areas of Brazil.

Primary Objective:

To estimate the incidence rates of a predefined set of adverse events (AEs) which constitute safety concerns according to the VLA1553 Risk Management Plan (RMP) following the administration of the live-attenuated VLA1553 vaccine in individuals that are target for the pilot vaccination program, within a defined risk window following vaccination.

Secondary objective:

1. To measure the relative risk associated with VLA1553 administration for a predefined set of AEs which constitute safety concerns as per the VLA1553 RMP within a defined risk window following vaccination.

Study period:

The entire process, from the start of the pilot vaccination program, the 24 week data collection from the last enrolled participant, concluding with the study report may span a total duration of approximately 2 to 3 years.

Sample size:

A planned final study sample size of approximately 5.000 participants is to be recruited.

Study design:

This is an observational study, with primary data collection, which will combine a prospective safety cohort study and an SCRI study.

The study will be conducted in selected municipalities in Brazil and will start along with the VLA1553 pilot vaccination program. The Sponsor will aim to make the recruited sample as representative as possible to the target population.

Study population:

The study population will be a representative sample of individuals that are target for the pilot vaccination program residing in selected municipalities of Brazil or who are expected to be residents in the study municipalities for 24 weeks after vaccination.

Milestones:

Final protocol with SAP: 31 Mar 2025

Start of data collection: 01 Oct 2025

Study completion: 31 Dec 2026

Final study report: 31 Dec 2027

III.3 Summary Table of additional Pharmacovigilance activities

Table 24: Summary table of 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			
None.			
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			
None.			
Category 3 – Required additional pharmacovigilance activities			
VLA1553-303 Ongoing	Primary objective: To evaluate persistence of antibodies annually from 1 to 10 years after single immunization with VLA1553. Secondary objective: To evaluate long-term safety (i.e. SAEs) 6 months to 2 years after single immunization with VLA1553.	Long-term safety	First Participant In: 02 April 2021 The overall trial duration (First Participant In – Last Participant Out) is estimated to be approximately 122 months. Completion: CSR Part A (Visit 1, Year 1): 01 March 2023 CSR Part B (Visit 2, Year 2): 17 January 2024 CSR Part C (Visit 3, Year 3): planned Q4 / 2024 CSR Part D (Visit 4, Year 4): planned Q4 / 2025 CSR Part E (Visit 5, Year 5): planned Q4 / 2026 and accordingly up to CSR Part J (Visit 10, Year 10): planned Q1 2031

Study / Status	Summary of objectives	Safety concerns addressed	Milestones / Due dates
VLA1553-321 Ongoing	Primary objective: to evaluate the immunogenicity and safety of the full dose of the live-attenuated CHIKV vaccine candidate (VLA1553) 28 days following vaccination in adolescents aged 12 years to <18 years after a single immunisation. Secondary objectives: to assess the immunogenicity and safety of the full dose of VLA1553 following vaccination in adolescents aged 12 years to <18 years up to Month 12 after a single immunization. In addition, the immunogenicity and safety of VLA1553 in participants previously exposed to CHIKV are assessed.	Chikungunya-like adverse reactions (broad definition) Vaccine-associated arthritis Cardiac events Long-term safety	First participant in: 14 Feb 2022 Last participant out: 16 Feb 2024 CSR Part A (Visit 3, Day 29): 21 Dec 2023 CSR Part B (Visit 5, Month 6): 24 May 2024 CSR Part C (Visit 6, Month 12): planned Q1 2025

Study / Status	Summary of objectives	Safety concerns addressed	Milestones / Due dates
Post-Authorisation Safety Study VLA1553-401 Planned	To estimate the incidence of medically attended adverse events of special interest (AESIs), including infection with chikungunya virus as well as Chikungunya-like adverse reactions, vaccine-associated arthralgia, and cardiac events following the administration of live-attenuated chikungunya virus vaccine (VLA1553) in adults aged 18 years and above in the US planning to travel to endemic areas. To quantify the relative risk associated with VLA1553 and each medically attended AESI for which a risk window after vaccination can be defined using a self-controlled risk interval (SCRI) analysis. To compare the observed incidence rate with the expected rate in the population for each medically attended AESI. To describe the risk of medically attended AESIs following live-attenuated CHIKV vaccine (VLA1553) administration, and co-administration with other vaccines. To describe the use of the live-attenuated CHIKV vaccine (VLA1553) and the risk of medically attended AESIs in individuals aged ≥ 65 years, HIV positive participants, patients with autoimmune or inflammatory disorders, patients with acute or progressive, unstable, or uncontrolled clinical conditions, individuals with an infection in the past 3 days from the index date or with known or suspected defect of the immune system.	Chikungunya-like adverse reactions (broad definition) Vaccine-associated arthritis Cardiac events Safety in frail patients Safety in patients with autoimmune or inflammatory disorders Co-administration with other vaccines Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses.	From the date of first US participant receiving IXCHIQ, the study inclusion period will be estimated to last 36 months, and data collection will last 42 months with the last participant enrolled followed for 6 months. An overall duration of 3,5 years from IXCHIQ US launch early 2024 is anticipated.

Study / Status	Summary of objectives	Safety concerns addressed	Milestones / Due dates
Post-Authorisation Pregnancy Study VLA1553-403 Planned	To evaluate pregnancy and infant health up to 12 weeks post-delivery among pregnant women who received IXCHIQ up to 30 days before their last menstrual period (LMP) or at any point during their pregnancy. To describe the frequency of adverse events among pregnant women exposed to IXCHIQ within 30 days before their last menstrual period or anytime during their pregnancy.	Safety in pregnant women	Protocol submission to FDA: 05 Mar 2024 Start of data collection: 01 Oct 2025. Last participant in: 30 Jun 2026. Study completion: 30 Sep 2027. Final report submission: 31 Dec 2027.
Post-Authorisation Pregnancy Study VLA1553-405 Planned	To monitor and evaluate the outcomes of pregnancy and infant health up to 12-weeks among women in the United States who received IXCHIQ while pregnant.	Safety in pregnant women	Protocol update submission: 31 Jan 2025 Start of data collection: 31 Mar 2025 Interim Study Report: 31 May 2027 Last participant in:31 May 2028 End of data collection: 30 Nov 2028 Final study report: 31 May 2029
Prospective Safety Cohort Study VLA1553-406 Planned	To estimate the incidence rates of a predefined set of adverse events (AEs) which constitute safety concerns according to the VLA1553 Risk Management Plan (RMP) following the administration of the live-attenuated VLA1553 vaccine in individuals that are target for the pilot vaccination program, within a defined risk window following vaccination.	Chikungunya-like adverse reactions Vaccine-associated arthritis Cardiac events Safety in frail patients Safety in patients with autoimmune or inflammatory disorders Co-administration with other vaccines Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions Safety in individuals 12-64 years old with clinical conditions associated with impaired or	Final protocol with SAP: 31 Mar 2025 Start of data collection: 01 Oct 2025 Study completion: 31 Dec 2026 Final study report: 31 Dec 2027

