

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA ADDENDUM

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To: Sudhakar Agnihothram, B. Pharm., Ph.D.
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Through: Kerry Welsh, M.D., Ph.D.
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OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Sponsor: Valneva Austria GmbH

Product: Chikungunya Vaccine, Live-Attenuated
(IXCHIQ)

Application Type / Number BLA 125777/0

Proposed Indication Active immunization for the prevention of
disease caused by Chikungunya virus in
individuals 18 years and above

Submission Date: December 22, 2022

Action Due Date: November 22, 2023

OVERVIEW & ASSESSMENT

After DPV finalized its pharmacovigilance original BLA memorandum for the IXCHIQ prevention of disease caused by Chikungunya indication (STN 125777/0), a new safety issue of “Chikungunya-like illness” was identified from the clinical trial data. In a clinical trial, 361 (11.7%) of 3,082 IXCHIQ recipients and 6 (0.6%) of 1,033 placebo recipients reported Chikungunya-like illness. Severe Chikungunya-like illness that prevents daily activity and requires medical intervention was reported by 47 (1.5%) IXCHIQ recipients and no placebo recipients. Two of the 3,082 IXCHIQ recipients experienced prolonged Chikungunya-like illness: one participant with severe arthralgia and back pain that lasted for at least 51 days after vaccination, and the other with polyarthralgia and nodular swelling of joints that lasted for 6 months after vaccination. For two of the IXCHIQ recipients, the Chikungunya-like illness was serious, resulting in hospitalization; both serious adverse events were considered causally related to vaccination. Per FDA request, the sponsor revised their accelerated approval draft protocol (VLA 1553-404) entitled “Trial on the Effectiveness and Safety of the VLA1553 Vaccine Against Chikungunya Virus Disease in an Endemic Country: A Pragmatic Randomized Controlled Trial” to evaluate Chikungunya-like illness.

Reviewer comment: The sponsor submitted a draft study protocol to evaluate the serious risk of Chikungunya-like illness. As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the Important Identified Risk of Chikungunya-like illness.

The CBER Biologics Effectiveness and Safety (BEST) Program is not sufficient to assess the serious risk of Chikungunya-like illness following vaccination with IXCHIQ in lieu of a post-marketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). As per the 2019 draft guidance, [Postmarketing Studies and Clinical Trials—Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry](#), this determination “takes into consideration multiple factors, some of which may be uncertain at the time of the sufficiency assessment (e.g., the future uptake of a newly approved drug, subsequent exposure of patients to a drug).” At this time, the data sources in the CBER BEST Program are not sufficient to identify the safety outcomes due to the available data sources in BEST system do not support a randomized controlled trial study design with patient level data collection. Of note, the BEST Program does not include foreign data sources. Should there be future use of the product outside U.S., then the sponsor may access foreign data sources in addition to U.S. data sources, for assessment of such rare serious risks. A finding of insufficiency based on uncertainty at the time of approval is consistent with current Guidance.

Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA. Therefore, if IXCHIQ is

approved, the sponsor will be required to conduct a PMR safety study under FDAAA Title IX to characterize the Important Identified Risk of Chikungunya-like illness.

DPV presented the PMR to the CBER Safety Working Group (SWG) on September 28, 2023 and the sponsor was notified that the post-marketing study will be a PMR.

In addition to the PMR study, DPV has additional pharmacovigilance recommendations that include reclassifying “vaccine associated arthralgia” from an *Important Potential Risk* to include “Chikungunya-like illness including vaccine associated arthralgia” as an *Important Identified Risk*. DPV requested enhanced pharmacovigilance activities for “Chikungunya-like illness”, i.e., submit all spontaneous reports of “Chikungunya-like illness”, including prolonged cases as expedited reports (i.e., submission of 15-day reports) to VAERS, regardless of label status or seriousness for three years post-approval, and include a summary and analysis of all reports of “Chikungunya-like illness” in the periodic safety reports for interval and cumulative data. The sponsor was requested to include the study protocol VLA 1553-404 that further evaluates the risk of Chikungunya-like illness as one of the pharmacovigilance actions for Chikungunya-like illness. DPV also requested that the sponsor include the prospective safety cohort study (Annex 8.10) within the observational study protocol VLA 1553-402 “Effectiveness of VLA1553 vaccine against chikungunya virus disease in the adolescent and adult population in endemic areas of Brazil” in the PVP, as one of the pharmacovigilance activities for safety (see below for description of this study).

