

Summary Basis for Regulatory Action

Date:	December 08, 2023
From:	Sudhakar Agnihothram, B. Pharm., Ph.D., Review Committee Chair
BLA STN:	125777
Applicant:	Valneva Austria GmbH
Submission Receipt Date:	December 22, 2022
Action Due Date:	November 21, 2023
Proper Name:	Chikungunya Vaccine, Live
Proprietary Name:	IXCHIQ
Indication:	IXCHIQ is a vaccine indicated for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years of age and older who are at increased risk of exposure to CHIKV

Recommended Action: The Review Committee recommends approval of this product.

Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC <ul style="list-style-type: none"> • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC) 	Shufeng Liu CBER/OVRR/DVP/LVBD Viviana Ramirez CBER/OCBQ/DMPQ/MRB2 Alicia Howard CBER/OCBQ/DBSQC/LBVI Karla Garcia CBER/OCBQ/DBSQC/LMIVTS Marie Anderson CBER/OCBQ/DBSQC/QAB Tao Pan CBER/OTP/OGT/DGT1/GTB3
Clinical <ul style="list-style-type: none"> • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DPV) • BIMO 	Sixun Yang CBER/OVRR/DVRPA/CRB2 Linda Forsyth CBER/OBPV/DPV/PB3 Diane Gubernot CBER/OBPV/DABRA/ARWEB Marisabel Rodriguez CBER/OBPV/DABRA/BRAB Triet Tran CBER/OCBQ/DIS/BMB
Statistical <ul style="list-style-type: none"> • Clinical data (OBPV/DB) • Non-clinical data 	Ruoxuan Xiang CBER/OBPV/DB/VEB Ho-Hsiang Wu CBER/OBPV/DB/DNCE
Non-clinical/Pharmacology/Toxicology <ul style="list-style-type: none"> • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology 	Ching-Long (Joe) Sun, CBER/OVRR/DVRPA Shufeng Liu CBER/OVRR/DVP/LVBD
Clinical Pharmacology	N/A
Labeling <ul style="list-style-type: none"> • Promotional (OCBQ/APLB) • Carton/Container (OVRR/DVRPA) 	Oluchi Elekwachi CBER/OCBQ/DCM/APLB Alisa Gilliard CBER/OCBQ/DCM/APLB Daphne Stewart CBER/OVRR/DVRPA Ching Yim-Banzuelo CBER/OVRR/DVRPA
Regulatory Project Managers	Konstantin Virnik CBER/OVRR/DVRPA/RRB2 Georgeta Crivat CBER/OVRR/DVRPA/RRB2
Other reviews not captured above categories, for example: <ul style="list-style-type: none"> • Consults • Devices • Software • Human Factors • FONSI 	Andrea Gray CBER/ORO/DROP/RPB Brenda Baldwin CBER/OVRR/DVRPA/CMC3 Hussein Ezzeldin CBER/OBPV/DABRA/ARWEB Ujwani Nukala CBER/OBPV/DABRA/BRAB Cara Fiore CBER/OVRR/DVRPA Florence Mwangi CDER/OSE/OMEPRM/DMEPAI Adrienne Hornatko-Munoz /PREA Coordinator
Advisory Committee Summary	No advisory committee meeting was held

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1. Introduction

Valneva Austria GmbH (the Applicant) submitted a Biologics License Application (BLA) on December 22, 2022, to support licensure of their chikungunya vaccine IXCHIQ [Chikungunya Vaccine, Live (Company Code: VLA1553)] via the accelerated approval pathway. IXCHIQ is a live attenuated chikungunya vaccine that is based on the La Réunion strain of chikungunya virus (LR-CHIKV clone LR2006-OPY1) of (b) (4) constructed by a deletion in the non-structural protein 3 (nsP3) viral replicase complex gene. IXCHIQ vaccine is a sterile and lyophilized product to be reconstituted with the supplied prefilled syringe of diluent (sterile water for injection (sWFI)). A single dose is 0.5 mL volume after reconstitution. The vaccine is administered intramuscularly (IM) into the deltoid muscle as a single injection.

IXCHIQ is indicated for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years and older who are at increased risk of exposure to CHIKV. This indication is being approved under accelerated approval based on an evaluation of seroresponse defined as CHIKV-specific neutralizing antibody titer ≥ 150 as determined by micro-plaque reduction neutralization test (μ PRNT₅₀), used as a surrogate endpoint in the pivotal effectiveness study (VLA 1553-301). At Day 29, 98.9% participants in the VLA1553 group had a CHIKV antibody titer ≥ 150 compared with no participants in the placebo group. The results met the pre-specified success criterion of a lower bound (LB) of the 95% confidence interval (CI) of $>70\%$. Seroresponse rate, defined as a percentage of participants who achieved an anti-CHIKV neutralizing antibody titer ≥ 150 at 28 days postvaccination, remained at 98.0% and 96.3% at 84 days and 180 days postvaccination, respectively. The lot-to-lot consistency Study VLA 1553-302 demonstrated that the 95% CIs of the anti-CHIKV GMT ratios between any two lots were within 0.67 and 1.5, which met the pre-specified immunogenicity criteria to demonstrate lot consistency.

The overall reactogenicity profile of IXCHIQ is acceptable. However, the frequency and severity of adverse events of special interest (AESIs) of chikungunya (CHIK)-like adverse reactions associated with IXCHIQ administration, including severe, serious, and/or prolonged adverse reactions, and atypical presentations such as cardiac events warrant the following: (1) restricting the indication of the vaccine to individuals 18 years of age and older who are at increased risk of exposure to CHIKV; (2) inclusion of information on the risk of severe or prolonged CHIK-like adverse reactions in Section 5 (Warnings and Precautions) of the United States Prescribing Information (USPI); (3) enhanced postmarketing surveillance to include expedited reporting (arthritis/arthralgia, cardiac events, and spontaneous abortion), a summary and analysis in periodic safety reports, and dedicated AE questionnaires; and (4) a postmarketing requirement (PMR) to include evaluation of severe CHIK-like adverse reactions (including typical and atypical presentations and cases that result in hospitalization) and prolonged arthralgia in approximately 10,000 individuals who receive IXCHIQ compared with individuals in the control group in an individual-level randomized, observer-blind, controlled trial conducted across multiple centers in an endemic country (PMR Study #2, see below).