Study / Status	Summary of objectives	Safety concerns addressed	Milestones / Due dates
		dysregulated immune responses	

Part IV: Plans for post-authorisation efficacy studies

Table 25: Planned and on-going post-authorisation effectiveness studies that are conditions of the marketing authorization or that are specific obligations

Study	Summary of objectives	Efficacy uncertainties addressed	Milestones / Due dates
Effectiveness studies which are conditions of the marketing authorisation			
Post Authorisation Study on the Effectiveness and Safety of IXCHIQ in an endemic country (VLA1553-404) Planned	To assess vaccine effectiveness (VE) in preventing symptomatic virologically confirmed Chikungunya virus (CHIKV) disease among adults, in IXCHIQ vaccinees compared to control participants during the same trial period, both overall and by age groups. To evaluate VE against symptomatic probable or suspected CHIKV disease among adults, in IXCHIQ vaccinees compared to control participants during the same trial period, both overall and by age groups. To evaluate VE against occurrence of chronic CHIKV disease and CHIKV disease leading to hospitalization in confirmed and suspected cases of CHIKV disease. To assess IXCHIQ safety in IXCHIQ vaccinees compared to control participants during the same trial period. The following safety concerns will be assessed: Chikungunya-like adverse reactions, vaccine-associated arthritis, cardiac events, and long-term safety	The ability of IXCHIQ to prevent disease due to chikungunya virus was based on a serological surrogate endpoint. A threshold of CHIKV-specific neutralizing antibody µPRNT50 titre of ≥150 was selected as surrogate marker for protection. This threshold was determined from a non-human primate passive transfer study and supported by data obtained from a prospective human sero-epidemiological study. This study is designed to assess the effectiveness of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in adults.	Final protocol submission: 30 Sep 2024 Study progress reports will be shared with EMA every 6 months, starting in Nov 2024 Feasibility assessment report: 31 Dec 2024 Study initiation: 01 Oct 2025 Interim Report: 30 Nov 2027 Study completion: 31 Jul 2029 Final report submission: 31 Dec 2029
Effectiveness studies which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances			
None.			

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

The EU product information is sufficient to mitigate the currently defined potential risks of Chikungunya Vaccine. The necessary information to ensure appropriate use of the product is included in the relevant sections of the SmPC or package leaflet. No additional measure for risk minimisation is considered necessary at this point in time. The proposed minimisation measures are summarized in Table 25 below for each safety concern.

Table 26: Routine Risk Minimisation Measures

Safety concern	**Routine risk minimisation activities**
Important Identified Risk	
Chikungunya-like adverse reactions	Routine risk communication: SmPC section 4.4 “Special warnings and precautions for use” and section 4.8. “Undesirable effects” / PL section 4. “Possible side effects”. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions	Routine risk communication: SmPC section 4.4 “Special warnings and precautions for use” and section 4.8 Post-marketing Adverse Reactions / PL section 2. “What you need to know before you receive IXCHIQ”. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation of an individualised benefit-risk evaluation by HCPs for individuals ≥65 years of age with chronic medical conditions. SmPC section 4.4 “Special warnings and precautions for use”. Other routine risk minimisation measures beyond the Product Information: None.

Important Potential Risks	
Vaccine-associated arthritis	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Cardiac events	Routine risk communication: None. Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other routine risk minimization measures beyond the Product Information: None.
Safety in pregnant or breastfeeding women	Routine risk communication: SmPC section 4.6 “Fertility, pregnancy and lactation” / PL section 2. “What you need to know before you receive IXCHIQ”. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Missing Information	
Safety in patients with autoimmune or inflammatory disorders	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Long-term safety data	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Co-administration with other vaccines	Routine risk communication: SmPC section 4.5 “Interaction with other medicinal products and other forms of interaction” / PL section 2. “What you need to know before you receive IXCHIQ”. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease	Routine risk communication: SmPC section 4.4 “Special warnings and precautions for use”: “IXCHIQ should only be given when there is a significant risk of acquiring chikungunya infection, and after careful consideration of the potential risks and benefits.” Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

V.2. Additional Risk Minimisation Measures

None.

V.3 Summary of risk minimisation measures

Table 27**:** Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Chikungunya-like adverse reactions	Routine risk minimisation measures: SmPC section 4.4 “Special warnings and precautions for use” and section 4.8. “Undesirable effects” / PL section 4. “Possible side effects”. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire (see Annex IV). Additional pharmacovigilance activities: Prospective Safety Cohort Study VLA1553-406. Post-Authorisation Safety Study VLA1553-401. Clinical Trial VLA1553-321 in adolescents.
Increased risk for SAEs in individuals ≥65 years of age with chronic medical conditions	Routine risk minimisation measures: SmPC section 4.4 “Special warnings and precautions for use” and section 4.8. “Post-marketing Adverse Reactions” / PL section 2. “What you need to know before you receive IXCHIQ”. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.
Vaccine-associated arthritis	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire (see Annex IV). Additional pharmacovigilance activities: Prospective Safety Cohort Study VLA1553-406. Post-Authorisation Safety Study VLA1553-401. Clinical Trial VLA1553-321 in adolescents.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac events	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire (see Annex IV). Additional pharmacovigilance activities: Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406. Clinical trial VLA1553-321 in adolescents.
Safety in pregnant or breastfeeding women	Routine risk minimisation measures: SmPC section 4.6 “Fertility, pregnancy and lactation” / PL section 2. “What you need to know before you receive IXCHIQ”. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up Questionnaire (see Annex IV). Additional pharmacovigilance activities: Post-Authorisation Pregnancy Study VLA1553-405. Post-Authorisation Pregnancy Study VLA1553-403.
Safety in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.
Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	Routine risk minimisation measures: None. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Clinical Trial VLA1553-303. Clinical Trial VLA1553-321 in adolescents.
Co-administration with other vaccines	Routine risk minimisation measures: SmPC section 4.5 “Interaction with other medicinal products and other forms of interaction” / PL section 2. “What you need to know before you receive IXCHIQ”. Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.
Safety in individuals 12-64 years old with clinical conditions associated with impaired, dysregulated immune responses	Routine risk minimisation measures: SmPC section 4.4 “Special warnings and precautions for use”: “IXCHIQ should only be given when there is a significant risk of acquiring chikungunya infection, and after careful consideration of the potential risks and benefits.” Additional risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for IXCHIQ. The RMP details important risks of IXCHIQ, how these risks can be minimised, and how more information will be obtained about IXCHIQ's risks and uncertainties (missing information).

