Summary Basis for Regulatory Action

Date:	February 14, 2025
From:	Konstantin Virnik, Ph.D. Review Committee Chair, OVRR/DRMRR
BLA STN:	125820
Applicant:	Bavarian Nordic A/S
Submission Receipt Date:	June 17, 2024
Action Due Date:	February 14, 2025
Proper Name:	Chikungunya Vaccine, Recombinant
Proprietary Name:	VIMKUNYA
Indication:	VIMKUNYA is a vaccine indicated for the prevention of disease caused by chikungunya virus in individuals 12 years of age and older.

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

Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ, Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	 Shufeng Liu, OVRR/DVP Wei Wang, OCBQ/DMPQ Wei Wang, OCBQ/DMPQ Jared Greenleaf, OCBQ/DMPQ Neetu Dahiya, OCBQ/DMPQ Jie He, OCBQ/DMPQ Sharmila Shrestha, OCBQ/DMPQ Shufeng Liu, OVRR/DVP Robin Levis, OVRR/DVP Marie Anderson, OCBQ/DBSQC Karla Garcia, OCBQ/DBSQC Hsiaoling (Charlene) Wang, OCBQ/DBSQC Alicia Howard, OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety • Pharmacovigilance review (OBPV) • BIMO	 Judith Anesi, OVRR/DCTR Sixun Yang, OVRR/DCTR Stephanie Ajuzie, OBPV/DPV Diane Gubernot, OBPV/DABRA Marisabel Rodriguez, OBPV/DABRA Malcolm Nasirah, OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data (OBPV/DB)	 Ross Peterson, OBPV/DB Yuan Hu, OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology/ Developmental toxicology (Product Office) • Animal pharmacology	 Claudia Wrzesinski, OVRR/DCTR Shufeng Liu, OVRR/DVP
Labeling • Promotional (OCBQ/APLB) • Carton and Container	 Alisa Gilliard, OCBQ/DCM/APLB Daphne Stewart, OVRR/DRMRR Ching Yim-Banzuelo, OVRR/DRMRR
Other Reviews: • Regulatory Project Management • PNR (OCBQ/APLB) • Data integrity • Devices • DHT • Data Analyst • PMC/PMR • Consults	 Georgeta Crivat, OVRR/DRMRR Vera Stupina, OVRR/DRMRR Katherine Berkhousen, OVRR/DRMRR Oluchi Elekwachi, OCBQ/DCM/APLB Brenda Baldwin, OVRR/DRMRR Andrea Gray, ORO/DROP Jessica Zhou, OBPV/DABRA Elin Cho, OBPV/DB Helen Gemignani Jiang (Jessica) Hu, OBPV/DB Adrienne Hornatko-Munoz /PREA Coordinator
Advisory Committee Summary	No advisory committee meeting was held

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1. Introduction

Bavarian Nordic A/S (the Applicant) submitted Biologics License Application (BLA) STN BL 125820 for licensure of the chikungunya vaccine VIMKUNYA (Chikungunya Vaccine, Recombinant) via the accelerated approval pathway (21 CFR Part 601 Subpart E). VIMKUNYA is also referred to as "PXVX0317" throughout this document. VIMKUNYA contains purified virus-like particles (VLPs) containing three recombinant chikungunya virus (CHIKV) structural proteins derived from CHIKV Senegal strain 37997: Capsid (C), Envelope 1 (E1), and Envelope 2 (E2). These proteins are expressed in Human Embryonic Kidney (HEK) cells and self-assemble to form spherical, highly ordered VLPs. VIMKUNYA is formulated as a sterile aqueous buffered injectable suspension for intramuscular (IM) use. Each 0.8-mL dose contains approximately 40 µg of CHIKV VLPs adsorbed on aluminum hydroxide adjuvant (approximately 300 µg aluminum) and stabilized with formulation buffer. The vaccine is supplied in a single dose 1-mL pre-filled glass syringe with 0.8-mL deliverable dose volume. The dating period for VIMKUNYA is 36 months from the date of manufacture when stored at 2 - 8°C.

VIMKUNYA is a vaccine indicated for the prevention of disease caused by CHIKV in individuals 12 years of age and older. The indication is being approved using an accelerated approval pathway based on an evaluation of anti-CHIKV serum neutralizing antibody (SNA) response (determined by a luciferase-based CHIKV neutralization assay) serving as a surrogate endpoint that is reasonably likely to predict a clinical benefit in two Phase 3 studies (study EBSI-CV-317-004 in individuals 12 to <65 years of age and study EBSI-CV-317-005 in adults ≥65 years of age). Specifically, the primary immunogenicity endpoint for these studies was an anti-CHIKV SNA titer ≥100 at Day 22 post-vaccination. The anti-CHIKV SNA titer of ≥100 was selected based on logistic regression analysis of data from a nonhuman primate (NHP) study, in which the quantity of human anti-CHIKV immune sera needed to prevent viremia in the NHP following wild-type CHIKV challenge was determined. The anti-CHIKV SNA titer measured by the neutralization assay was expressed as the serum dilution achieving 80% CHIKV neutralization (NT80).

All participants in the Immunogenicity Evaluable Population (IEP) in study EBSI-CV-317-004 (004) had an anti-CHIKV SNA titer <15 at baseline (no measurable anti-CHIKV SNA). At Day 22, 97.8% of participants in the PXVX0317-vaccinated group and 1.2% of participants in the placebo group had an anti-CHIKV SNA titer ≥100, resulting in a seroresponse rate difference of 96.6% with a 95% confidence interval (CI) of 95.0%, 97.5%. The results met the pre-specified success criterion of a lower bound (LB) of the 95% CI of ≥70%. The results of a nested lot-to-lot consistency substudy in adults 18 to <46 years of age demonstrated that the 95% CIs of the anti-CHIKV geometric mean titer (GMT) ratios between any two lots were within 0.67 and 1.5, which met the pre-specified immunogenicity criteria to demonstrate lot equivalency.

In the second Phase 3 study, study EBSI-CV-317-005 (005), the IEP and primary immunogenicity endpoint were defined the same as in study 004. At Day 22, 87.3% of participants in the PXVX0317-vaccinated group and 1.1% of participants in the placebo group had an anti-CHIKV SNA titer ≥100. This resulted in a seroresponse rate (%)

difference of 86.2% (95% CI: 80.0, 90.3). The results met the pre-specified success criterion of a LB of the 95% CI of ≥70%.

The immunogenicity data from studies 004, 005, and other supportive studies indicate that in the majority of recipients, a single IM injection of VIMKUNYA elicits a seroresponse that is reasonably likely to predict a clinical benefit based on the surrogate endpoint of seroresponse. 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. Bavarian Nordic has agreed to the following postmarketing requirement (PMR) to confirm the efficacy of VIMKUNYA:

PMR #1 (EBSI-CV-317-007): A randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of VIMKUNYA, an adjuvanted chikungunya virus virus-like particle (CHIKV VLP) vaccine for the prevention of chikungunya disease in adolescents (12 to <18 years) and adults (≥18 years).