Vertical transmission of wild-type CHIKV to neonates from pregnant individuals with viremia at delivery is common and can cause severe, potentially fatal CHIKV disease in

neonates. Vertical transmission of wild-type CHIKV and fetal death attributable to CHIKV in the context of antepartum infection has been reported to occur infrequently. Vaccine viremia occurs in the first week following administration of IXCHIQ, with resolution of viremia by 14 days after vaccination. It is not known if the vaccine virus can be transmitted from a pregnant individual to the fetus or neonate and cause fetal or neonatal adverse reactions. Decisions to administer IXCHIQ during pregnancy should take into consideration the individual's risk of exposure to wild-type CHIKV, gestational age, and risks to the fetus or neonate from vertical transmission of wild-type CHIKV.

In accordance with the accelerated approval regulations, adequate and well-controlled confirmatory studies to verify and describe clinical benefit must be conducted with due diligence to fulfill the regulatory requirements. Valneva has agreed to the two post-marketing required studies to confirm the effectiveness of IXCHIQ.

PMR Study # 1 (VLA 1553-402): An observational study with a test-negative, case-control design to assess the effectiveness of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in the adolescent and adult population (12 years of age and older) in endemic areas of Brazil.

PMR Study #2 (VLA 1553-404): A pragmatic randomized controlled trial to assess the effectiveness and safety of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in adults in an endemic country. This study will also serve as the PMR study to assess the known serious risk of severe chikungunya-like adverse reactions.

Valneva is expected to complete the design, implementation readiness verification, initiation, accrual, completion, and reporting of these studies within the framework described in their BLA submission.

Based on the review of the clinical, nonclinical, and product-related data submitted in the original BLA and PMR studies required to confirm the effectiveness of IXCHIQ, the review committee recommends approval of IXCHIQ under accelerated approval for the labeled indication and usage.

2. Background

CHIK is a mosquito-borne disease caused by CHIKV, an alphavirus first isolated in 1953. Although there is only one serotype for CHIKV, phylogenetic analyses reveal three distinct CHIKV lineages: the West African, Asian, and East/Central/South African (ECSA) lineages. The ECSA lineage includes the Indian Ocean lineage (IOL) subgroup, now recognized as a strain of ECSA. CHIK is an emerging global health threat with at least five million cases of CHIKV infection reported during the past 15 years. In areas where CHIKV circulates, sudden large outbreaks often occur that affect 33-75% of the population. Up to 97% of those infected become symptomatic ([CDC, 2022](#)); That said, it is worth noting that in one study >80% CHIKV infected individuals remained asymptomatic. ([Yoon, 2020](#)). Depending on the study report, approximately 2% to 57% patients developed chronic or recurrent arthralgia ([Suhrbier, 2012](#)). A study in post-epidemic CHIK on Réunion Island showed that 36% of patients developed persistent joint pain over 15 months (15.5% with moderate and 1.2% with severe joint pain)

([Sissoko, 2009](#)). Recent evidence suggests that the lineages may differentially activate inflammatory responses in mouse models ([Teo, 2015](#)) and vary in virulence and cross-protective ability in mice and nonhuman primates ([Langsjoen, 2018](#)) and differ in transmissibility by competent mosquitoes ([Tsetsarkin, 2007](#)). The highest risk of CHIKV infection is in tropical and subtropical regions of Africa, Southeast Asia, and parts of the Americas where CHIKV-carrying mosquitos are endemic. However, because of environmental, epidemiological, ecological, and social factors, such as global warming, land use and industry, and population movement due to migration, tourism, and cross-border trade, CHIKV has spread to new geographical areas causing a rise in global prevalence.

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

CHIKV infections typically present in three stages that differ in clinical features and treatment. During the acute stage, clinical symptoms appear 4 to 7 days post-infection and manifest as rapid onset of high fever, transient maculopapular rash and multiple mild to severe arthralgia/arthritis episodes. This is followed by a subacute stage and then chronic stage of disease leading to impaired quality of life in some people due to persistent incapacitating rheumatic symptoms up to months and years after infection ([Simon, 2015](#); [Couderc, 2009](#); [Suhrbier, 2012](#)). Viremia in the acute stage may lead to death; however, mortality due to CHIKV infection is low, with an estimated rate of 0.07%. On the contrary, morbidity is high and may lead to significant, long-term disability ([Kumar, 2021](#)). Although CHIKV infection is self-limited and characterized mainly by severe joint pain and myalgia, rare, atypical presentations of CHIK occur. Atypical CHIK manifestations that have been reported during outbreaks include cardiac and neurological complications such as arrhythmias, myocarditis, dilated cardiomyopathy, heart failure, encephalitis, meningitis, and Guillain–Barré Syndrome ([Traverse, 2021](#); [Cotella, 2021](#); [Alvarez, 2017](#); [de Lima Cavalcanti, 2022](#)).

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

The exact mechanism of protection has not been determined for IXCHIQ. IXCHIQ elicits CHIKV-specific immune responses.

(b) (4) other chikungunya vaccines are currently in late phase clinical development. No safety concerns have been observed with these investigational products.

Clinical development of IXCHQ was conducted under IND 17854. [Table 1](#) lists the key regulatory activities during clinical development.