IXCHIQ's Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how IXCHIQ should be used.

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

I. The medicine and what it is used for

IXCHIQ is a vaccine that helps protect adults and adolescents aged 12 years and older against disease caused by the Chikungunya virus (CHIKV) (see SmPC and Package Leaflet for the full indication).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of IXCHIQ, together with measures to minimise such risks and the proposed studies for learning more about IXCHIQ's 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.

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

II.A List of important risks and missing information

Important risks of IXCHIQ 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 IXCHIQ. 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).

Table 28: List of Important Risks and Missing Information

Important Identified Risks	Chikungunya-like adverse reactions
	Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions
Important Potential Risks	Vaccine-associated arthritis (swelling and tenderness of one or more joints after vaccination)
	Cardiac events
	Safety in pregnant or breastfeeding women
Missing Information	Safety in patients with autoimmune or inflammatory disorders
	Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions
	Long-term safety data
	Co-administration with other vaccines
	Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease

II.B Summary of important risks

Table 29: Important Identified Risk: Chikungunya-like adverse reactions

Evidence for linking the risk to the medicine	The following broad definition was used to identify Chikungunya-like adverse reactions in individuals who experienced at least one adverse event of special interest (AESI) in clinical trials with IXCHIQ: a) Fever (≥38 °Cor 37.8°C depending on the clinical trial) AND b) any single of the following symptoms: joint pain/arthritis (not only in extremities), an extreme sense of tiredness and lack of energy, chills, pain, peripheral oedema, headache, dizziness, paraesthesia (the feeling of tingling, numbness or “pins and needles”), muscle pain, back pain, rash, excessive sweating, eye disorders [e.g., conjunctivitis (inflammation of the outermost layer of the white part of the eye and the inner surface of the eyelid), inflammation of the retina, inflammation of the middle layer of tissue in the eye wall, swelling of the eye’s optic nerve,…] and cardiac events [e.g., a heart rate of more than 100 beats per minute, abnormality of the heart's rhythm, myocarditis and other cardiac complications]) AND c) occurring within 30 days post vaccination (regardless of the order of their onset and duration). Adverse event combinations qualifying as Chikungunya-like adverse reactions were reported in 12.1% of participants. Among those, combinations of fever with headache, an extreme sense of tiredness and lack of energy, muscle pain or joint pain were the most common, all other symptoms were reported in fewer than 10% of Chikungunya-like adverse reactions. The reported symptoms were mostly mild. 1.8% of participants reported at least one severe symptom, most commonly fever or joint pain. Median onset of Chikungunya-like adverse reactions was 3 days after vaccination, and median time to resolution was 4 days. Longer-lasting symptoms ≥30 days occurred in 0.4% of participants.” The vast majority of Chikungunya-like adverse reactions were unspecific symptoms consistent with a strong innate immune response, which are also seen after vaccination with other licensed, highly immunogenic vaccines and do not appear to reflect chikungunya-associated events. Clinically, the hallmark of chikungunya infection is high-grade fever and severe joint pain, while the AESI analysis used a very broad definition that factually allows any individual with fever and (among others) one of the solicited systemic AEs of joint pain, muscle pain, headache, and an extreme sense of tiredness and lack of energy, to qualify. In a typical presentation of chikungunya, it would be expected to see about 40% of individuals with acute disease to progress to chronic symptoms. If the approx. 12% of individuals with Chikungunya-like adverse reactions really were representing chikungunya-associated disease, the resulting rate of chronic disease would be a hypothetical 4%. This has, however, not been observed with VLA1553 at all: the overall rate of longer-lasting joint pain was not different between VLA1553 and placebo.
Risk factors and risk groups	Unknown.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 “Special warnings and precautions for use” and section 4.8. “Undesirable effects” / PL section 4. “Possible side effects”. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Safety Cohort Study VLA1553-406. Post-Authorisation Safety Study VLA1553-401. Clinical Trial VLA1553-321 in adolescents.

Table 30: Increased risk for serious adverse events in individuals ≥65 years of age with chronic medical conditions

Evidence for linking the risk to the medicine	A clustering of SAEs, thereof one with fatal outcome, has been noted in individuals ≥65 years of age with comorbidities from post-marketing use of IXCHIQ. Of the serious adverse events reported between 09 November 2023 and 30 June 2025, 77% occurred in individuals aged ≥65, highlighting a significant increase in frequency beginning at this threshold. For the majority of individuals aged ≥65, underlying medical conditions were reported. Epidemiological data show that approximately 40–50% of adults aged 65–69 have two or more chronic conditions; this rises to over 60% in those aged 70–74 and exceeds 75% in adults aged ≥75.
Risk factors and risk groups	Individuals ≥65 years of age with chronic medical conditions
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 “Special warnings and precautions for use” and section 4.8. “Post-marketing Adverse Reactions” / PL section 2. “What you need to know before you receive IXCHIQ”. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

Table 31: Important Potential Risk: Vaccine-associated arthritis

Evidence for linking the risk to the medicine

In the Pooled Dataset (VLA1553-101, VLA1553-301, VLA1553-302), the proportion of subjects who experienced musculoskeletal stiffness, joint stiffness, joint swelling, arthritis, or osteoarthritis was comparable between the VLA1553 and placebo group (1.1% and 1.2%). All events were reported with low frequency (≤0.5% in the VLA1553 group).