The safety of PXVX0317 was assessed in 3522 healthy participants ≥12 years of age who received at least one dose of PXVX0317 in five clinical studies conducted in the U.S. In safety analyses from study 004, solicited adverse reactions (ARs) were reported by 38.3% and 27.1% of those who received PXVX0317 and placebo, respectively. In study 005, solicited ARs were reported by 12.2% and 14.0% of those who received PXVX0317 and placebo, respectively. The overall reactogenicity profile of VIMKUNYA is acceptable. Additionally, there was no evidence of an increased incidence of chikungunya-like illness, including in a prospective analysis of new onset or worsening arthralgia that was medically attended, in post hoc analyses of chikungunya-like ARs, and in analyses of arthritis and rash using SMQs. Overall, the safety profile of PXVX0317 is considered favorable with no major concerns that substantively affect the benefit-risk assessment.

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

2. Background

Chikungunya (CHIK) is a mosquito-borne disease caused by CHIKV, an alphavirus first isolated in 1953. Although only one serotype has been described for CHIKV, phylogenetic analyses reveal three distinct CHIKV lineages: West African, Asian, and East/Central/South African (ECSA). The ECSA lineage includes the Indian Ocean lineage 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. CHIKV often causes sudden large outbreaks affecting 33% to 75% of the population in areas where the virus is circulating; up to 97% of infected individuals are symptomatic (CDC, 2022) though estimates vary, with another study showing >80% CHIKV-infected individuals are asymptomatic (Yoon, 2020). Depending on the study

report, approximately 2% to 57% of patients developed chronic or recurrent arthralgia (Suhrbier, 2012). A study in post-epidemic CHIK on Reunion 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), vary in virulence and cross-protective ability in mice and NHPs (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 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 and 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. 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 incapacitating arthritic symptoms that may persist months or years after infection (Simon, 2015; Couderc, 2009; Suhrbier, 2012). Acute illness may lead to death but 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).

CHIKV infection is usually self-limited and characterized mainly by severe joint pain and myalgia. Rare, atypical 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).

On November 9, 2023, IXCHIQ (Chikungunya Vaccine, Live) was approved via accelerated approval for the prevention of disease caused by CHIKV in individuals 18 years of age and older who are at increased risk of exposure to CHIKV. Immunogenicity data from clinical studies indicate that a single intramuscular injection of IXCHIQ induces a seroresponse that is reasonably likely to predict a clinical benefit based on a surrogate endpoint of seroresponse; however, postmarketing studies are needed to confirm clinical benefit. The reactogenicity profile of IXCHIQ was acceptable. The frequency and severity of CHIK-like illness following IXCHIQ administration, including

severe, serious, and/or prolonged events, and atypical presentations such as cardiac events warranted 1) an indication restricted to individuals at increased risk of exposure to CHIKV; 2) inclusion of CHIK-like adverse reactions in Section 5 (Warnings and Precautions); 3) enhanced postmarketing surveillance to include expedited reporting for events of arthritis/arthralgia, cardiac events, and spontaneous abortion, periodic safety reporting, and dedicated AE questionnaires; and 4) a PMR to evaluate severe CHIK-like illness and prolonged arthralgia in a pragmatic, randomized, observer-blind, controlled trial conducted across multiple centers in an endemic country (see Supporting Documents in FDA, 2023).

No CHIK-specific treatments are currently available. Treatment of CHIK is based on supportive care and includes adequate fluid intake and medications for relief of pain during the acute, subacute, and chronic phases of infection.

Clinical development of VIMKUNYA (PXVX0317) was conducted under IND 17998. No previous human experience exists with the product outside of the prelicensure studies submitted in this BLA. VIMKUNYA elicits CHIKV-specific immune responses, however, the exact mechanism of protection has not been determined for this vaccine.

Table 1 summarizes key regulatory activities related to the clinical development program.

Table 1. Regulatory History

Regulatory Events / Milestones	**Date**
Pre-IND meeting	April 12, 2017
IND submission	February 26, 2018
Fast Track designation granted	April 26, 2018
VRBPAC meeting to discuss pathways for development and licensure of Chikungunya vaccines	November 8, 2019
Breakthrough Therapy designation granted	October 16, 2020
Pre-BLA meeting Nonclinical and Clinical CMC	 December 5, 2023 January 5, 2024
BLA 125820/0 submission – Rolling review application Part 1 (Nonclinical) Part 2 (Clinical) Part 3 (CMC)	 April 29, 2024 June 10, 2024 June 17, 2024
BLA filed	August 13, 2024
Mid-Cycle communication	Canceled by Applicant
Late-Cycle meeting	Canceled by Applicant
Action Due Date	February 14, 2025

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

VIMKUNYA, Chikungunya Vaccine, Recombinant, is a sterile injectable suspension for IM use.

Drug Substance (DS)

The active substance of VIMKUNYA contains non-replicating CHIKV VLPs formed by three recombinant CHIKV structural proteins derived from CHIKV Senegal strain 37997: capsid protein C, and two envelope glycoproteins E1, and E2. Both the E1 and E2 (b) (4) The DS is manufactured at BN's (b) (4) (b) (4) facility. To produce VLPs, HEK 293 (b) (4) cells (b) (4) are transfected with an expression plasmid (b) (4) encoding the CHIKV structural polyprotein C-E3-E2-6K-E1. (b) (4)

Bulk Drug Product

The BDP manufacturing process is a continuation of the DS manufacturing process at the BN (b) (4) facility. As manufacturing of the DS and the BDP is performed at the same site, the DS is not exposed to shipping conditions. VIMKUNYA BDP is produced by (b) (4)

Drug Product (DP)

The formulated and adjuvanted BDP is shipped to (b) (4) (b) (4) and stored at (b) (4) until use for DP production. The manufacturing process for the DP includes the following major steps: (b) (4) (b) (4) DP filling, visual inspection, packaging, storage, and shipping of the DP syringes. The BDP is filled as a single dose of 0.8 mL into 1-mL Type (b) (4) glass syringe barrels with a luer lock adapter and rigid cap. After filling, the syringe is sealed with a chlorobutyl rubber plunger stopper.

Each 0.8-mL dose contains approximately 40 µg CHIKV VLPs, 300 µg aluminum, 59.7 mg sucrose, 5.9 mg sodium citrate, 0.9 mg potassium phosphate dibasic, 0.4 mg potassium phosphate monobasic, and water for injection. The dating period for VIMKUNYA is 36 months from the date of manufacture when stored at 2 - 8°C. The date of manufacture is defined as the date when the (b) (4) Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. VIMKUNYA does not contain a preservative or antibiotics.
The filled VIMKUNYA DP is transported from (b) (4) for assembly, labeling, and packaging to create the finished drug product (FDP). The syringe trays are packaged in pre-labeled cartons (secondary) and shipper boxes (tertiary).

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

- DS release tests include (b) (4)
- BDP release tests include (b) (4)
- DP release tests consist of appearance, pH, aluminum content, (b) (4) identity, total protein concentration, (b) (4) (b) (4) potency, bacterial endotoxin, Sub-visible particles, % adsorbed VLP, container content, container closure integrity, as well as syringe functionality for (b) (4) (b) (4)
- FDP release test is performed to confirm identity.