Table 1. Key Regulatory Activities During Clinical Development Program

Date	Regulatory Activity	Comments
March 15, 2017	PTS 3183, Pre-IND meeting	None
December 5, 2017	IND 17854 submitted	None
December 21, 2018	Fast Track Designation Granted	None
March 28, 2019	Type C Meeting post conduct of VLA 1553-101, to discuss clinical development	Discussed potential for licensure via the Accelerated Approval (AA) pathway and challenges for confirmatory study to verify the clinical benefit.
November 8, 2019	VRBPAC meeting to discuss pathways for development and licensure of Chikungunya vaccines	VRBPAC recommended using anti-CHIKV titer that completely prevented viremia and fever in NHP adoptive transfer model as a surrogate endpoint to support licensure via AA. During discussions of the VRBPAC recommendation with CHIKV vaccine developers, there was a concern to include fever as a component of the endpoints in NHP studies because fever is not consistently observed in NHPs after CHIKV challenge. CBER agreed to not include fever in the endpoints in NHP studies.
February 24, 2020	End-of-Phase 2 Meeting	CBER conceptually agreed with AA licensure pathway and requested lot-consistency equivalence bounds of (0.67, 1.5) for GMT ratios.
March 29, 2021	Reached agreement with FDA on surrogate end point for use in pivotal Phase 3 trials	CBER accepted an anti-CHIKV μ PRNT ₅₀ titer ≥ 150 as a surrogate endpoint to support licensure via AA. Refer to Non-Clinical Review for details.
July 6, 2021	Breakthrough Therapy Designation (BTD) Granted	BTD was granted based on anti-CHIKV μ PRNT ₅₀ titer ≥ 150 achieved in VLA1553 vaccinated participants.
December 7, 2021	Agreement on initial pediatric study plan (iPSP)	None
April 1, 2022	PreBLA meeting WRO issued	Rolling submission was granted.

3. Chemistry Manufacturing and Controls (CMC)

A. Product Quality

IXCHIQ contains live, attenuated chikungunya virus (generated by reverse genetics from La Réunion strain LR-CHIKV clone LR2006 OPY1). The attenuated virus has a deletion in nsp3, which encodes a component of the viral replicase complex, and replicates less efficiently than the wild-type CHIKV.

Drug Substance (DS)

The vaccine virus is propagated in Vero cells (a continuous line of monkey kidney cells) in media containing amino acids, vitamins, minerals, and fetal bovine serum. The viral harvests are pooled, clarified, and concentrated. The virus is purified by

chromatography and ultracentrifugation. (b) (4)

into the drug product.

Drug Product (DP)

IXCHIQ DP is a sterile and lyophilized powder to be reconstituted before injection with sWFI for a final 0.5 mL single dose presentation. The manufacturing of IXCHIQ DP consists of formulation, sterile filtration, filling, lyophilization, and packaging. During the formulation step, (b) (4) to contain final concentrations of (b) (4) recombinant human albumin (rHA), (b) (4) sucrose, (b) (4) D-sorbitol, (b) (4) L-methionine, (b) (4) magnesium chloride, (b) (4) trisodium citrate di-hydrate and (b) (4) potassium phosphate. After filtration, the DP is filled into Type (b) (4) glass (b) (4) vials and lyophilized. Labeled vials are stored at 2-8°C for up to 24 months from the date of manufacture, which is defined as the date of unloading of the lyophilized vials from the freeze-dryer unit. The vaccine contains no preservatives or adjuvants.

Release Testing

Testing is performed at multiple stages of the manufacturing process to ensure the product meets the pre-defined specifications.

- Release testing for DS includes (b) (4)
- Release testing for final DP (lyophilized product) includes appearance and solubility, (b) (4), identity, infectious virus concentration, rHA content, sucrose content, D-sorbitol content, L-methionine content, residual moisture, bacterial endotoxin, and sterility.
- Release testing for final DP (sWFI) includes appearance of solution, appearance of solution / (b) (4)

The DP is formulated to a targeted concentration of (b) (4) TCID₅₀/dose, which is (b) (4) than the release test titer of (b) (4) TCID₅₀/dose. The upper limit specification of (b) (4) TCID₅₀/dose is consistent with clinical studies that evaluated the safety of the product. Regarding the lower limit specification, the sponsor has set a lower limit specification of (b) (4) TCID₅₀/dose to ensure a titer of 3.0 log₁₀ TCID₅₀/dose at the end of the expiry period of 24 months. Data from clinical studies have shown that the vaccine is immunogenic when administered at (b) (4) TCID₅₀/dose. Therefore, the end of shelf-life specification of 3.0 log₁₀ TCID₅₀/dose is acceptable.

Dating Period:

The dating period for the Lyophilized Antigen Component of Chikungunya Vaccine, Live shall be 24 months from the date of manufacture when stored at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The date of manufacture shall be defined as the date of unloading of the lyophilized vials from the freeze-dryer unit. The dating period for the Sterile Water Diluent Component of Chikungunya Vaccine, Live shall be 60 months from the date of manufacture when stored at (b) (4). Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for the drug substance shall be (b) (4) when stored at (b) (4). The expiration date for the packaged product, Lyophilized Antigen Component plus Sterile Water Diluent Component shall be dependent on the earliest expiration date of any component.

Product-related assays

Valneva validated their TCID₅₀ and (b) (4) assays for (b) (4) DP by assessing the accuracy, precision, linearity, and range. The design and results of the TCID₅₀ (b) (4) validation study and the (b) (4) validation studies for (b) (4) DP were appropriate and met their acceptance criteria. The TCID₅₀ DP validation study design did not allow assessment of the precision at high concentrations and lacked sufficient sample size at high concentrations. While the totality of evidence, including the accuracy results from the DP positive control lot (high concentration lot), indicates the assay is likely to have acceptable performance, CBER recommended Valneva provide additional data in a post-approval supplement to validate performance at high concentrations. In response to CBER recommendation, Valneva committed to submit the requested study in a post-approval supplement.

Valneva submitted stability data from (b) (4) phase 1 DS lot, (b) (4) phase 3 DS lot, and (b) (4) DS consistency lots to support a (b) (4) shelf-life at (b) (4) for DS, and stability data from (b) (4) clinical lot and (b) (4) process qualification lots to support a shelf-life of 24 months at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for DP. The stability results do not suggest a concerning level of risk of lots going out-of-specification within the proposed shelf-lives. Therefore, the proposed shelf-lives are acceptable.

Overall, Valneva has adequately validated their DS potency assays, has adequately validated their DP potency assays up to normal concentrations, has committed to submit additional evidence to validate performance at high concentrations, and has submitted adequate justification for their proposed shelf-lives.

B. Testing Specifications

The analytical method and their qualifications reviewed for the IXCHIQ DS and DP were found to be adequate for their intended use.

C. Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

D. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of IXCHIQ are

listed in the table below. The activities performed and inspectional histories are noted in in the [Table 2](#) below.

Table 2. Manufacturing Facilities for Chikungunya Vaccine, Live-Attenuated (IXCHIQ)

Name/Address	FEI Number	DUNS number	Inspection/Waiver	Justification /Results
Valneva Scotland Ltd. Oakbank Park Road Livingston, Scotland UK EH53 0TG <i>Manufacture of Drug Substance</i>	3005315117	737272380	Waiver	ORA/OBPO Sept. 2022 VAI
(b) (4) <i>Formulation, Filling and Lyophilization of Drug Product</i>	(b) (4)	(b) (4)	Waiver	CBER/DMPQ PAI (b) (4) VAI
Valneva (b) (4) <i>Drug Product Release Testing</i>	(b) (4)	(b) (4)	Waiver	ORA/DFI/IOG (b) (4) VAI (b) (3) (A), (b) (4) satisfactory conclusion; GMP certificate issued
(b) (4) <i>Manufacture of sterile water for injection in prefilled syringes, visual inspection, and release testing</i>	(b) (4)	(b) (4)	Waiver	CDER (b) (4) VAI
(b) (4) 	(b) (4)	(b) (4)	Waiver	CDER/OPMA (b) (4) VAI CDER (b) (4) NAI

Name/Address	FEI Number	DUNS number	Inspection/Waiver	Justification /Results
(b) (4) <i>Visual inspection and release testing of sterile water for injection in pre-filled syringes</i>				
(b) (4) <i>Visual Inspection and release testing of sterile water for injection in pre-filled syringes</i>	(b) (4)	(b) (4)	Waiver	CDER/OPMA (b) (4) VAI ORA/FOR-MPT (b) (4) NAI
(b) (4) <i>Visual inspection of sterile water for injection</i>	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) VAI MRA (b) (4) VAI
(b) (4) <i>Drug product release testing</i>	(b) (4)	(b) (4)	Waiver	ORA/FOR-MPT (b) (4) VAI MRA (b) (4) NAI
(b) (4) <i>Final assembly, primary labeling, and packaging</i>	(b) (4)	(b) (4)	Waiver	ORA/FOR-MPT (b) (4) NAI

Abbreviations: CDER – Center for Drug Evaluation and Research; DFI – Division of Foreign Inspections; DMPQ – Division of Manufacturing and Product Quality; FOR-MPT – Foreign Operations – Medical Products and Tobacco; DS – drug substance; DP – drug product; IOG – International Operations Group; MRA – Mutual Recognition Agreement; OBPO – Office of Biological Products Operations;; OPMA – Office of Pharmaceutical Manufacturing Assessment; OPQO – Office of Pharmaceutical Quality Operations;; ORA – Office of Regulatory Affairs; NAI – No Action Indicated; PAI – Pre Approval Inspection; PLI – Pre-license Inspection; VAI – Voluntary Action Indicated.

Valneva Scotland Ltd:

ORA/OBPO covered the quality system, production system, facilities, and equipment in 2022. In 2009, the firm was licensed by FDA to manufacture inactivated Japanese

Encephalitis (JE) vaccine IXIARO. The (b) (4) clean room suite is the designated area for the commercial manufacture of the Chikungunya Vaccine drug substance. The (b) (4) clean room suite is a dedicated area for multi-virus development, clinical trial manufacture of new vaccine candidates and the commercial manufacture of the SARS-CoV-2 Vaccine (Inactivated, Adsorbed) which has been approved by European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA).

The firm is experienced in cell culture, viral amplification, viral harvest, pooled harvest concentration and filtration. The filtration of the DS is for bioburden control. Single-use materials are used in the commercial manufacture of the Chikungunya Vaccine for the DS.

Based on the acceptable compliance history, process experience and cross-contamination controls, the PLI of this firm was waived.

(b) (4)

An inspection was performed in (b) (4) by DMPQ and the firm was approved for the manufacture of (b) (4) drug product. Coverage of the inspection included facilities, equipment, utilities, and processes associated with the (b) (4) drug product manufacturing. The same facilities are used for the Chikungunya vaccine drug product.

The inspection by DMPQ did not include the lyophilizer used in the manufacturing process for the subject BLA. (b) (3) (A), (b) (4) and covered the lyophilizer in Building (b) (4) Room (b) (4) which is used for Chikungunya vaccine. The report was requested and coverage of the lyophilization process including qualification, cleaning and maintenance was verified. In addition, visual inspection of lyophilized product was covered. The inspection outcome was satisfactory.

Based on acceptable compliance history, process experience, and contamination controls, the PLI of this firm was waived.

Valneva (b) (4)

A limited inspection was conducted in (b) (4) by ORA/DFI/IOG covering laboratory and facility controls and was classified as VAI. (b) (3) (A), (b) (4) The report was requested per the confidentiality agreement between the US and (b) (3) (A), (b) (4) and inspection coverage of the laboratory and quality system was verified. The outcome of the inspection was satisfactory and a PLI may be waived based on this coverage.

(b) (4)

CDER conducted a PLI from (b) (4) for (b) (4) drug product manufacturing. The inspection covered the firm's quality, production, materials, facilities and equipment, and laboratory controls systems. The inspection was classified as VAI and all FDA Form 483 issues were adequately resolved. Filled and stoppered WFI syringes are (b) (4) sterilized.

(b) (4)
 CDER conducted a PLI in (b) (4) and covered quality, facilities and equipment, manufacturing, materials, packaging and labeling. The inspection was limited to (b) (4) drug product manufacture. The inspection was classified as VAI and all FDA Form 483 issues were adequately resolved. CDER conducted a compliance inspection in (b) (4). No 483 was issued and the inspection was classified as NAI.

(b) (4)
 CDER conducted a PLI in (b) (4) and covered the quality, facilities and equipment, materials, production, packaging and labeling and laboratory control systems. The inspection was limited to (b) (4) drug product manufacture. The inspection was classified as VAI and the FDA Form 483 issues were adequately resolved. ORA/FOR-MPT conducted a surveillance inspection in (b) (4). No FDA Form 483 was issued, inspection classified as NAI.