Frequency of selected PTs per treatment group for the pooled dataset

	Statistic	**VLA1553 (N=3610)**	**Placebo (N=1033)**	**Overall (N=4643)**
Any Selected PTs	n (%) Obs [95% CI]	41 (1.1) 48 [0.8, 1.5]	12 (1.2) 12 [0.7, 2.0]	53 (1.1) 60 [0.9, 1.5]
Musculoskeletal and connective tissue disorders	n (%) Obs [95% CI]	41 (1.1) 48 [0.8, 1.5]	12 (1.2) 12 [0.7, 2.0]	53 (1.1) 60 [0.9, 1.5]
Musculoskeletal stiffness	n (%) Obs [95% CI]	17 (0.5) 20 [0.3, 0.8]	5 (0.5) 5 [0.2, 1.1]	22 (0.5) 25 [0.3, 0.7]
Osteoarthritis	n (%) Obs [95% CI]	11 (0.3) 11 [0.2, 0.5]	2 (0.2) 2 [0.1, 0.7]	13 (0.3) 13 [0.2, 0.5]
Joint stiffness	n (%) Obs [95% CI]	9 (0.2) 10 [0.1, 0.5]	2 (0.2) 2 [0.1, 0.7]	11 (0.2) 12 [0.1, 0.4]
Joint swelling	n (%) Obs [95% CI]	5 (0.1) 5 [0.1, 0.3]	2 (0.2) 2 [0.1, 0.7]	7 (0.2) 7 [0.1, 0.3]
Arthritis	n (%) Obs [95% CI]	2 (0.1) 2 [0.0, 0.2]	1 (0.1) 1 [0.0, 0.5]	3 (0.1) 3 [0.0, 0.2]

Note. n = number of participants experiencing an event; Obs = number of events.

All events of arthritis and osteoarthritis were assessed as not related to study vaccination by the investigator.

In the pivotal clinical trial VLA1553-301, 16.7% of subjects reported solicited joint pain in the IXCHIQ arm, and 4.8% in the placebo arm. Of the cases reported in the IXCHIQ arm, 13.8% of cases were mild, 2.6% were moderate, and 0.3% of cases were severe. Of the total number of solicited cases of joint pain, 15.2% were considered related by the investigator in the IXCHIQ group compared to 4.5% in the placebo group.

In the IXCHIQ group, most solicited systemic AEs occurred at a lower frequency in the elderly study population. Mild joint pain was reported in 14.3% of subjects aged 18 to 64 years compared to 10.1% of subjects ages ≥65 years.

The most frequently observed AESIs were a combination of fever and joint pain.

Risk factors and risk groups

Unknown.

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Safety Cohort Study VLA1553-406. Post-Authorisation Safety Study VLA1553-401. Clinical Trial VLA1553-321 in adolescents.

Table 32: Important Potential Risk: Cardiac events

Evidence for linking the risk to the medicine	Cardiac events have been observed as rare events following vaccination such as influenza vaccination, COVID-19 vaccination, or smallpox vaccination (43). A limited number of cardiac events have been reported in IXCHIQ clinical trials. There were 5 participants in the IXCHIQ group for whom the following serious adverse events were reported: atrial fibrillation (2 individuals), cardiac arrest (1), cardiomyopathy (1), coronary artery disease (1). These serious events were assessed as not related to vaccination by the investigator. There is currently limited clinical evidence to attribute the possibility of a causal relationship between the occurrence of serious cardiac disorders and IXCHIQ vaccination. In addition, occurrence of cardiac events is rather frequent in the general population.
Risk factors and risk groups	E.g., age, positive family history, tobacco use, obesity.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406. Clinical Trial VLA1553-321 in adolescents.

Table 33: Important Potential Risk: Safety in pregnant or breastfeeding women

Evidence for linking the risk to the medicine	Live vaccines tend not to be administered during pregnancy as a precaution because of the theoretical risk of foetal infection. There has been no evidence to date of direct foetal injury after the administration of live viral vaccines to pregnant women (42). Animal studies with IXCHIQ did not indicate direct or indirect harmful effects with respect to reproductive toxicity. Pregnant and lactating women were excluded from clinical trials with IXCHIQ so far. Nevertheless, 16 pregnancies were reported in adult women vaccinated with IXCHIQ. One participant was lost to follow-up. For 15 participants who were vaccinated with IXCHIQ during pregnancy outcomes were reported as follows: - live births with no congenital anomalies (10/15), spontaneous abortions (5/15, thereof one foetal death, i.e. foetus with Turner syndrome, 45 X genetic disorder). None of these outcomes were assessed as related to the vaccine by the investigator. An independent Data Safety Monitoring Board conducted a detailed review of all available data on the reported miscarriages and did not identify any safety concerns. The observed rate of spontaneous abortion (31.3%) is higher than those which typically occurs in the general population (about 12-16%); or in women vaccinated with mRNA COVID-19 vaccine (14.1%). However, these data should be interpretated with caution due to the small sample size compared to the general population. Furthermore, 3 pregnancies were reported in the adolescent population. Thereof, for two pregnancies both the mother and child were reported as being healthy. For the third pregnancy, the outcome is pending. On the other hand, pregnant women are at increased risk of complications associated with CHIKV infection compared to non-pregnant women. Pregnant women with CHIKV infection may be at increased risk for adverse pregnancy outcomes, including preterm labour and delivery. Vertical transmission of CHIKV from mothers with viraemia at delivery to their infants has been reported and can cause severe, potentially fatal neurological disease in neonates. It is unknown if IXCHIQ is excreted in human milk. A risk to the breastfed child cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IXCHIQ and any potential adverse effects on the breastfed child from IXCHIQ.
Risk factors and risk groups	Risk of exposure to wild-type CHIKV, gestational age, risks to the foetus or neonate from vertical transmission of wild-type CHIKV.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 “Fertility, pregnancy and lactation” / PL section 2. “What you need to know before you receive IXCHIQ”. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Pregnancy Study VLA1553-403. Post-Authorisation Pregnancy Study VLA1553-405.

Table 34: Missing Information: Safety in patients with autoimmune or inflammatory disorders

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

Table 35: Missing Information: safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

Table 36: Missing Information: Long-term safety

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Clinical Trial VLA1553-303. Clinical Trial VLA1553-321 in adolescents.

Table 37**:** Missing Information: Co-administration with other vaccines

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.5 “Interaction with other medicinal products and other forms of interaction” / PL section 2. “What you need to know before you receive IXCHIQ”. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

Table 38: Missing Information: Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease

Risk minimisation measures	Routine risk minimisation measures: . SmPC section 4.4 “Special warnings and precautions for use”: “IXCHIQ should only be given when there is a significant risk of acquiring chikungunya infection, and after careful consideration of the potential risks and benefits.” Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Randomised Controlled Trial on Effectiveness and Safety VLA1553-404

Purpose of the Study: To evaluate vaccine effectiveness of a single dose of IXCHIQ in preventing symptomatic, virologically confirmed CHIKV disease among adults, in IXCHIQ vaccinees compared to control participants during the same trial period in an endemic country. To assess IXCHIQ safety in IXCHIQ vaccinees compared to control participants during the same trial period.

II.C.2 Other studies in post-authorisation development plan

Clinical Trials with IXCHIQ

Clinical Trial VLA1553-303:

Purpose of the Study: to evaluate antibody persistence and long-term safety of IXCHIQ in adults aged 18 years and above.