(b) (4)

Stability of the DP
In support of the proposed shelf-life and storage conditions for the DP, (b) (4) Phase 3 batches and three process performance qualification (PPQ) batches were enrolled in long-term stability studies at 2 - 8°C and accelerated stability studies at (b) (4). Long-term stability data were provided for up to 36 months for six Phase 3 clinical trial material (CTM) batches, up to 24 months for (b) (4) and up to 6 months for three PPQ batches. All results met the pre-defined acceptance criteria. The 6-month accelerated stability study at (b) (4) is complete. All results were within the pre-defined acceptance criteria. (b) (4) Phase 3 clinical batches and three PPQ batches of FDP were placed on stability at long-term storage conditions of 2 - 8°C. The stability indicating attributes included visual inspection of package and components, container

content, container closure integrity testing (CCIT), and sterility. The stability results were provided up to 36 months for three Phase 3 batches, up to three months for the three PPQ batches. All results met the pre-defined acceptance criteria. In addition, an in-use stability study was performed to assess the CHIKV VLP compatibility in the syringe and any effects on product quality at room temperature in the syringe. This study demonstrated that the prefilled syringes (PFSs) from (b) (4) Phase 3 DP Lots are stable for up to (b) (4) hours at room temperature. In the BLA, the applicant requested an in-use shelf-life duration of 2 hours at room temperature.

Overall, the information provided in the application and amendments demonstrates that the manufacturing process is adequately controlled with appropriate validations and in-process control testing. Adequate quality control testing has been conducted and stability data have been accrued with the BDP and DP.

Combination Product Information
VIMKUNYA is a single-entity drug/device combination product consisting of the DP filled into a PFS. The PFS consists of a Type (b) (4) glass syringe barrel with a luer lock adapter and rigid cap, chlorobutyl rubber plunger stopper, polypropylene finger flange and plunger rod. The needle is not a component of the CHIKV VLP vaccine product and is not co-packaged with the PFS. The cap will be unscrewed and removed to assemble an off-the-shelf needle before IM administration. The PFS is intended to be used by Healthcare Professionals (HCP) only. Based on the review of the PFS design (including device essential performance, e.g., deliverable volume, (b) (4)
PFS biocompatibility, verification of device essential performance over the proposed shelf life and after shipping, and control strategy, the final combination product meets the essential performance requirements and is in compliance with applicable device quality system regulations (management responsibility (21 CFR 820.20), design controls regulations (21 CFR 820.30), purchasing control regulations (21 CFR 820.50), corrective and preventive action (21 CFR 820.100)).

CMC-related Postmarketing Commitments (PMCs)
1. The glass barrel, rubber closure, and rubber plunger stopper, which are parts of the primary container closure system of FDP (b) (4)
(b) (4) are product contact components. An elemental extractables study using (b) (4) was performed on the syringe, syringe tip cap, and rubber plunger. (b) (4) compounds originated from the rubber plunger had potential worst-case concentrations in the DP at levels higher than the acceptable concentrations based on the permitted daily exposure (PDE). However, due to the (b) (4) coating of the rubber plunger and the aqueous vaccine formulation, leaching of these compounds is not expected to reach levels that could impact product safety. A leachables study on the DP syringes is ongoing. This study included PPQ batch (b) (4) (Batch (b) (4) , which will be stored at 2 - 8°C for 36 months (end of shelf life) and tested for leachables periodically per (b) (4) Samples are analyzed by (b) (4) for (b) (4)
(b) (4) by (b) (4) for (b) (4) , and by (b) (4) for
(b) (4) The (b) (4) screening methods applied were confirmed to reliably detect the (b) (4) extractables with concentrations exceeding

the PDE. Results from the initial time point (Time = 0 months) have not shown any leachable compounds at or above the reporting threshold of (b) (4) This ongoing study is designated as a PMC:

- To submit leachable data for unlabeled CHIKV VLP Drug Product syringes.

A design for the leachables study of DP syringes was submitted to STN 125820/0 (Amendment 2). The protocol was reviewed and deemed acceptable with regard to tests and specifications.

2. Potential impurities in (b) (4) consist of product-related impurities, process-related impurities, and potential contaminants. The potential impurities were assessed during the validation of the (b) (4) manufacturing process, and during process development and characterization. The expression plasmid DNA (pDNA) (b) (4) is one of potential impurities derived from the (b) (4) production process. The presence of residual pDNA was assessed on (b) (4) Phase 3 lots, (b) (4) engineering lot representatives of the commercial manufacturing process, (b) (4) PPQ lots, and (b) (4) GMP post-PPQ lots. The results for all baches met the acceptance criterion of (b) (4) except for (b) (4) of the (b) (4) for batch (b) (4) that returned an OOS result of (b) (4) corresponding to (b) (4) The initial acceptance criterion of (b) (4) (b) (4) VLP was established based on (b) (4) early development batches and without consideration of the relevant clinical safety or assay variance. Based on greater process understanding and a clinical risk assessment, including the well-documented positive safety profile of pDNA-based vaccines, the acceptance criterion for residual pDNA by (b) (4) was revised to (b) (4) corresponding to (b) (4) All residual pDNA results observed throughout development are shown to be (b) (4) (b) (4) showing consistent clearance to levels with a large safety factor. Safety-risk assessment was performed and showed that the levels of residual plasmid DNA were well below the safety concern threshold. Based on this assessment, the attribute residual pDNA is not included in the commercial (b) (4) release test panel. During the (b) (4) pre-license inspection, it was noted that in document BN0193450 titled "CHIK: CAPA-003802–Characterization plan–residual pDNA testing on the next (b) (4) manufacturing runs," the firm proposed to quantify residual pDNA for the first consecutive (b) (4) (b) (4) lots. For CAPA-003802 (Characterization of the pDNA level) to be closed, all (b) (4) lots must meet the updated acceptance criterion. The characterization plan was reviewed and deemed acceptable in terms of tests and specifications. This study is designated as a PMC:

- To conduct a study to quantify the residual (b) (4) plasmid DNA (pDNA) levels on the first (b) (4) consecutive CHIKV VLP (b) (4) lots, and to submit data from this study.

3. The BDP is transported from Bavarian Nordic (b) (4) (b) (4) to (b) (4) in a passive (b) (4) shipping container at (b) (4) by (b) (4) A shipping validation has been conducted by monitoring (b) (4) consecutive shipments from Bavarian Nordic (b) (4)

(b) (4) to (b) (4). For each shipment, temperature loggers were placed. The shipping performance validation demonstrated that the shipping container and packaging configuration can maintain shipping temperatures within the pre-determined acceptance criteria.

The DP is transported in a qualified refrigerated (b) (4) from (b) (4) to (b) (4) for final assembly and packaging. As part of DP transport validation, a simulated shipping study was performed using filled DP PFS from an engineering lot (Batch (b) (4)) to evaluate the impact of (b) (4) and (b) (4) on product during transportation from (b) (4) to (b) (4) In this study, a pallet of DP was shipped to (b) (4) (b) (4) for simulated transport testing and visual inspection. After simulated transport conditioning, representative product samples were then shipped to (b) (4) for CCIT, and to (b) (4) for syringe functionality testing (b) (4). Additionally, after transport testing at (b) (4) the PFS samples were shipped to Bavarian Nordic Inc. (b) (4) for analytical testing to evaluate the drug stability after the shipping stress. Test results for appearance, container content, pH, (b) (4) % adsorption, potency, total protein content, aluminum content, subvisible particles, and headspace met the pre-defined specifications.