(b) (4)
 ORA/OBPO conducted a surveillance inspection in (b) (4). The inspection covered quality, facilities and equipment, materials, production, packaging and labeling and laboratory control systems. The inspection was classified as VAI and the FDA Form 483 issues were adequately resolved. An MRA inspection was performed in (b) (4). The on-site inspection included the areas of aseptic production lines (b) (4) support areas, and secondary packaging. The inspection was classified as VAI.

(b) (4)
 (b) (4), conducted an inspection under MRA in (b) (4) covering the quality and laboratory systems. The inspection was classified as NAI.

(b) (4)
 ORA/FOR-MPT conducted a PLI in (b) (4). The inspection was limited to the application drug product (b) (4). Labeling and secondary packaging operations were covered. The inspection was classified as NAI.

E. Container/Closure System

Lyophilized DP

The container closure system for the lyophilized DP is listed in [Table 3](#) below.

Table 3. IXCHIQ DP Container Closure Components

Component	Description	Manufacturer	Standards
Vial	(b) (4) injection vial (b) (4) Type ^(b) clear borosilicate glass, 13 mm neck	(b) (4)	(b) (4)
Stopper	13 mm stopper of (b) (4) (Bromobutyl) compound free from natural rubber and natural rubber latex, not containing (b) (4)	(b) (4)	(b) (4)

Component	Description	Manufacturer	Standards
Cap	13 mm Aluminum caps with polypropylene closure (flip-off), color silver-blue.	(b) (4)	(b) (4)

All lots included in the container closure integrity testing (b) (4) met acceptance criteria. The IXCHIQ DP container closure system integrity appears to be appropriately validated.

Sterile Water for Injection (sWFI) Pre-filled Syringe (PFS)

The container closure system components for the sterile WFI PFS are listed in [Table 4](#).

Table 4. Description of Container Closure Components

Component	Description	Supplier
Syringes	1.5 mL syringe: Borosilicate glass, type (b) (4) with Luer cone and groove, compliant with (b) (4)	(b) (4)
Rubber stopper	Bromobutyl rubber, type (b) (4)	(b) (4)
(b) (4)	Consisting of a tip cap, a Luer lock and a tamper-evident seal Tip cap: bromobutyl rubber	(b) (4) (b) (4)

All lots included in the container closure integrity testing (no (b) (4) migration into the interior of the test system) met acceptance criteria. The sterile WFI PFS container closure system appears to be appropriately validated.

F. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

A. Non-Clinical Pharmacology

A passive transfer study was performed in non-human primates (NHPs) using human anti-CHIKV immune sera collected from a Phase 1 study (NCT03382964). In the Phase 1 study, participants received a single dose of a vaccine formulation containing the same attenuated CHIKV used in IXCHIQ. Sera obtained between Days 14 and 180 after vaccination were pooled to generate 8 serum pools representing varying anti-CHIKV neutralizing antibody titers. In the passive transfer study, 40 CHIKV-naïve (b) (4) macaques (b) (4) were administered human anti-CHIKV immune sera from the 8 serum pools (n=5 per group) and 6 CHIKV-naïve (b) (4) macaques were administered non-immune control sera by intravenous injection. One day after the transfers, serum samples were obtained from the macaques to determine pre-challenge anti-CHIKV neutralizing antibody titers by μ PRNT₅₀ assay. Animals were challenged with 100 times the 50% animal infectious dose of wild-type CHIKV strain La Réunion 2006-OPY1, corresponding to 7,000–10,000 Plaque Forming Units. Animal monitoring included assessment of wild-type CHIKV-induced viremia by RT-qPCR and body temperature through 14 and 28 days after challenge, respectively. None of the animals receiving post-vaccination serum pools developed fever after the challenge. Fever and viremia within 7 days post-challenge were detected in all 6 macaques receiving non-immune human sera. Data from the NHP study were analyzed by logistic regression and a μ PRNT₅₀ titer of ≥ 150 was determined to be reasonably likely to predict clinical benefit in the Phase 3 study.

B. Non-Clinical Toxicology

Repeat-Dose Toxicity Study:

In a repeat-dose toxicity study, two groups of rabbits received intramuscular administration of control or a full human dose of VLA1553 (test-article) on Days 1 and 15 followed by a 30-day recovery period. There were no test article-related effects on clinical signs or observation, dermal scoring, body weight, food consumption, body temperature, ophthalmic examination, blood chemistry, coagulation, gross pathology, organ weights and systemic microscopic findings. Slightly higher monocyte, eosinophil and neutrophil counts were reported in animals receiving VLA 1553. Administration of VLA1553 was associated with an acute inflammation that was noted by ~3-5-fold rise in C-reactive protein (CRP) levels compared to control group, after each injection. Microscopic findings at the injection sites demonstrated an increase in mixed cell infiltration, hemorrhage and myofiber necrosis in animals receiving VLA1553. These findings were absent after the 30-day recovery period. Significantly higher anti-antibody titers to CHIKV were reported in animals receiving the vaccine compared to the control group, indicating active delivery of the test article to the animals.

Developmental Assessment and Embryo-Fetal Development Toxicity Study:

In a pre- and post-natal developmental study with an embryo-fetal development toxicity phase conducted in female rats, a full human dose of IXCHIQ (0.5 mL) was administered by intramuscular injection on 2 occasions to determine the effect on female fertility, reproductive performance, and pre- and post-natal development: 14 days prior to mating, and on gestation day 6. No vaccine related adverse effects on fetal development, reproductive performance, and pre- and post-natal development were reported.

5. Clinical Pharmacology

The exact mechanism of protection has not been determined. IXCHIQ elicits CHIKV-specific immune responses. Although the exact mechanism of protection is unknown, immune responses induced by vaccination with IXCHIQ that protect humans against CHIK is thought to be mediated by CHIKV-specific neutralizing antibodies.