Reviewer comment: The sponsor submitted a revised PVP that incorporates the above request changes to STN 125777/0.101. A summary of the revised PVP is provided in the Appendix.

Prospective safety cohort study

The sponsor outlined the following prospective safety cohort study parameters in the observational study protocol VLA1553-402 Annex 8.10 on pages 74-75 under STN 125777/0.88 submitted on September 28, 2023 and further updated under STN125777/0.109:

Study Design

This is a prospective observational multi-center, non-interventional, post-marketing study to evaluate the safety of the live-attenuated CHIKV vaccine (VLA1553) using primary data collection.

Study Objectives

Primary:

- To estimate the incidence of medically attended adverse events of special interest (AESIs), including laboratory-confirmed infection with CHIKV following the administration of the live-attenuated CHIKV vaccine (VLA1553), in adults aged 18 years.

Secondary:

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

Sample Size and Study Duration

The sponsor estimates a sample size of 5,000 subjects. Planned overall duration of 1.5-2 years from approval of the vaccine in Brazil.

Reviewer comment: The safety study protocol described within VLA1553-402 Annex 8.10 is a similar study design to the voluntary safety study of U.S. travelers entitled "A post-marketing safety study of live-attenuated chikungunya virus vaccine (VLA1553) routinely administered in adults aged 18 years and above in the U.S. planning to travel to endemic areas" (please see the Pharmacovigilance Original BLA Memorandum for details). This safety protocol will be considered a voluntary safety analysis.

AESI Definition: The sponsor added the AESI definition to Annex 8.10 in protocol 402 under STN 125777/0.109 submitted on November 7, 2023. AESIs, i.e., Chikungunya-like adverse reactions, are defined as: 1.) Fever ($\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$) AND 2.) One or more of any of the following: (poly)arthralgia or (poly)arthritis, back pain, neurological symptoms (e.g., confusion, optic neuritis, meningoencephalitis, or polyneuropathy), cardiac symptoms (e.g., myocarditis), rash, polyadenopathies; AND 3.) Occurring within 30 days after the vaccination, regardless of the order of their onset and duration. DPV defers to the OVR clinical team for acceptability of this AESI definition.

Pregnancy PMC study

The sponsor updated the milestone dates for VLA1553-403 study entitled "*Observational study to evaluate the safety of live attenuated chikungunya virus vaccine (VLA1553) in pregnant women aged 18-45 years exposed to the vaccine*" from the Final Protocol Submission date of November 30, 2023 to February 28, 2024 (response to IR submitted to STN 125777/0.101). The sponsor provided a Study Completion of September 30, 2027 and Final Report Submission date of December 31, 2027

(response to IR submitted to STN 125777/0.103). Clarifications on study P403 milestones in the PVP were addressed in STN 125777/0.107 and STN 125777/0.109 and the study milestones (PVP submitted to STN 125777/0.109) are acceptable.

DPV Recommendation

Should IXCHIQ be approved for the active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years and above, the updated PVP (version 0.9, dated November 7, 2023), submitted under STN 125777/0.109, is acceptable. DPV will review the final protocol of the pregnancy PMC study upon submission.

**APPENDIX
SPONSOR'S PHARMACOVIGILANCE PLAN**

The sponsor will perform routine pharmacovigilance for all adverse events per the requirements of 21 CFR 600.80. A summary of the sponsor's PVP¹ for IXCHIQ is displayed in the table below.

Table 1 Sponsor's 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 reactions, including vaccine-associated arthralgia (including prolonged arthralgia and arthritis) will be included in the PSURs/PAERs for both interval and cumulative data. • Post-marketing 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

¹ STN 125777/0.101, submitted on 11/2/23, Risk Management Plan, Version 0.7; STN 125777/0.107 submitted on 11/6/23, Version 0.8; STN 125777/0.109 submitted on 11/7/23, Version 0.9

		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"> • Post-marketing 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 Post-marketing Safety Study.
Missing	Safety in patients with autoimmune or inflammatory disorders	<ul style="list-style-type: none"> • Routine pharmacovigilance. • Data collected in Post-marketing Safety Study.
Missing	Interaction with other vaccines	<ul style="list-style-type: none"> • Routine pharmacovigilance. • Data collected in Post-marketing 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 Post-marketing Safety Study.