To provide additional confirmatory data, the applicant proposed to conduct a performance qualification study to cover summer and winter shipments of DP from (b) (4) to (b) (4) The protocol for the DP PPQ lots was submitted to STN 125820/0 (Amendment 2). The protocol was reviewed and appeared acceptable as to tests and specifications. This study is designated as a PMC study:

- To perform DP transportation validation using the DP PPQ lots.

In addition, Bavarian Nordic submitted a validation protocol for the commercial FDP transport from (b) (4) for finished product distribution. This simulated shipping from (b) (4) to intermediate storage and to customers will be representative of all forms of transit the commercial product will experience. The protocol was submitted to STN 125820/0 (Amendment 48). The protocol was reviewed and deemed acceptable with regard to tests and specifications. This study is designated as a PMC:

- To conduct Finished Drug Product (FDP) transport validation studies (b) (4) (b) (4) as described in section 3.2.P.3.5 (2.5.3.3) of your BLA 125820/0.

The packaging, stability, and shipping information provided in the submission and in response to information requests provides reasonable assurance that the device will meet the essential performance requirements after shipping and throughout its shelf life.

Diagnostic Assay for Clinical Efficacy Endpoint Assessments
A luciferase-based chikungunya virus (CHIKV-Luc) neutralization assay was used to quantify the titer of neutralizing antibodies against CHIKV in human serum. This *in vitro* infectivity assay is based on using a CHIKV that expresses luciferase and measuring the reduction of luciferase activity in infected cultures of Vero cells following treatment of virus with test serum. The assay is quantitative, reporting values as a CHIKV neutralizing antibody titer 80 (NT80). NT80 is the reciprocal of the serum dilution that provides an 80% reduction of luciferase activity compared with virus only control. Assay validation information was reviewed under the IND prior to testing of clinical samples. The CHIKV-Luc neutralization assay met pre-determined acceptance criteria and was found suitable for the quantitative determination of anti-CHIKV antibodies in human serum samples. An anti-CHIKV SNA titer (b) (4) was established as a lower limit of quantitation (LLOQ) in the assay validation studies. A similar validated CHIKV-Luc neutralization assay was also used in the passive transfer studies in NHPs to establish a protective SNA threshold titer to be reasonably likely to predict protection in humans.

b. Testing Specifications
The methods and specifications applied for release and stability testing of the DP are provided in Table 2.

The analytical methods reviewed for VIMKUNYA drug substance and drug product were found to be adequate for their intended use.

Table 2. Methods and specifications applied for release and stability testing of the DP

Test	Method	Release Specification	Stability Specification
Appearance	(b) (4)	Transparency/Turbidity: Cloudy Color: White State: Liquid Particles: Free from visible extraneous particles	Transparency/Turbidity: Cloudy Color: White State: Liquid Particles: Free from visible extraneous Particles
pH	(b) (4)	(b) (4)	(b) (4)
Aluminum content	(b) (4)	(b) (4)	Not tested
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Identity	(b) (4)	Identity confirmed	Identity confirmed
Total protein concentration	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4) potency	(b) (4)	(b) (4)	(b) (4)
Bacterial endotoxins	(b) (4)	(b) (4)	Not tested

Test	Method	Release Specification	Stability Specification
		(b) (4)	
Sterility	(b) (4)	(b) (4)	(b) (4)
Sub-visible particles	(b) (4)	(b) (4)	(b) (4)
% Adsorbed VLP	(b) (4)	(b) (4)	(b) (4)
Container content	(b) (4)	(b) (4)	(b) (4)
Container closure integrity	(b) (4)	Not tested	(b) (4)
Syringe functionality for: (b) (4)	(b) (4)	(b) (4)	(b) (4)

Release testing for FDP includes identity by (b) (4)

c. CBER 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 STN 125820/0 were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Chikungunya Vaccine, Recombinant (VIMKUNYA) are listed in Table 3 below. The activities performed and inspectional histories are noted in the table.

Table 3. Manufacturing Facilities for VIMKUNYA (Chikungunya Vaccine, Recombinant)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Bavarian Nordic (b) (4) (b) (4) *Manufacture of drug substance (DS); Manufacture of bulk drug product (BDP); Release and stability testing of BDP, DP and finished drug product (FDP)*	(b) (4)	(b) (4)	PLI	CBER (b) (4) NAI
(b) (4)	(b) (4)	(b) (4)	PLI	CBER (b) (4) VAI

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
(b) (4) *Manufacture of DP* *Release testing of DP*				
(b) (4) *Release testing (Syringe Functionality) of DP*	(b) (4)	(b) (4)	PLI	CBER (b) (4) NAI
(b) (4) *Manufacture and release/stability testing of purified* (b) (4) *plasmid*	(b) (4)	(b) (4)	PLI	CBER (b) (4) VAI
(b) (4) *FDP final assembly, labeling and packaging*	(b) (4)	(b) (4)	Waiver	CDER (b) (4) VAI
Bavarian Nordic A/S (BN A/S) (b) (4) *Release testing (endotoxin, biological and chemical) of DP and FDP*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) VAI
(b) (4) *Release testing* (b) (4) *of bulk DP*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) VAI
(b) (4) *Release testing (sterility) of DP*	(b) (4)	(b) (4) 4	Waiver	ORA (b) (4) VAI

Abbreviations: DS – drug substance; BDP – bulk drug product; DP – drug product in prefilled syringes (PFS); FDP – finished individually labeled and packaged DP in PFS; CDER – Center for Drug Evaluation and Research; ORA – the former Office of Regulatory Affairs; NAI – No Action Indicated; PLI – Pre-license Inspection; VAI – Voluntary Action Indicated.

CBER conducted a PLI of the BN (b) (4) facility in (b) (4) No Form FDA 483 was issued at the conclusion of the PLI, and the inspection was classified as no action indicated (NAI).

CBER conducted a PLI of the (b) (4) facility in (b) (4) All 483 issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

CBER conducted a PLI of the (b) (4) facility in (b) (4) No Form FDA 483 was issued at the end of the PLI, and the inspection was classified as NAI.

CBER conducted a PLI of the (b) (4) facility in (b) (4) All 483 issues were resolved, and the inspection was classified as VAI.

CBER waived PLIs of the following facilities (listed in the table above) based on criteria outlined in CBER SOPP 8410, "*Determining When Pre- Licensing/Pre-Approval Inspections (PLI/PAI) are necessary*", and all 483 issues were resolved when the inspections were classified as VAI:

- (b) (4) is a contract-manufacturer of packaging and labeling of finished drug products (DP) in various forms, including sterile DP filled in vials or syringes. This facility has been routinely inspected by FDA. The last FDA inspection (b) (4) covered the Quality, Facility and Equipment systems with focus on a CDER regulated sterile liquid PFS product.

- BN A/S (b) (4) is a contract manufacturing and testing facility. This facility has been routinely inspected by FDA. The last FDA inspection (b) (4) covered the quality, production, laboratory, facilities, and equipment systems with focus on CBER approved product (e.g., (b) (4)

- (b) (4) is a contract testing laboratory and performs microbiological (e.g., sterility), biological, and chemical/physical testing. This facility has been routinely inspected by FDA. The last FDA inspection (b) (4) covered the Quality, Laboratory, and Equipment/Facilities systems.

