Our STN: BL 125777/0

ACCELERATED BLA APPROVAL

Valneva Austria GmbH
Attention: John Kanaras
Valneva USA, Inc.
4550 Montgomery Avenue
Bethesda, MD 20814

November 9, 2023

Dear Mr. Kanaras:

Please refer to your Biologics License Application (BLA) received December 22, 2022, under section 351(a) of the Public Health Service Act (PHS Act) for Chikungunya Vaccine, Live.

LICENSING

Effective this date, we have approved your BLA for Chikungunya Vaccine, Live, under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and the regulations for accelerated approval, 21 CFR 601.41. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Chikungunya Vaccine, Live under your existing Department of Health and Human Services U.S. License No. 1909. Chikungunya Vaccine, Live is indicated for active immunization for the prevention of disease caused by chikungunya virus in individuals 18 years of age and older who are at increased risk of exposure to chikungunya virus.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT03382964, NCT04546724, NCT04786444.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval statutory provisions and regulations we may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical studies establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. This approval requires you to study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Approval under these statutory provisions and regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as prevention of disease caused by chikungunya virus.

Accelerated Approval Required Studies

We remind you of your postmarketing requirements (PMRs) specified in your submission under amendment 94 and 113, dated October 20, 2023, and November 9, 2023, respectively.

1. To conduct 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

2. To conduct 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

We expect you to complete design, implementation readiness verification, initiation, accrual, completion, and reporting of these studies within the framework described in your submission under amendment 94, dated October 20, 2023.

Please submit the protocols to your IND 17854, with a cross-reference letter to this BLA, STN BL 125777 explaining that these protocols were submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

You must conduct these studies with due diligence. If required postmarketing studies fail to verify that clinical benefit is conferred by Chikungunya Vaccine, Live, or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval.

You must submit reports of the progress of each study listed above as required under section 506(c) of the FDCA to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c) of the FDCA. The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval. Submit the subsequent 180-day report with your application's annual status report. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.

Your 180-day report must include the information listed in 21 CFR 601.70(b). FDA recommends that you use form FDA 3989 PMR/PMC Annual Status Report for Drugs and Biologics, to submit your 180-day reports. Form FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

180-day reports, including both the standalone 180-day report submitted 180 days after the date of approval and the 180-day report submitted with your annual status report, must be clearly designated as **180-Day AA PMR Progress Report.**

FDA will consider the submission of your annual status report under section 506B(a)(1) of the FDCA and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year, to satisfy the periodic reporting requirement under section 506B(a)(2) of the FDCA. You are also required to submit information related to your confirmatory studies as part of your annual reporting requirement under section 506B(a)(1) of the FDCA until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Postmarketing Requirements and 506B Commitments are fulfilled or released.

Submit final study reports as a supplement to this BLA, STN BL 125777. For administrative purposes, all submissions related to these postmarketing study requirements must be clearly designated as "**Subpart E Postmarketing Study Requirements**."

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Chikungunya Vaccine, Live drug substance at Valneva Scotland Ltd., Oakbank Park Road, Livingston, Scotland, United Kingdom. The final formulated product will be manufactured and filled at (b) (4) (b) (4), and, labeled and packaged at (b) (4). The diluent (Sterile Water Diluent Component) will be manufactured at (b) (4)

You may label your product with the proprietary name IXCHIQ and market it in a carton that contains one single-dose vial of Lyophilized Antigen Component and one single-dose prefilled ungraduated syringe of Sterile Water Diluent Component.

ADVISORY COMMITTEE

We did not refer your application to the Vaccines and Related Biological Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefitted from advisory committee discussion.

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°C ± 3°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 your 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.

COMPARABILITY PROTOCOL

This approval includes comparability protocols as identified below:

For manufacture of Drug Substance:

- Comparability Protocol for manufacture and testing of serum-containing Vero (b) (4) .

For manufacture of Drug Substance and Drug Product:

- Protocol for the preparation and qualification of CHIKV RNA Reference Standard Lots.

Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. In your annual report (21 CFR 601.12(d)), you should report information confirming that the changes meet the requirements specified in your approved comparability protocol. Include the information described in 21 CFR 601.12(d)(3).

FDA LOT RELEASE

Please submit final container samples of the product and each kit component in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on FORM FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations.

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Chikungunya Vaccine, Live, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert and Patient Package Insert submitted under amendment 114, dated November 8, 2023, and the draft carton and container labels submitted under amendment 83, dated September 6, 2023.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert, Patient Package Insert, submitted on November 8, 2023. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on September 6, 2023, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125777 at the time of use and include implementation information on Form FDA 356h.

PROMOTIONAL MATERIALS

Please note that the accelerated approval regulation concerning promotional materials (21 CFR 601.45) stipulates that all advertising and promotional labeling items that you wish to distribute in the first 120 days following approval, must have been received by FDA prior to the approval date. After approval, promotional items intended for dissemination after the first 120 days following approval must be submitted to the FDA at least 30 days prior to the anticipated distribution date. Please submit draft materials with a cover letter noting that the items are for accelerated approval, and an accompanying FORM FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by FORM FDA 2253 (21 CFR 601.12(f)(4)).

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs* at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

For information on the postmarketing safety reporting requirements for combination products as described in 21 CFR 4, Subpart B, and the dates by which combination product applicants must comply with these requirements, please refer to the Postmarketing Safety Reporting for Combination Products webpage available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a tropical disease priority review voucher (PRV), as provided under section 524 of the FDCA. This PRV has been assigned a tracking number, PRV BLA 125777. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a tropical disease PRV.

- The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "**Notification of Intent to Submit an Application with a Tropical Disease Priority Review Voucher**."
- This PRV may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred. When redeeming this PRV, you should refer to this letter as an official record of the voucher.

For additional information regarding the PRV, see FDA's guidance, *Tropical Disease Priority Review Vouchers,* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies, because the product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70

require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

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

Submit the protocols to your IND 17854, with a cross-reference letter to this BLA, STN BL 125777 explaining that these protocols were submitted to the IND.

Submit final study reports to this BLA STN BL 125777. In order for your PREA PMRs to be considered fulfilled, you must submit and receive approval of either an efficacy or a labeling supplement. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated as:

- **Required Pediatric Assessment(s)**

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to

- assess a known serious risk of severe chikungunya-like adverse reactions.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

8. To conduct 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.

This study will also serve as the accelerated approval confirmatory study #2 above.

We acknowledge the timetable you submitted under amendment 94 on October 20, 2023, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: September 30, 2024

Study Implementation Readiness Verification Submission: June 30, 2025

Study Initiation: October 1, 2025

Study Completion: July 31, 2029

Final Report Submission: December 31, 2029

Please submit the protocol to your IND 17854, with a cross-reference letter to this BLA, STN BL 125777 explaining that this protocol was submitted to the IND. Please refer to the sequential number for the study and the submission number as shown in this letter.

Please submit the final study report to the BLA. If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement to this BLA, STN BL 125777. For administrative purposes, all submissions related to this postmarketing study required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence Status Update under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;

- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your correspondence of November 3, 2023, as outlined below:

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 submit the clinical protocol to your IND 17854, and a cross-reference letter to this BLA, STN BL 125777 explaining that this protocol was submitted to the IND.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Managers for this application.

Sincerely,

David C. Kaslow, MD
Director
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research