Clinical trial VLA1553-321:

Purpose of the study: to evaluate the safety and immunogenicity of IXCHIQ in adolescents aged 12-17 years of age.

Post-Authorisation Studies

Post-Authorisation Safety Study VLA1553-401

Purpose of the Study: to estimate the incidence of medically attended adverse events of special interest, including infection with chikungunya virus, Chikungunya-like adverse reactions, vaccine-associated arthritis, and cardiac events following the administration of IXCHIQ in adults aged 18 years and above in the US planning to travel to endemic countries.

To describe the use of IXCHIQ and the risk of medically attended adverse events of special interest in individuals aged ≥ 65 years, HIV positive participants, patients with autoimmune or inflammatory disorders, patients with acute or progressive, unstable, or uncontrolled clinical conditions, subjects with an infection in the past 3 days after vaccination or with known or suspected defect of the immune system.

Post-Authorisation Pregnancy Study 1553-403:

Purpose of the Study: to evaluate the safety of live-attenuated chikungunya virus vaccine in pregnant women exposed to the vaccine in Brazil.

Prospective Safety Cohort Study VLA1553-406

Purpose of the Study: to evaluate the safety of IXCHIQ using primary data collection.

Post-Authorisation Pregnancy Study VLA1553-405

Purpose of the Study: To monitor and evaluate the outcomes of pregnancy and infant health up to 12-weeks among women in the United States who received IXCHIQ while pregnant.

Part VII: Annexes

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Annex IV - Specific adverse drug reaction follow-up forms

Annex IV.1 – Pregnancy Questionnaire

valneva

Valneva Date of Receipt:

Case ID#

PREGNANCY QUESTIONNAIRE

1. Reporter Information:

First Name		**Is the reporter a Healthcare professional** ☐ Yes ☐ No Specialty: Grade:		
Last Name				
Address		**Hospital/Practice**		
Telephone				
Fax				
email				
Signature		**Date**		

2. Patient Details:

Initials: __ ... **Date of birth** *(DD/MM/YYYY)*: **Age in Years:** **Weight in kg** **Height in cm**

Race: ☐ White ☐ Black ☐ Asian ☐Other ☐ Refused or Unknown

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Other ☐ Unknown

3. IXCHIQ (Chikungunya vaccine, live):

Single Dose received	☐ Yes ☐ No	Date:	☐ Valneva ☐ Others please specify
Batch/Lot number			
Has the patient been diagnosed with Chikungunya since having the vaccine? If so, please provide the date and test used.	☐ Yes ☐ No ☐ Unknown	Date:	

When in relation to the pregnancy was the vaccination given (e.g. '2 weeks before pregnancy' or 'after 10 weeks of pregnancy'

4. Adverse Event Details after vaccination:

Adverse Event(s) (Check any/both as applicable)	**Start Date** (DD/MM/YY)	**Stop Date** (DD/MM/YY)	**Outcome**	
			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing	☐ Resolved with sequelae, *please specify*

			☐ Recovering	☐ Patient died ☐ Unknown

5. Current Pregnancy Details:

Method and Date of pregnancy positive test *(DD/MM/YYYY)*

Was pregnancy known when product administered? ☐ *No* ☐ *Yes*

First day of last menstrual period *(DD/MM/YYYY)* **Estimated delivery date** *(DD/MM/YYYY)*

Complications during pregnancy: ☐ Pre-eclampsia ☐ Diabetes ☐ Infection

☐ Other *(please specify)*

Hospitalization during pregnancy: ☐ No ☐ Yes *(please specify reasons)*:

5. Current Pregnancy Details:

Please provide and attach results of relevant laboratory test and procedures

Medical History			Start Date	Stop Date	Is the patient treated for this condition?
Resident or visitor in areas with local transmission of chikungunya since the last 15 days or Chikungunya infection in past	☐ Yes	☐ No			
Pre-existing complications	☐ Yes	☐ No			
Depression, postpartum depression	☐ Yes	☐ No			
Respiratory or gastrointestinal infection	☐ Yes	☐ No			
Gestational/Diabetes Mellitus	☐ Yes	☐ No			
HIV positive	☐ Yes	☐ No			
Systemic lupus erythematosus	☐ Yes	☐ No			
Vasculitis	☐ Yes	☐ No			
Other autoimmune disorders	☐ Yes	☐ No			
Hypertension	☐ Yes	☐ No			
Thyroid issues	☐ Yes	☐ No			
Heart Disease (*please specify*)	☐ Yes	☐ No			
Lung Disease (*please specify*)	☐ Yes	☐ No			
Kidney disease (*please specify*)	☐ Yes	☐ No			
Liver disease (*please specify*)	☐ Yes	☐ No			
Coagulation disorders	☐ Yes	☐ No			
Blood Transfusions	☐ Yes	☐ No			
Genetic disorders	☐ Yes	☐ No			
Obesity	☐ Yes	☐ No			
Current or Former Smoker:	☐ Yes	☐ No			
If yes, please provide details					

Conception: ☐ Natural ☐ In vitro fertilisation (IVF)

Medical history (including previous pregnancies) _____

Medical illnesses or any surgical interventions during pregnancy:

Exposure to substances during pregnancy: ☐ Alcohol ☐ Tobacco smoking ☐ Other (*please specify*)

Was this patient's first pregnancy: ☐ Yes ☐ No If no, please complete the table below.

S.No.	LMP Date (DD/MM/YY)	Outcome of pregnancy*	Sex	APGAR Score	Weight of the baby (kg)	Mode of delivery
1			☐ Male ☐ Female			☐ Vaginal ☐ C-section ☐ Other (*please specify*)
2			☐ Male ☐ Female			☐ Vaginal ☐ C-section ☐ Other (*please specify*)
3			☐ Male ☐ Female			☐ Vaginal ☐ C-section ☐ Other (*please specify*)
4			☐ Male ☐ Female			☐ Vaginal ☐ C-section ☐ Other (*please specify*)

**Pregnancy outcomes are term labor, pre-term labor, fetal death/stillbirth, spontaneous abortion, elective termination and ectopic pregnancy.*

Other details of previous pregnancies:
Have amniocentesis or any genetic tests been performed: ☐ Yes ☐ No If yes, please add the results
Any other significant events during pregnancy: ☐ Yes ☐ No If yes, please specify.

7. Other Suspect Drug:

Please only include drugs consider to be contributory (causality related) to the adverse event(s) and NOT concomitant medications.