- (b) (4) is a contract testing laboratory and performs microbiological (e.g., sterility and non-sterility) testing. This facility has been routinely inspected by FDA. The last FDA inspection (b) (4) covered the Quality, Laboratory, and Equipment/Facilities systems.

e. Container/Closure System

The VIMKUNYA DP is aseptically filled into pre-assembled sterile syringe with Type (b) (4) glass barrel (b) (4) luer lock adapter (b) (4) and a rigid cap (b) (4) and then aseptically stoppered with a rubber plunger stopper (b) (4) (b) (4) The container-closure integrity testing (CCIT) is performed for stability of DP in prefilled syringe using a validated (b) (4) method.

f. Environmental Assessment

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

4. Nonclinical Pharmacology/Toxicology

Nonclinical Pharmacology

A passive transfer study was performed in NHPs using human anti-CHIKV immune sera collected from two Phase 2 studies (NCT03483961 and NCT03992872), from participants who received a single dose of a vaccine formulation containing the same CHIKV VLP used in VIMKUNYA. Sera obtained on Day 22 after vaccination were pooled to generate a serum pool with an NT80 titer of 2470, as determined by a CHIKV luciferase neutralization assay. In the passive transfer study, 20 CHIKV-naïve cynomolgus macaques (*M. fascicularis*) were administered human anti-CHIKV immune sera at four dose levels (2.4, 1.2, 0.6 and 0.3 mL/kg) and 6 CHIKV-naïve cynomolgus 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 the CHIKV luciferase neutralization assay. On the same day following sera collection, animals were challenged via the subcutaneous route with 100,000 Plaque Forming Units of wild-type CHIKV strain La Réunion 2006-OPY1, corresponding to 1000 times the 50% animal infectious dose. Animal monitoring included assessment of wild-type CHIKV-induced viremia by plaque assay and RT-qPCR through 10 days after challenge. For those NHPs that received anti-CHIKV sera, no infectious virus was detected in the blood, and the amounts of CHIKV RNA in the blood were reduced in a dose-dependent manner compared with NHPs who received non-immune human sera. Data from the NHP study were analyzed by logistic regression and a NT80 titer of ≥100 was determined to be reasonably likely to predict clinical benefit in the Phase 3 studies.

Nonclinical Toxicology

Repeat-dose toxicity study

The safety and toxicity of unadjuvanted CHIKV VLP vaccine was evaluated in a repeat-dose toxicity study in rabbits. The study did not demonstrate any safety concerns and confirmed that the rabbit is a pharmacologically relevant species. A dose of 1 mL CHKVLP059 (40 µg VLP) was given four times at 3-week intervals. No CHIKV VLP-attributable adverse effects were observed for body weight changes, clinical signs, body temperature, injection site reactions, ophthalmic assessments, hematology, clinical chemistry, necropsy, and histopathology. Any changes observed were either within the normal variation observed for the species or procedure-related (IM injection trauma). The test article in this repeat-dose toxicity study was unadjuvanted CHIKV VLP vaccine (CHKVLP059). However, aluminum hydroxide has been safely used for over six decades in other licensed vaccines (FDA Common Ingredients in U.S. Licensed Vaccines (FDA, 2019)). Therefore, a second repeat-dose toxicity study using adjuvanted CHIKV VLP vaccine was not considered necessary.

Developmental Assessment and Embryo-Fetal Development Toxicity Studies
In a pre- and postnatal developmental study with an embryo-fetal development toxicity phase performed in female rabbits, a full human dose (0.8 mL) of VIMKUNYA was administered by IM injection on five occasions: 28 and 14 days prior to start of cohabitation, on Gestation Days 7 and 21 and on Lactation Day 7. Among kits born in the control group, 69% of the kits [95% confidence interval (CI) (57.8%, 80.1%)] survived compared with the 42% of kits [95% CI (31.5%, 52.8%)] born to vaccinated mothers (the historical control data showed a range for postnatal survival from 47.6% to 91.4% with a mean of 71%, from 18 studies); other postnatal development parameters were not affected. There were no adverse effects on female fertility; and there was no evidence of harm to the fetus due to the vaccine.

In a pre- and postnatal developmental study performed in female rats, a full human dose (0.8 mL) of VIMKUNYA was administered by IM injection on five occasions: 28 and 14 days prior to start of cohabitation, on Gestation Days 7 and 21 and on Lactation Day 7. No vaccine related adverse effects on female fertility or postnatal development were observed.

5. Clinical Pharmacology

The exact mechanism of protection has not been determined. VIMKUNYA elicits CHIKV-specific neutralizing antibody responses which are thought to mediate the immune response that protects humans against chikungunya disease.

6. Clinical/Statistical

a. Clinical Program

This BLA included data from five clinical studies evaluating the safety and immunogenicity of PXVX0317: (1) a Phase 2 dose-escalation study (PXVX-CV-317-001 [study 001]); (2) a Phase 3 safety, immunogenicity, and lot consistency study in individuals 12 to <65 years of age (EBSI-CV-317-004 [study 004]); (3) a Phase 3 safety and immunogenicity study in individuals 65 years of age and older (EBSI-CV-317-005 [study 005]); (4) a Phase 2 study evaluating the impact of prior alphavirus vaccination on the safety and immunogenicity of PXVX0317 (EBSI-CV-317-002 [study 002]); and (5) a Phase 2 study performed to collect plasma and serum samples for NHP studies (EBSI-CV-317-010 [study 010]).

Table 4. Clinical Studies Supporting the Efficacy of PXVX0317

Study	NCT ID	Description	Participants	Sites
EBSI-CV-317-004 (Study 004)	NCT05072080	Phase 3 safety, immunogenicity, and lot-consistency trial of PXVX0317 in participants 12 to <65 years of age	3258 randomized participants	47 U.S. sites
EBSI-CV-317-005 (Study 005)	NCT05349617	Phase 3 safety and immunogenicity trial of PXVX0317 in adults ≥65 years of age	413 randomized participants	10 U.S. Sites

Source: eCTD module 5.2

Studies 004 and 005 (Table 4) are considered essential to support the proposed indication. The indication is being approved using an accelerated approval pathway based on an evaluation of anti-CHIKV SNA response serving as a surrogate endpoint that is reasonably likely to predict a clinical benefit in these two Phase 3 studies. Studies 001, 002, and 010 are supportive. The primary immunogenicity endpoint for studies 004 and 005 was an anti-CHIKV SNA titer ≥100 at Day 22 post-vaccination. The titer of ≥100 was selected based on experiments in an NHP adoptive transfer model, in which the quantity of human anti-CHIKV immune sera needed to prevent viremia in the NHP 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.

Immunogenicity data from the two Phase 3 studies were analyzed separately in the IEP and also pooled with data from Phase 2 studies 002 and 010 in integrated summary of effectiveness (ISE) analyses. All participants included in the IEP had no measurable anti-CHIKV SNA at Day 1 (< 15, LLOQ for the CHIKV-Luc neutralization assay). Safety data from all five studies were pooled for the integrated summary of safety (ISS) analyses, since all five studies used similar definitions of adverse events (AEs), adverse event collection tools, and duration of follow-up.