6. Clinical/Statistical

A. Clinical Program

The BLA included data from three clinical studies evaluating the safety and immunogenicity of VLA1553: a Phase 1 dose escalation study (VLA1553-101), a Phase 3 pivotal effectiveness study (VLA1553-301), and a Phase 3 lot-to-lot consistency study (VLA1553-302); hereafter referred to as Study 101, Study 301, and Study 302, respectively ([Table 5](#)). Immunogenicity data from the two Phase 3 studies were analyzed separately and pooled in integrated summary of effectiveness (ISE) analyses. Study 101 differed from the Phase 3 studies in the immune assay used to assess seroresponse and in the doses and formulation of VLA1553. Therefore, immunogenicity data from Study 101 were not included in the ISE. As all three studies had similar study populations, definitions of adverse events (AEs), adverse event collection tools, duration of follow-up, and safety data from the three studies were pooled in integrated summary of safety (ISS) analyses.

Table 5. Clinical Trials That Support the Application

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

Study ID	Study 101	Study 301	Study 302
Treatment dose	Low: 3.2×10^3 TCID ₅₀ in 0.1 mL Medium: 3.2×10^4 TCID ₅₀ in 1 mL High: 3.2×10^5 TCID ₅₀ in 1 mL	1×10^4 TCID ₅₀ in 0.5 mL placebo in 0.5 mL	1×10^4 TCID ₅₀ in 0.5 mL Lot 1, Lot 2, or Lot 3
Primary endpoint	Safety	Percentage of participants with a seroresponse titer μ PRNT ₅₀ ≥ 150 at 28 days postvaccination	Geometric mean titer of CHIKV-specific neutralizing antibodies at 28 days postvaccination
Follow-up duration	12- or 13-months follow-up after initial dose	6 months	6 months

Source: Adapted from STN125777, VLA1553-301 Clinical Study Report, Module 5.2, Tabular Listing of all Clinical Studies; and VLA1553-302 CSR

*Participants in low and medium dose groups in Study 101 also received a high dose of VLA1553 at Month 12, and 50% participants in the high dose group received a second high dose at Month 6 and the other 50% participants received a second high dose at Month 12.

Abbreviations: NCT ID, National Clinical Trials Identifier; IM, intramuscular; TCID₅₀, median tissue culture infectious dose; μ PRNT₅₀, 50% plaque reduction in a micro-plaque reduction neutralization test.

In the pivotal trial Study 301, adults ≥ 18 years of age were enrolled at 43 sites in the United States (U.S.) and randomized 3:1 to VLA1553 or placebo. The primary immunogenicity endpoint was a CHIKV-specific neutralizing antibody titer ≥ 150 as determined by μ PRNT₅₀ at 28 days postvaccination. The anti-CHIKV titer of ≥ 150 was selected based on experiments in a non-human primate (NHP) adoptive transfer model, in which the quantity of human anti-CHIKV immune sera needed to prevent viremia in the NHPs following wild-type CHIKV challenge was determined. The prevention of viremia following adoptive transfer of anti-CHIKV immune sera and subsequent wild-type CHIKV challenge supports the use of the anti-CHIKV titer as a surrogate endpoint that is reasonably likely to predict a clinical benefit and serves as the basis for approval of the vaccine under the accelerated approval program. All participants in the Per-Protocol (PP) population had a μ PRNT₅₀ titer < 20 at baseline. At Day 29, 98.9% (263/266) participants in the VLA1553 group had a CHIKV antibody titer ≥ 150 compared with no participants in the placebo group. The results met the pre-specified success criterion of a lower bound (LB) of the 95% confidence interval (CI) of $> 70\%$. Sensitivity analyses demonstrated that different thresholds for baseline serostatus or different visit windows did not impact immunogenicity outcomes.

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

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

The ISE (VLA1553 recipients=655; placebo recipients=103) showed similar seroresponse rates at 28 days postvaccination among the pooled populations compared with seroresponse rates reported from Study 301.

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

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

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

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

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

exposure to CHIKV; (2) inclusion of information on the risk of severe or prolonged CHIK-like adverse reactions in Section 5 (Warnings and Precautions) of the Prescribing Information; (3) enhanced postmarketing surveillance to include expedited reporting (arthritis/arthralgia, cardiac events, and spontaneous abortion), a summary and analysis in periodic safety reports, and dedicated AE questionnaires; and (4) a PMR to evaluate severe CHIK-like adverse reactions (including typical and atypical presentations and cases that result in hospitalization) and prolonged arthralgia in approximately 10,000 individuals who receive VLA1553 compared with individuals in the control group in an individual-level randomized, observer-blind, controlled trial conducted across multiple centers in an endemic country (see [Recommendation for Postmarketing Activities](#), below).

B. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for three domestic clinical investigator (CI) sites participating in the conduct of study Protocol VLA1553-301. The inspections did not reveal significant problems impacting the data submitted in support of this original BLA.

C. Pediatrics

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

D. Other Special Populations

Human Reproduction and Pregnancy Data

Eighteen pregnancies were recorded for female participants, including 15 pregnancies in Study 301 (13 in the VLA1553 group and two in the placebo group) and three pregnancies in Study 302. There was no report of pregnancy in Study 101. The pregnancy outcomes for the placebo recipients included delivery of a full-term infant and a pregnancy outcome lost to follow-up. In the VLA 1553 group, 62.5% of participants who became pregnant had full term infants, 6.2% were lost to follow-up and 31.3% reported spontaneous abortion, which were reported as SAEs. Spontaneous abortions were not found to be related to the vaccine. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data available from clinical trials with IXCHIQ are insufficient to establish the presence or absence of vaccine-associated risk during pregnancy.

Vertical transmission of wild-type CHIKV to neonates from pregnant individuals with viremia at delivery is common and can cause severe, potentially fatal CHIKV disease in neonates as described above. Decisions to administer IXCHIQ during pregnancy should take into consideration the individual's risk of exposure to wild-type CHIKV, gestational age, and risks to the fetus or neonate from vertical transmission of wild-type CHIKV. A postmarketing commitment (PMC) study is warranted to further address the concern of potential adverse pregnancy outcomes.

i) Use During Lactation

No data available.

ii) Immunocompromised Individuals

IXCHIQ is contraindicated in individuals who are immunodeficient or immunosuppressed 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).

iii) Geriatric Use:

Of the total number of participants in clinical studies of IXCHIQ, 9.6% (n=346) were 65 years of age and older, while 1.6% (n=59) were 75 and older. [See Adverse Reactions (6.1) and Clinical Studies (14)]. In Study 1, no overall difference in effectiveness was observed between participants 65 years of age and older and younger participants. Study 1 did not include sufficient numbers of participants 65 years of age and older to determine if there was an overall difference in safety between these participants and younger participants.