Suspected Drug Name	Indication	Daily Dose	Route	Start Date *(DD/MM/YY*	Stop Date *(DD/MM/YY)*	Was Suspect drug Withdrawn
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

If any of the above drugs were stopped, did the event(s) improve after stopping?
☐ No ☐ Yes ☐ Not applicable.
If applicable please provide the Date Drug was stopped/Altered (DD-I/M/-YY) _____
Did the event(s) recur after reintroduction?
☐ No ☐ Yes ☐ Not applicable.
If applicable please provide Date Drug was reintroduced (DD-I/M/-YY) _____

8. Concomitant Drugs/ Vaccines:

Please include drugs used to treat the event(s) during pregnancy or 30 days before pregnancy. List all medications, including over-the-counter drugs and supplements.

Concomitant Drug Name	Indication	Daily Dose	Route	Start Date *(DD/MM/YY*	Stop Date *(DD/MM/YY)*	Withdrawn
						☐ Yes ☐ No
						☐ Yes ☐ No

						☐ Yes ☐ No

Have you used folate during pregnancy? ☐ Yes | ☐ No *If yes please add treatment details into the table above.*

---

9. Pregnancy Outcome:

Please provide and attach results of relevant laboratory test and procedures

Mode of delivery: ☐ Spontaneous ☐ Cesarean section ☐ Other, *please specify*:

Date of delivery (DD/MM/YYYY):

☐ **Term labor,** (*please specify gestational age*):

☐ **Pre-term labor,** (*please specify gestational age*):

☐ **Fetal Death / Stillbirth** *(pregnancy loss ≥20 weeks of gestation)*

☐ **Spontaneous abortion,** *(pregnancy loss <20 weeks of gestation)*

☐ **Elective termination,** (*please specify gestational age*):

☐ **Ectopic pregnancy**

Neonate: ☐ Single ☐ Multi *(please specify #)* **Sex:** ☐ Male ☐ Female

☐ **Live birth, with no congenital anomalies**

☐ **Live birth, with congenital anomalies** *(please specify)*

Weight of the baby*(kg)*

Height of the baby*(cm)*

Cranial circumference*(cm)*

Apgar score

☐ **Neonatal illness** *(please specify diagnoses, hospitalization, therapy)*

☐ **Stillbirth** ☐ **Was an autopsy performed** *(if yes please attach the autopsy report)*

Comments *(please specify all pregnancy outcome relevant info)*

Please complete sections 10-13 depending on the outcome of the pregnancy.

10. In Case of Early/Ongoing Pregnancy or If Unknown:

Is the pregnancy still ongoing? ☐ Yes | ☐ No

I. **If yes, please provide:**

Estimated due date (*DD/MM/YYYY*): Estimated delivery date (*DD/MM/YYYY*):

II. **If no, please respond to questions below:**

When did the pregnancy end (*DD/MM/YYYY*)?

Were any problems identified with foetus or baby?

We may contact you again to obtain further information on the outcome of the pregnancy.

11. In Case of Miscarriage or Elective Termination of Pregnancy:

Please provide and attach results of relevant laboratory test and procedures

The stage of pregnancy when the pregnancy loss occurred (*please specify gestational age*):

Last Menstrual Period (*DD/MM/YY*):

Any problems with the foetus identified before or after the pregnancy loss (eg ultrasound and/or additional imaging studies):

Laboratory Finding(s)	**Date** (DD/MM/YY)	**Result**

---

12. In Case of Term or Preterm Live Birth:

Please provide and attach results of relevant laboratory test and pncentiwes

Gestational Age at Birth (*DD/M/YY*):

Method of delivery: ☐ Spontaneous ☐ Cesarean section ☐ Emergency Cesarean section

If emergency Cesarean section, the indication for emergency delivery:

☐ Pre-eclampsia ☐ Foetal distress ☐ Other, please specify:

Any complications noted after delivery for baby :

☐ Low birth weight
☐ Small for gestational age
☐ Hypoglycaemia
☐ Respiratory distress
☐ Jaundice
☐ Retinopathy
☐ Anaemia
☐ Infection
☐ Intraventricular hemorrhage
☐ Other, please specify

Congenital anomalies: ☐ Yes ☐ No If yes, please specify:

---

13. In Case of 2 Years Follow-Up for Reports of Term or Preterm Live Birth

Please provide and attach results of relevant laboratory test and pncentiwes

Has the child had any further health issues? ☐ Yes ☐ No If yes, please specify

Has the child met their key development milestones? ☐ Yes ☐ No If yes, please specify

---

Thank you for completing this form

Annex IV.2 – Arthritis / Arthralgia Questionnaire

valneva

Valneva Date of Receipt:
Case ID#: _____

Arthritis /Arthralgia

1.Reporter Information

First Name		Is the reporter a Healthcare professional ☐ Yes ☐ No		
Last Name		Specialty: Grade:		
Address		Hospital/Practice		
Telephone				
Fax				
email				
Signature		**Date**		

2.Patient details.

Initials **Sex:** ☐ Male ☐ Female **Date of birth** (DD/MM/YYYY) **Age** (years)

Race: ☐ White ☐ Black or African American ☐ Asian ☐ Other ☐ Refused or Unknown

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Other ☐ Unknown

3. IXCHIQ (Chikungunya vaccine, live):

Single Dose received	☐ Yes ☐ No	Date:	☐ Valneva ☐ Other
Batch/Lot number			
Has the patient been diagnosed with Chikungunya since having the vaccine? If so, please provide the date and test used.	☐ Yes ☐ No ☐ Unknown	Date:	

4. Symptoms and signs.

Symptoms ~~onset~~ start date (DD/MM/YYYY):

Time to onset of symptoms after receiving Chikungunya vaccination (Days/weeks/months)

Duration of symptoms less than 6 weeks

☐ Yes
☐ No
☐ Unknown

Please specify the duration (Days/weeks/months) ...