Study EBSI-CV-317-004 (NCT05072080)

Study 004 was a Phase 3, randomized, placebo-controlled, double-blind, parallel-group study with four treatment groups. A total of 3,258 participants were randomized in a 2:2:2:1 ratio within each age stratum (12 to <18, 18 to <46, and 46 to <65 years) to receive one of three consecutively manufactured lots of PXVX0317 or placebo. A nested lot consistency sub-study was planned for 1,050 adult participants 18 to <46 years of age in the PXVX0317 treatment group (b) (4) The study was conducted at 47 investigational sites in the U.S.

Immunogenicity Analyses

The seroresponse rate in the IEP at Day 22 was 97.8% (2503/2559 participants) in the pooled PXVX0317 group and 1.2% (5/424 participants) in the placebo group, resulting in a seroresponse rate difference of 96.6% (95% CI: 95.0, 97.5). The pre-specified success criterion of a LB of the 95% CI ≥70% was met. The Day 22 anti-CHIKV SNA GMT was 1597 for the pooled PXVX0317 group and 8 for the placebo group, resulting in a GMT ratio of 203 (95% CI: 181, 228). The immune response persisted through Day

183 in the majority of participants (85.5%) though there was some waning of the antibody titers (a GMT of 338 at Day 183 vs. 1597 at Day 22). Day 22 differences in seroresponse rate (PXVX0317 minus placebo) did not vary substantially by demographic subgroups, including sex, race, ethnicity, and age. Day 22 anti-CHIKV SNA GMTs were numerically higher in female participants and the 12 to <18 years of age group.

Pairwise lot comparison of anti-CHIKV SNA response to PXVX0317 in adults aged 18 to <46 years demonstrated equivalence. The Day 22 GMT ratios and 95% CIs for the pairs of lots (A:B, B:C and A:C) were 0.99 (95% CI: 0.86, 1.13), 0.97 (95% CI: 0.84, 1.12), and 0.96 (95% CI: 0.83, 1.10), respectively. 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 equivalency.

Safety Analyses

In safety analyses from study 004 the percentage of participants reporting any adverse event (AE), including solicited adverse reactions (ARs), was higher in the PXVX0317 group (45.1%) than placebo group (34.7%). Solicited ARs were reported by 38.0% and 26.7% of participants who received PXVX0317 and placebo, respectively. Systemic solicited ARs were reported by 891 (32.2%) PXVX0317 recipients and 114 (24.9%) placebo recipients. Most solicited systemic ARs were mild or moderate, with 1.5% of participants in the PXVX0317 group and 0.4% of participants in the placebo group reporting severe reactions. The most common solicited systemic ARs were fatigue (19.9% of PXVX0317 recipients, 17.0% of placebo recipients), headache (18.0% of PXVX0317 recipients, 16.6% of placebo recipients), and myalgia (17.6% of PXVX0317 recipients, 9.6% of placebo recipients). Solicited local ARs were reported by 662 (24.0%) PXVX0317 recipients and 49 (10.7%) placebo recipients, with the most common being injection site pain (23.7% of PXVX0317 recipients, 10.7% of placebo recipients). Most solicited local ARs were mild or moderate in severity. Severe events were reported by five (0.2%) participants in the PXVX0317 group (four with pain, one with redness) and no (0%) participants in the placebo group. The median day of onset was Day 1 for local reactions (Day 1 was the day of vaccination) and Day 2 for systemic reactions following administration of PXVX0317. The median duration of solicited ARs was 1 day following PXVX0317 (range 1-168 days) and 1 day following placebo (range 1-115 days). Solicited ARs were reported by 94 (44.1%) participants 12 through 17 years of age, 676 (41.8%) participants 18 through 45 years of age, and 289 (31.0%) participants 46 through 64 years of age in the PXVX0317 group.

Unsolicited AEs that occurred within 28 days following vaccination were reported in 15.5% of 2,790 participants who received PXVX0317 and 12.7% of 464 participants who received placebo. There was one report of severe dehydration considered related to PXVX0317. One death occurred following PXVX0317 (<0.1%), which was assessed as not related to the investigational product. Nonfatal serious adverse events (SAEs) were reported by 0.8% of PXVX0317 recipients and 0.2% of placebo recipients. No treatment-related SAEs were observed following PXVX0317 administration. New onset or worsening arthralgia that was medically attended was reported by a similar

percentage of PXVX0317 (0.1%) and placebo (0.2%) recipients. All arthralgia events were mild or moderate in severity.

Study EBSI-CV-317-005 (NCT05349617)
Study 005 was a Phase 3, randomized, placebo-controlled, double-blind, parallel-group study with two treatment groups. A total of 413 participants were randomized in a 1:1 ratio to receive either a single dose of PXVX0317 or placebo. Participants were stratified by age (65 to <75 and ≥75 years of age), with a target of 25% enrollment of participants ≥75 years of age. The study was conducted at 10 investigational sites in the U.S.

Immunogenicity Analyses
The seroresponse rate in the IEP at Day 22 was 87.3% (165/189 participants) in the PXVX0317 group and 1.1% (2/183 participants) in the placebo group, resulting in a seroresponse rate (%) difference of 86.2% (95% CI: 80.0, 90.3). The success criterion of a pre-specified LB of the 95% CI was ≥70% was met. The Day 22 anti-CHIKV SNA GMT was 721 for the PXVX0317 group and 8 for the placebo group, resulting in a GMT ratio of 89 (95% CI: 68, 116). The seroresponse rate at Day 183 post-vaccination was 75.5%. The anti-CHIKV SNA GMT decreased from 721 at Day 22 to 233 at Day 183 post-vaccination. Day 22 anti-CHIKV seroresponse rates following PXVX0317 were higher in female participants (90.7%) than male participants (81.7%). Day 22 anti-CHIKV GMT were numerically higher in female participants (967) than male participants (424). Seroresponse rates and GMT values did not vary notably across race, ethnicity, and age subgroups.

Safety Analyses
In study 005, the percentage of participants reporting any AE, including solicited ARs, was comparable in the PXVX0317 (22.8%) and placebo (25.1%) groups. Solicited ARs were reported by a similar percentage of PXVX0317 (12.2%, 25/206) and placebo (14.0%, 28/207) recipients. Solicited systemic ARs were reported by 22 (10.7%) PXVX0317 and 27 (13.5%) placebo recipients. Most solicited systemic ARs were mild or moderate in severity. One participant (0.5%) in the PXVX0317 group reported severe systemic ARs (fatigue and headache) and no participants (0%) in the placebo group reported severe systemic ARs. The most common solicited systemic ARs were fatigue (6.3% in the PXVX0317 group and 6.0% in the placebo group), myalgia (6.3% in the PXVX0317 group and 6.5% in the placebo group), and headache (4.4% in the PXVX0317 group and 7.5% in the placebo group). Solicited local ARs were reported by a slightly higher percentage of PXVX0317 recipients (5.4%) than placebo recipients (2.0%). All solicited local ARs were mild or moderate in severity. The most common solicited local AR was injection site pain (5.4% in the PXVX0317 group, 1.5% in the placebo group). The median day of onset was Day 2 for both local and systemic reactions (Day 1 was the day of vaccination) following administration of PXVX0317. Local ARs resolved with a median duration of 1 day and systemic ARs resolved with a median duration of 2 days.