7. Safety and Pharmacovigilance

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

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

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

A summary of the sponsor's pharmacovigilance plan (PVP) is provided in [Table 6](#) below. The sponsor will perform routine pharmacovigilance for all adverse events per the requirements of 21 CFR 600.80.

Table 6. Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Identified	Chikungunya-like adverse reactions, including vaccine associated arthralgia	<ul style="list-style-type: none"> • Follow-up by dedicated Questionnaire (vaccine associated arthralgia/arthritis). • Spontaneous reports of Chikungunya-like adverse reactions, including vaccine associated arthralgia will be submitted as expedited reports (i.e., submission of 15-day reports) to VAERS for three years post-licensure, regardless of label status or seriousness. • Summary and analysis of Chikungunya-like adverse reactions, including vaccine-associated arthralgia (including prolonged arthralgia and arthritis) will be included in the PSURs/PAERs for both interval and cumulative data. • Postmarketing safety study.
Potential	Leukopenia, especially neutropenia	<ul style="list-style-type: none"> • Follow-up by dedicated Questionnaire.
Potential	Cardiac events	<ul style="list-style-type: none"> • Follow-up by dedicated Questionnaire. • Spontaneous reports of cardiac adverse events, including atrial fibrillation, will be submitted as expedited reports (i.e., submission of 15-day reports) to VAERS, regardless of label status or seriousness, for three years post-licensure. • Summary and analysis of all reports of spontaneous cardiac adverse events (including atrial fibrillation) will be included in the periodic safety reports for interval and cumulative data.
Missing	Safety in pregnant and breastfeeding women	<ul style="list-style-type: none"> • Postmarketing Safety Study. • Pregnancy questionnaire. • Spontaneous reports of spontaneous abortion will be submitted to VAERS as expedited reports (i.e., submission of 15-day reports), regardless of label status or seriousness, for three years post-licensure. • Company assessment based on interval and cumulative data, including a summary and analysis of safety in pregnancy, will be included in the periodic safety reports.
Missing	Safety in frail patients with acute or progressive, unstable, or uncontrolled clinical conditions, e.g., cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions	<ul style="list-style-type: none"> • Routine pharmacovigilance. • Data collected in Postmarketing Safety Study.
Missing	Safety in patients with autoimmune or inflammatory disorders	<ul style="list-style-type: none"> • Routine pharmacovigilance. • Data collected in Postmarketing Safety Study.

Type of Concern	Safety Concern	Proposed Action
Missing	Interaction with other vaccines	<ul style="list-style-type: none"> • Routine pharmacovigilance. • Data collected in Postmarketing Safety Study.
Missing	Long-Term Safety Data	<ul style="list-style-type: none"> • Safety data collected in Study VLA1553-303 six months to two years following immunization with IXCHIQ and adolescents' study VLA1553-321 in the endemic country Brazil (12 months follow up). • Data collected in Postmarketing Safety Study.

8. Labeling

The proposed proprietary name, IXCHIQ, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on January 26, 2023, and was found to be acceptable. CBER communicated the acceptability of the proprietary name to the applicant on March 10, 2023.

Valneva submitted a draft package insert (PI), carton and container labels for both vial and syringe in the last BLA roll (125777/0.3) December 22, 2022. No separate patient package insert (PPI) was submitted. APLB reviewed the PI, PPI, package, and container labels and found them acceptable from a promotional and comprehension perspective. The regulatory project managers on file in conjunction with the assigned consumer safety officer also reviewed the Carton and Container labels and found them to be acceptable.

During the review cycle, Valneva submitted a linear barcode exemption request in response to an information request (IR) inquiring about the absence of linear barcodes on the vial and syringe labels. The linear barcode exemption request was granted. Key labeling recommendations in the PI as an outcome of the benefit-risk analysis include:

i) Indication Statement:

Limiting the indication to individuals who are at increased risk of CHIKV exposure.

ii) Warnings and Precautions:

- Inclusion of “Severe or Prolonged CHIK-like Adverse Reactions” in individuals vaccinated with IXCHIQ.
- Potential for Vertical Transmission of Vaccine Virus and Fetal/Neonatal Adverse Reactions
- Syncope

iii) Contraindications

- Immunocompromised individuals
- Individuals with history of severe allergic reactions (e.g., anaphylaxis) to any component of IXCHIQ

9. Advisory Committee Meeting

The application was not referred to the Vaccines and Related Biological Products Advisory Committee since the review of information submitted in the BLA, including the

clinical study design and trial results, did not raise concerns or controversial issues which would have benefitted from advisory committee discussion.

10. Other Relevant Regulatory Issues

The application was granted priority review. Valneva requested a tropical disease-priority review voucher. The request met the eligibility criteria, and a tropical-disease priority review voucher was granted. A major amendment acknowledgement letter categorizing the submission (received on July 31, 2023) that contained a substantial amount of new information on PMR studies (VLA 1553-402 and VLA1553-404), not previously submitted for review by the Agency, was issued on August 11, 2023. However, review of STN 125777 was completed prior to the PDUFA action due date of November 21, 2023.

11. Recommendations and Benefit-Risk Assessment

A. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of IXCHIQ under accelerated approval for the labeled indication and usage.

B. Benefit-Risk Assessment

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

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

The Phase 3 immunogenicity trial demonstrated that over 98% participants achieved an anti-CHIKV neutralizing antibody titer ≥ 150 at 28 days after a single dose of VLA1553 and the anti-CHIKV neutralizing antibody response persisted for at least 6 months after the single-dose vaccination, indicating that vaccination with VLA1553 is reasonably likely to prevent disease caused by CHIKV infection. Some of the residual uncertainty of relying upon anti-CHIKV neutralizing antibody responses as a surrogate reasonably

likely to predict clinical benefit come from nonclinical studies in a NHP model. Administration of anti-CHIKV neutralizing antibodies completely prevented CHIKV viremia in plasma but did not reduce CHIKV loads (compared to the control group) in arm muscles, joints spleen and draining lymph nodes ([Pal, 2014](#)). The PMR confirmatory studies are designed to address this uncertainty.