Recorded temperature (≥38.0°C [100.4°F] measured orally	☐ Yes ☐ No ☐ unknown

Joint pain with acute onset ☐ Yes ☐ No ☐ Unknown	If yes, please select ☐ New generalized joint pain ☐Aggravated generalized joint pain (preexisting) ☐ Single joint (please specify .....) ☐ Multiple joints (please specify .....)
Please elaborate on what was the nature of the joint pain	If yes, please select as applicable ☐ Swelling in and around the joints ☐ Associated with redness ☐ Increase in warmth in and around the swelling ☐ Restricted range of movement ☐ Debilitating in nature
Was the joint pain associated with any of the following additional signs/ symptoms?	☐ Back pain ☐ myalgia ☐ rash ☐ cardiac symptoms ☐ Neurological symptoms (e.g., confusion, optic neuritis, meningoencephalitis, or polyneuropathy

Physical Examination *(Other relevant symptoms and signs, including systemic features:)*

5. Treatment received for Adverse event:

Drug name	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Route	Daily dose/ Any additional information

Was there any intervention done to treat the condition? ☐ Yes ☐ No ☐ Unknown	*If yes, please specify the measures taken including date and time*

6.Adverse event outcome

Date of evaluation (last follow up):	
Maximum level of care required:	☐ Outpatient ☐ Inpatient ward ☐ High dependency unit (intermediate care unit) ☐ Intensive care unit If the patient was hospitalized for the adverse event, please provide the admission and the discharge dates (DD/MM/YYYY) and Discharge report if available

	Admission date ..... Discharge date .....
Please specify outcome of the event as applicable	☐ Recovered ☐ Event ongoing ☐ Recovering ☐ Resolved with sequelae, please specify ☐ Patient died ☐ Unknown

Please provide if any other details:

Was The vaccine responsible for occurrence of adverse event

☐ Yes ☐ No ☐ Unknown

Please provide reasoning for your selection

In the event of Death, please provide the date and cause of death .....

Was cause of death included on the death certificate:

☐ Yes ☐ No ☐ Unknown

Was an autopsy performed ☐ Yes ☐ No

(If yes please attach the autopsy report)

7. Medical History/Concurrent Disease condition

Medical History or Concurrent Disease condition	Start date	Stop date	Details
Resident or visitor in areas with local transmission of chikungunya since the last 15 days or Chikungunya infection in past ☐ Yes ☐ No ☐ unknown			
Resident or visitor in areas with local transmission of Zika for the last 15 days or Zika virus infection in the past ☐ Yes ☐ No ☐ unknown			
Family history of arthritis ☐ Yes ☐ No ☐ unknown			
History of any other vaccination in last100 days (e.g., Covid 19, measles, mumps, rubella, HBV, Ebola) ☐ Yes ☐ No ☐ unknown			
History of arthralgia/arthritis with any other vaccination previously received ☐ Yes ☐ No ☐ unknown			
History of trauma ☐ Yes ☐ No ☐ unknown			
History and concurrent condition of any infectious illness ☐ Yes ☐ No ☐ unknown			
Connective tissue / Autoimmune disease ☐ Yes ☐ No ☐ unknown			

History of HIV positive, hepatitis B surface antigen or hepatitis C virus. ☐ Yes ☐ No ☐ unknown			
Other *(please specify)*			

7. Suspect Drugs/ Vaccines

Please only include drugs consider to be contributory (causality related) to the adverse event(s) and NOT concomitant medications.

Suspected Drug Name	Indication	Daily Dose	Route	Start Date *(DD/MM/YY*	Stop Date *(DD/MM/YY)*	Was Suspect drug Withdrawn
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

If any of the above drugs were stopped, did the event(s) improve after stopping?
☐ No ☐ Yes ☐ Not applicable.
If applicable please provide the Date Drug was stopped/Altered (DD-MM-YY) _____

Did the event(s) recur after reintroduction?
☐ No ☐ Yes ☐ Not applicable.
If applicable please provide Date Drug was reintroduced (DD-MM-YY) _____

8. Concomitant Drugs/ Vaccines

Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations. Add vaccine administered within the last 100 days

If patient received **any antibiotic treatment** before obtaining the first synovial fluid sample ☐ Yes, ☐ No ☐ Unknown

If yes, please provide details.....

Concomitant Drug Name		Indication	Daily Dose	Route	Start Date *(DD/MM/YY*	Stop Date *(DD/MM/YY)*	Withdrawn
							☐ Yes ☐ No
							☐ Yes ☐ No
							☐ Yes ☐ No

9.Lab test/ diagnostic procedures *Please provide and attach results of relevant laboratory test and procedures*

Laboratory test	Results	Dates	Abnormal findings details
Synovial Fluid examination if abnormal	Please tick as applicable: ☐ If leucocyte count is increased, ---------- (please mention value) ☐ Any pathological synovial fluid cells ☐ Any microorganism on Gram stain, microscopy or PCR in synovial fluid ☐ Any Bacterial growth on routine culture of synovial fluid ☐ Crystals Any other abnormal finding		
Complete blood count with differential count	☐ Normal ☐ Abnormal ☐ Not done ☐Unknown		
Vasculitis screen if any performed: ESR, ANA, anti-ds DNA, SS-A (Ro), SS-B (La), ANCA, Complement, RhF, Anti-cardiolipin Ab and lupus anti-coagulant	☐ Normal ☐ Abnormal ☐ Not done ☐Unknown		
RT-PCR to directly detect Chikungunya if performed	☐ Normal ☐ Abnormal ☐ Not done ☐Unknown		
RT-PCR to directly detect Dengue if performed	☐ Normal ☐ Abnormal ☐ Not done ☐Unknown		
Serology: for (anti-CCP); rheumatoid factor (RF)	☐ Normal ☐ Abnormal ☐ Not done ☐Unknown		
Radiography	☐ Normal ☐ Abnormal ☐ Not done ☐Unknown		
Magnetic resonance imaging	☐ Normal ☐ Abnormal ☐ Not done ☐Unknown		
Ultrasonography of affected joint	☐ Normal ☐ Abnormal ☐ Not done ☐Unknown		
Please provide details of any other abnormal findings:			

Thank you for completing this form.

Annex IV.3 – Cardiac Events Questionnaire

valneva

Valneva date of receipt:
Case ID#: _____

Cardiac Events

1. Reporter information

First Name		Is the reporter a Healthcare professional ☐ Yes ☐ No	
Last Name		Specialty:	Grade:
Address		Hospital/Practice	
Telephone		**Email**	
Date	**Signature**		

2. Patient details

Initials: **Sex:** ☐ Male ☐ Female **Date of birth** (DD /MM/ YYYY): **Age** (years):

Race: ☐ White ☐ Black or African American ☐ Asian ☐ Other ☐ Refused or Unknown

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Other ☐ Unknown

3. IXCHIQ (Chikungunya vaccine, live):

Single dose received	☐ Yes ☐ No	Date:	☐ Valneva ☐ Other
Batch/Lot number			
Has the patient been diagnosed with Chikungunya since having the vaccine? If so, please provide the date and test used.	☐ Yes ☐ No ☐ Unknown	Date: Test (as appl.):	

4. Cardiac (and other) adverse events

Event	Onset date (DD MMM YYYY)	Time to onset after vaccination (days/weeks/months)	End date (if appl., DD MMM YYYY)	Outcome (e.g., resolved, ongoing)