Unsolicited AEs occurred within 28 days following vaccination were reported in 12.6% of 206 participants who received PXVX0317 and 15.5% of 207 participants who received placebo. There were no severe unsolicited adverse events considered related to PXVX0317. Two deaths occurred (one following PXVX0317, one following placebo), both of which were assessed as unlikely to be related to the investigational product. Non-fatal SAEs were reported by 1.9% of PXVX0317 recipients and 1.4% of placebo recipients. No treatment-related SAEs were observed following PXVX0317 administration. New onset or worsening arthralgia that was medically attended was reported by 0 (0%) participants in the PXVX0317 group and 1 (0.5%) participant in the placebo group.

Integrated analyses

The results of the pooled ISE analyses were consistent with the findings from the individual studies, with a seroresponse rate (%) difference of 96.0% (95% CI: 94.6, 96.8) at Day 22 post-vaccination with PXVX0317. As such, the pooled data support the proposed indication.

The safety of PXVX0317 was assessed in the U.S. in 3522 healthy participants ≥12 years of age who received at least one dose of PXVX0317 (including 3141 participants who received the to-be-marketed single dose of 40/300µg PXVX0317) and 675 placebo recipients in five studies. No new safety issues were identified in the ISS analyses. In particular, no treatment-related deaths or treatment-related nonfatal SAEs were observed. SAEs were reported by 37 (1.1%) PXVX0317 and 4 (0.6%) placebo recipients.

Due to concern that a VLP vaccine could cause manifestations of CHIK in recipients, new onset or worsening arthralgia that was medically attended was collected as an adverse event of special interest (AESI). In the ISS analyses, AESIs were reported by 6 (0.2%) PXVX0317 and 2 (0.3%) placebo recipients. All AESIs were nonserious and grade 1 or 2 in severity. In addition, a post hoc analysis of CHIK-like ARs (defined as fever and one or more of any of the following: arthralgia or arthritis, myalgia, headache, back pain, rash, lymphadenopathy, or certain neurological, cardiac or ocular symptoms that occurred with an onset within 30 days after vaccination) was performed. A total of 14 (0.4%) participants in the PXVX0317 group and 2 (0.3%) in the placebo group met criteria for CHIK-like ARs. Overall, the constellation of signs and symptoms consistent with CHIK (CHIK-like ARs) was comparable between treatment and placebo groups with regard to the severity, duration, and percentage of participants with these findings.

Overall, the safety data of PXVX0317 demonstrated:

- Increased percentage of solicited local and systemic ARs compared with placebo.
- Slightly higher percentage of SAEs than placebo, though none were assessed to be treatment-related.
- Similar percentage of unsolicited adverse events compared with placebo.
- Similar percentage of new onset or worsening arthralgia that was medically attended compared with placebo.

As such, in general, the safety profile of the Applicant-proposed dose regimen of PXVX0317 is considered favorable and supports the proposed indication and populations.

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

BIMO Clinical Investigator (CI) inspection assignments were issued for three clinical study sites that participated in the conduct of studies EBSI-CV-317-004 and EBSI-CV-317-005. The completed inspections did not reveal substantive issues that impact the data submitted in this Biologics License Application (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. PXVX0317 was evaluated in adolescents 12 to <18 years of age in study 004. No clinically meaningful differences in the safety or immunogenicity were observed in this age group compared with adults.
The application included an agreed iPSP and the Applicant requested a deferral for the pediatric assessment for children <12 years of age. This BLA and request for deferral of pediatric assessments in children <12 years of age were presented to the Pediatric Research Committee (PeRC). The PeRC agreed with the proposed indication in individuals 12 years of age and older, as well as the requested deferral of pediatric studies for ages 0 to <12 years. CBER agreed to grant the deferral request.

d. Other Special Populations

Human Reproduction and Pregnancy Data

A total of 11 pregnancies occurred following administration of PXVX0317 and one following placebo: nine in study PXVX-CV-317-001 (one with twins) and two in study ESBI-CV-317-004. The outcomes included: one incomplete abortion; one ectopic pregnancy, terminated; four early term deliveries (37 to ≤38 6/7 weeks); two preterm deliveries (≤36 6/7 weeks); one full term delivery; and two with unknown outcomes.

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. There are no clinical studies of PXVX0317 in pregnant women. Because data on PXVX0317 administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy and decreased viability of rabbit kits in the vaccine group was observed in the rabbit DART study, the safety of PXVX0317 in pregnancy will be further evaluated in a postmarketing commitment pregnancy registry titled “An observational prospective study of the safety of PXVX0317 vaccine exposure in pregnant women and their offspring."

Use During Lactation

No data available.

Immunocompromised Patients
The safety and effectiveness of PXVX0317 have not been evaluated in immunocompromised patient populations.

Geriatric Use
In study 005, a total of 206 individuals 65 years of age and older received PXVX0317, including 47 individuals (22.8%) 75 years of age and older. The incidence of solicited adverse reactions in individuals 65 years of age and older was generally lower than that observed in individuals less than 65 years of age (see section 6a above). The seroresponse rate in individuals 65 years of age and older was lower than that observed in individuals less than 65 years of age (see section 6a above). A total of 87% of participants ≥65 years of age achieved an anti-CHIKV SNA titer ≥100 at Day 22 following a single dose vaccination with PXVX0317, which is considered reasonably likely to predict clinical benefit. The results met the pre-specified success criterion of a LB of the 95% CI of ≥70% and thus, are considered to support licensure in this age group.

7. Safety and Pharmacovigilance

Pharmacovigilance
The Applicant's pharmacovigilance plan (PVP) includes chikungunya-like illness (including vaccine associated arthralgia) as an important potential risk. There is no important identified risk at this time. Areas of missing information include safety in pregnant or breastfeeding women and use in immunocompromised individuals and persons on immunomodulators (persons with autoimmune disorders). The proposed PVP is adequate.

The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80, and enhanced pharmacovigilance for the following:

- CHIK-like illness: expedited (15-day) reporting regardless of seriousness for 3 years following licensure, follow-up with a targeted questionnaire, and inclusion of a summary and analysis in periodic safety reports.
- Exposure during pregnancy: follow-up with a targeted questionnaire, and inclusion of a summary and analysis in periodic safety reports.

The Applicant will also conduct a pregnancy registry in the U.S. and the European Union as a postmarketing commitment (see section 11c, PMC #4).

The available safety data do not substantiate a need for a safety-related postmarketing requirement (PMR) or Risk Evaluation and Mitigation Strategy (REMS).

8. Labeling

The proposed proprietary name, VIMKUNYA was reviewed by the Advertising and Promotional Labeling Branch (APLB) on August 29, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on September 10, 2024.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Prescribing Information (PI) and package and container labels January 21, 2025, and found them acceptable from a promotional and comprehension perspective.