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

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

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

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

C. Recommendation for Postmarketing Activities

Confirmatory Clinical Studies to Verify Clinical Benefit (PMRs)

In accordance with the accelerated approval regulations, adequate and well-controlled confirmatory studies to verify and describe clinical benefit must be conducted with due

diligence to fulfill the regulatory requirements. The Applicant submitted a test-negative case control observational study protocol VLA1553-402 to verify clinical benefit. To address concerns associated with potential limitations of the test-negative study design, the Applicant submitted a concept protocol upon CBER request for a randomized controlled PMR study to verify clinical benefit (VLA1553-404), which will also serve to further address the safety concern of CHIK-like illness associated with the vaccine. The totality of the evidence from these studies will inform our postmarketing assessment of benefit-risk.

- 1) An observational study with a test-negative, case-control design to assess the effectiveness of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in the adolescent and adult population (12 years of age and older) in endemic areas of Brazil.

Final Protocol Submission: May 31, 2025

Study Implementation Readiness Verification Submission: June 30, 2025

Study Initiation: March 1, 2026

Study/Trial Completion: March 1, 2028

Final Report Submission: September 30, 2028

Study VLA1553-402 is an observational Test Negative Design (TND) study to estimate the vaccine effectiveness of VLA1553 in Brazil, to be conducted following VLA1553 vaccine licensure in the country. This study will be initiated after implementation of the vaccine (VLA1553) in selected municipalities as part of a pilot vaccination program, once vaccination coverage reaches 20% of the eligible population in these municipalities, and an increase in CHIKV transmission has been detected through CHIKV routine epidemiological surveillance in these areas. We anticipate that this study design will allow collection of data to confirm efficacy through an adjusted comparison of the VLA1553 vaccination rates between cases and controls.

- 2) A pragmatic randomized controlled trial to assess the effectiveness and safety of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in adults in an endemic country.

Final Protocol Submission: September 30, 2024

Study Implementation Readiness Verification Submission: June 30, 2025

Study Initiation: October 1, 2025

Study/Trial Completion: July 31, 2029

Final Report Submission: December 31, 2029

Study VLA1553-404 is a pragmatic randomized controlled trial assessing a primary endpoint of vaccine effectiveness (VE) against symptomatic virologically confirmed CHIKV disease in vaccine recipients compared to controls (individuals receiving either placebo or another vaccine such as tetanus vaccine). Secondary objectives include assessment of VE against chronic and severe CHIKV disease and assessment of safety, in particular the characterization of the frequency and severity of CHIK-like adverse reactions. We anticipate that this randomized controlled design will allow collection of rigorous data to confirm efficacy.

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

Pediatric Studies

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

- 3) Deferred pediatric study under PREA (VLA1553-321) to evaluate safety and immunogenicity of IXCHIQ in adolescents 12 to <18 years of age.
Final Protocol Submission: October 31, 2020 (submitted)
Study Completion Date: February 29, 2024
Final Report Submission: November 30, 2024
- 4) Deferred pediatric study under PREA (VLA1553-221) to evaluate dose-finding safety and immunogenicity of IXCHIQ in children 1 to <12 years of age.
Final Protocol Submission: June 30, 2023 (submitted)
Study Completion Date: July 30, 2025
Final Report Submission: January 31, 2026
- 5) Deferred pediatric study under PREA (VLA1553-322) to evaluate safety and immunogenicity of IXCHIQ in children 1 to <12 years of age.
Final Protocol Submission: May 31, 2025
Study Completion Date: December 31, 2026
Final Report Submission: June 30, 2027
- 6) Deferred pediatric study under PREA (VLA1553-222) to evaluate dose-finding safety and immunogenicity of IXCHIQ in neonates and infants <1 year of age.
Final Protocol Submission: January 31, 2027
Study Completion Date: August 31, 2028
Final Report Submission: February 28, 2029
- 7) Deferred pediatric study (VLA1553-323) to evaluate safety and immunogenicity of IXCHIQ in neonates and infants <1 year of age.
Final Protocol Submission: September 30, 2028
Study Completion Date: April 30, 2030
Final Report Submission: October 31, 2030

Postmarketing Requirements Under Section 505(o)

- 8) A pragmatic randomized controlled trial to assess the effectiveness and safety of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in adults and possibly adolescents in an endemic country. This individual-level randomized, observer-blind, controlled trial conducted across multiple centers in an endemic country will evaluate severe chikungunya-like adverse reactions (including typical and atypical

presentations and cases that result in hospitalization) and prolonged arthralgia in at least 10,000 individuals vaccinated with IXCHIQ.

Final Protocol Submission: September 30, 2024

Study Implementation Readiness Verification Submission: June 30, 2025

Study Initiation: October 1, 2025

Study/Trial Completion: July 31, 2029

Final Report Submission: December 31, 2029

This study (VLA1553-404) will also serve as the accelerated approval confirmatory study #2 above.

Postmarketing Commitment Study

Since there was an imbalance in spontaneous abortions between VLA1553 and placebo groups, the review team recommends postmarketing commitment studies for pregnancy outcomes to address the potential safety concerns. The Applicant proposed to conduct an observational study (VLA1553-403) as follows:

- 9) Observational study to evaluate the safety of live-attenuated chikungunya virus vaccine (IXCHIQ) in pregnant women aged 18-45 years exposed to the vaccine. This prospective, observational registry study of pregnant women residing in Brazil will compare maternal and infant outcomes of at least 90 women exposed to IXCHIQ prior to or during pregnancy to a group of pregnant women who have not been exposed to IXCHIQ.

Final protocol submission: February 28, 2024

Study completion: September 30, 2027

Final Report Submission: December 31, 2027

Please refer to the review memo of the PMC by the OBPV reviewers.

12. References

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