Other relevant information:

5. Diagnostic measures

Physical Examination

Tests	Performed	(if appl.) Date performed (DD MMM YYYY)	Result
ECG	☐ Yes ☐ No ☐ Unknown		
Exercise stress test	☐ Yes ☐ No ☐ Unknown		
Blood test (please specify, e.g., Troponin (T))	☐ Yes ☐ No ☐ Unknown		
Echocardiogram	☐ Yes ☐ No ☐ Unknown		
Coronary angiogram	☐ Yes ☐ No ☐ Unknown		
Magnetic resonance imaging	☐ Yes ☐ No ☐ Unknown		
Other tests (please specify, e.g., Coronary computed tomography angiogram)	Test:		
	Test:		

6. Medical history / concurrent diseases

Medical History or Concurrent Diseases			
Resident or visitor in areas with local Chikungunya transmission in the last 15 days or past Chikungunya infection ☐ Yes ☐ No ☐ Unknown	Start date:	Stop date:	Details:
Resident or visitor in areas with local Zika transmission in the last 15 days or past Zika virus infection ☐ Yes ☐ No ☐ Unknown	Start date:	Stop date:	Details:
Family history of cardiac disease (incl. fatal outcome; if yes, please specify) ☐ Yes ☐ No ☐ Unknown			
History of other vaccinations in last 100 days (e.g., COVID-19, measles, mumps, rubella, HBV) (if yes, please specify type and date) ☐ Yes ☐ No ☐ Unknown			

History of relevant diseases	Start	Current details	Therapy
Hypertension ☐ Yes ☐ No ☐ Unknown			
High cholesterol ☐ Yes ☐ No ☐ Unknown			
Diabetes ☐ Yes ☐ No ☐ Unknown			
Obesity ☐ Yes ☐ No ☐ Unknown			
Tobacco use ☐ Yes ☐ No ☐ Unknown			
Thrombosis ☐ Yes ☐ No ☐ Unknown			
Other (please specify):			

7. Other drugs or vaccines (unless specified above)

Drug / vaccine name	Indication	Daily dose	Route	Start Date (DD MMM YYYY)	May have caused event(s)	Stop Date (if appl., DD MMM YYYY)
					☐ Yes ☐ No ☐ Unknown	
					☐ Yes ☐ No ☐ Unknown	
					☐ Yes ☐ No ☐ Unknown	
					☐ Yes ☐ No ☐ Unknown	
					☐ Yes ☐ No ☐ Unknown	

Thank you for completing this form.

Annex IV.4 – Chikungunya-like adverse reactions Questionnaire

valneva

Valneva Date of Receipt:
Case ID#: _____

Chikungunya-like adverse reactions

1. Reporter information

First Name		Is the reporter a Healthcare professional ☐ Yes ☐ No	
Last Name		Specialty:	
Address *(e.g., Hospital or Practice)*			
Phone		**Email**	
Date		**Signature**	

2. Patient details

Initials: **Sex:** ☐ Male ☐ Female **Date of birth** *(DD /MM/ YYYY)*: **Age** (years):

Race: ☐ White ☐ Black or African American ☐ Asian ☐ Other ☐ Refused or Unknown

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Other ☐ Unknown

3. IXCHIQ (Chikungunya vaccine, live):

Single Dose received	☐ Yes ☐ No	**Date:**	☐ Valneva ☐ Other:
Batch number			
Has patient been diagnosed with Chikungunya since vaccination? If so, please provide date and test used.	☐ Yes ☐ No ☐ Unknown Date *(DD /MM/ YYYY)*: Test used *(If appl.)*:		

4. Symptoms and signs

Fever: ☐ Yes ☐ No Body temperature: °C Chills: ☐ Yes ☐ No

Onset *(DD /MM/ YYYY)*: Interval to vaccination: days Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Acute (poly)arthralgia: ☐ Yes ☐ No Location(s):

Onset *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Back pain: ☐ Yes ☐ No Level:

Onset *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Neurological symptom(s): ☐ Yes ☐ No *Please specify, e.g., confusion, headache, dizziness, paresthesia, optic neuritis, retinitis, uveitis, meningoencephalitis, or polyneuropathy.*

Onset of on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Onset of on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Cardiac symptom(s): ☐ Yes ☐ No *Please specify, e.g., tachycardia, arrythmia, myocarditis, or other cardiac complications.*

Onset of on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Onset of on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Dermatological symptom(s): Rash ☐ Yes ☐ No ☐ Other *(Please specify)*

If rash, please specify: ☐ Macular ☐ Maculopapular ☐ Other *(Please specify)* Pruritus: ☐ Yes ☐ No

Onset on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Other symptom(s): *(Please check if applicable)*

Oedema ☐ Yes ☐ No *If yes, please specify location (e.g., facial, extremities):*

Onset on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Lymphadenopathy ☐ Yes ☐ No *If yes, please specify location:*

Onset on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Other symptoms *(not specified above, e.g., conjunctivitis or other eye disorders, myalgia, pain, fatigue, hyperhidrosis):* ☐ Yes ☐ No

Onset of on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

Onset of on *(DD /MM/ YYYY)*: Outcome: ☐ Recovered ☐ Recovering ☐ Ongoing

5. Medical history and concurrent disease

Medical history or concurrent disease	Start date *DD /MM/ YYYY*	Stop date *DD /MM/ YYYY*	Details
Resident or visitor in areas with local transmission of Chikungunya or Zika in last 15 days ☐ Unknown ☐ No ☐ Yes *(please specify:)* ☐ Chik ☐ Zika			
Chikungunya or Zika infection in the past ☐ Unknown ☐ No ☐ Yes *(please specify:)* ☐ Chik ☐ Zika			
History of any other vaccination in last 100 days *(e.g., COVID-19, Measles, Mumps, Rubella, HBV, Ebola)* ☐ Unknown ☐ No ☐ Yes *(please specify, incl. date of vaccination:)*			
History or concurrent condition of infectious illness *(Incl., e.g., HIV, Hepatitis B, Hepatitis C)* ☐ Unknown ☐ No ☐ Yes *(please specify, incl. type and time of infection:)*			
Other *(please specify, incl. possible other causes for symptoms, e.g., autoimmune disease, concomitant medication / vaccination etc.)*			

6. Lab tests / diagnostic procedures

Laboratory or other test	Date *DD /MM/ YYYY*	Result

Thank you for completing this form.

Annex VI - Details of proposed additional risk minimisation activities

Not applicable.

Annex VII - Other supporting data (including referenced material)

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