The review team negotiated revisions to the PI. All labeling issues regarding the PI and the carton and container labels were resolved following communications with the Applicant. The PI, and package and container labels submitted in amendments 72 and 65 on February 14, 2025, and January 31, 2025, respectively, were considered final for approval.

9. Advisory Committee Meeting

The application was not referred to a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting. There have been no major changes in the regulatory approaches for licensing chikungunya vaccines since a November 8, 2019, VRBPAC meeting to discuss and make recommendations on the development of chikungunya vaccines. The review of information submitted in the BLA did not identify safety and effectiveness issues with this vaccine or issues with the confirmatory study design that would warrant a discussion at a VRBPAC meeting.

10. Other Relevant Regulatory Issues

The application was reviewed under the accelerated approval program and received priority review designation because CHIK is a serious illness and there are no available CHIKV vaccines with verified clinical benefit. Bavarian Nordic requested a tropical disease priority review voucher. The request met the eligibility criteria, and a tropical-disease priority review voucher was granted. The applicant also requested reference product exclusivity for the full 351(a) BLA 125820 for Chikungunya Vaccine, Recombinant, and a decision under 351(k)(7)(C) on the date of first licensure for CHIKV VLP vaccine as a reference product submitted under 351(a). The final determination as to whether a proposed reference product is eligible for the corresponding periods of exclusivity and the date of first licensure is made upon approval. The exclusivity decision will be communicated to applicant within 30 calendar days of approval.

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 accelerated approval of VIMKUNYA for the labeled indication and usage.

b. Benefit/Risk Assessment

CHIKV infection typically results in mild and self-limited disease in 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 may occur and cause long-term disability. Serious atypical presentations of CHIK, including

cardiac and neurologic events, may occur rarely. 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 Carrillo, 2019; Yoon, 2015) and are believed to be lineage dependent, with more asymptomatic infections appearing to be associated with the Asian lineage than ECSA lineage (Bustos Carrillo, 2019).

Similarly, the prevalence of patients with severe arthralgia or chronic arthralgia has been reported to range from 2% to 57% (Yoon, 2020), while other studies did not identify any severe cases following natural CHIKV infection (Yoon, 2015; Langsjoen, 2016). The reasons for this variability remain unclear. Some investigators postulated that the variability may be due to persistent infectious virus, 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 trials demonstrated that 97.8% of participants 12 to <65 years of age and 87.3% of participants ≥65 years of age achieved an anti-CHIKV neutralizing antibody titer ≥100 at Day 22 after a single dose of PXVX0317, and the anti-CHIKV neutralizing antibody response persisted in most participants for at least 6 months after the single dose vaccination, indicating that vaccination with PXVX0317 is reasonably likely to prevent disease caused by CHIKV infection. The surrogate endpoint of an anti-CHIKV neutralizing antibody titer ≥100, which was considered reasonably likely to predict a clinical benefit, was based on prevention of CHIKV viremia in a passive transfer NHP challenge study. In a separate NHP study (Pal, 2014), administration of anti-CHIKV neutralizing monoclonal antibodies completely prevented CHIKV viremia but did not prevent high CHIKV RNA levels in the joints and muscles of the arms, and in the axillary lymph nodes. The required postmarketing confirmatory efficacy study is designed to verify and describe the anticipated clinical benefit of PXVX0317.

Risks of vaccination with PXVX0317 include local and systemic reactogenicity, but no treatment-related deaths, serious adverse events, or serious adverse events of special interest were identified.

The currently available data support a benefit-risk profile that is favorable for approving VIMKUNYA for use in individuals 12 years of age and older under the accelerated approval pathway. Mitigation of the observed risks and uncertainties will be accomplished through labeling (including statements regarding uncertainties of the clinical benefit), the postmarketing pharmacovigilance plan, and through an adequate and well-controlled postmarketing confirmatory study to confirm clinical benefit. Please refer to Recommendations for Postmarketing Activities below.

c. Recommendation for Postmarketing Activities

Bavarian Nordic A/S has committed to conduct the following postmarketing activities, which are specified in the approval letter.

ACCELERATED APPROVAL REQUIREMENTS (Confirmatory Clinical Studies to Verify Clinical Benefit)

In accordance with the accelerated approval statutory provisions and regulations (21 CFR 601.41 Subpart E), the Applicant is required to conduct further adequate and well-controlled studies to verify and describe clinical benefit of the biological product. Such studies must be conducted with due diligence. The Applicant has agreed:

1. To conduct a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of VIMKUNYA, an adjuvanted chikungunya virus virus-like particle (CHIKV VLP) vaccine for the prevention of chikungunya disease in adolescents (12 to <18 years) and adults (≥18 years).

   Final Protocol Submission: February 28, 2025
   Study implementation readiness verification submission and
   Study initiation: September 30, 2025
   Study/Trial Completion: September 30, 2029
   Final Report Submission: August 31, 2030

This event-driven study will evaluate efficacy of VIMKUNYA in preventing laboratory-confirmed acute CHIKV disease in up to 6,144 participants in arbovirus-endemic regions of Thailand and the Philippines.

POSTMARKETING REQUIREMENTS UNDER SECTION 505B(a) (PEDIATRIC REQUIREMENTS)

In accordance with the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)), the Applicant requested deferral of pediatric studies for pediatric population 0 to <12 years of age. The following proposed deferred pediatric studies are agreed upon by the Agency:

2. Deferred pediatric study under PREA (EBSI-CV-317-006) to evaluate the safety and immunogenicity of VIMKUNYA in children 2 to <12 years of age.

   Final Protocol Submission: February 28, 2025
   Study Completion Date: June 30, 2028
   Final Report Submission: January 31, 2029

3. Deferred pediatric study under PREA (EBSI-CV-317-009) to evaluate the safety and immunogenicity of VIMKUNYA in infants 0 to <2 years of age.

   Final Protocol Submission: April 30, 2028
   Study Completion Date: February 29, 2032
   Final Report Submission: November 30, 2032

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

The Applicant has proposed a pregnancy registry for postmarketing assessment of pregnancy outcomes:

4. Study titled "VIMKUNYA Pregnancy Registry: An observational prospective study of the safety of VIMKUNYA vaccine exposure in pregnant women and their offspring." This prospective, observational registry study of pregnant women residing in the United States and European Union will evaluate maternal and infant outcomes (until one year of age) in at least 50 women exposed to VIMKUNYA up to 28 days prior to or at any time during pregnancy.

   Final Protocol Submission: May 30, 2025
   Study Completion Date: August 31, 2030
   Final Report Submission: February 28, 2031

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

The Applicant made written commitments as outlined below:

5. To submit leachable data for unlabeled CHIKV VLP Drug Product syringes.

   Final Report Submission: October 31, 2028

6. To conduct a study to quantify the residual (b) (4) plasmid DNA (pDNA) levels on the first (b) (4) consecutive CHIKV VLP (b) (4) lots, and to submit data from this study.

   Final Report Submission: June 30, 2026

7. To conduct Finished Drug Product (FDP) transport validation studies (b) (4) (b) (4) as described in section 3.2.P.3.5 (2.5.3.3) of your BLA 125820/0.

   Final Report Submission: June 30, 2025

8. To perform Drug Product (DP) transportation validation using the DP PPQ lots.

   Final Report Submission: February 28, 2026

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