Application Type	BLA, Original Application
STN	125820/0
CBER Received Date	June 17, 2024
PDUFA Goal Date	February 15, 2025
Division / Office	DVRPA/OVRR
Committee Chair	Konstantin Virnik
Clinical Reviewers	Judith Anesi, Sixun Yang
Project Managers	Katherine Berkhousen, Georgeta Crivat, Vera Stupina
Priority Review	Yes
Reviewer Names	Ross Peterson Mathematical Statistician, VEB, DB, OBPV
Review Completion Date/Stamped Date	
Concurrence	Lei Huang Concurring Reviewer, VEB, DB, OBPV
Supervisory Concurrence	Tsai-Lien Lin Branch Chief, VEB, DB, OBPV
Supervisory Concurrence	John Scott Director, DB, OBPV
Applicant	Bavarian Nordic, Inc.
Established Name	Chikungunya Vaccine, Recombinant
(Proposed) Trade Name	VIMKUNYA
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Single dose of 0.8 mL
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by chikungunya virus infection in individuals 12 years of age and older

Table of Contents

Glossary

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
BLA	Biologics License Application
BMI	Body Mass Index
CHIKV	Chikungunya Virus
CI	Confidence Interval
CRF	Case Report Form
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
IEP	Immunogenicity Evaluable Population
IgG	Immunoglobulin G
IR	Information Request
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
LL	Lower Limit
LLOQ	Lower Limit of Quantitation
MAAE	Medically Attended Adverse Events
mITTP	Modified Intent-to-Treat Population
NHP	Non-Human Primate
RP	Randomized Population
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SNA	Serum Neutralizing Antibody
SP	Safety Population
SRR	Seroresponse Rate
STN	Submission Tracking Number
U.S.	United States
UL	Upper Limit
ULOQ	Upper Limit of Quantitation
VLP	Virus-like Particle
YOA	Years of Age

1. Executive Summary

Bavarian Nordic, Inc. submitted this Biologics License Application (BLA) to seek licensure of the Chikungunya Virus (CHIKV) Virus-like Particle (VLP) vaccine (PXVX0317) intended to prevent disease caused by chikungunya virus infection in individuals 12 years of age (YOA) and older. The rolling submission was completed on 17 June 2024. The Priority Review of this BLA was granted. The BLA is supported primarily by immunogenicity and safety data from two Phase 3 clinical studies, EBSI-CV-317-004 and EBSI-CV-317-005.

Prior to initiating Studies EBSI-CV-317-004 and EBSI-CV-317-005, the Food and Drug Administration (FDA) agreed that anti-CHIKV serum neutralization antibody (SNA) may be used as a surrogate endpoint to support licensure through the accelerated approval pathway provided that an SNA titer that is able to prevent viremia following wild-type CHIKV challenge in the human anti-CHIKV Immunoglobulin G (IgG) passive transfer non-human primate (NHP) model is identified. Subsequently, based on both the immunogenicity and efficacy results of NHPs in Study PAS-NHP-CHIK-003, it was agreed with FDA that an anti-CHIKV SNA titer ≥100 would be reasonably likely to predict protection from CHIKV disease.

The experimental design and main immunogenicity and safety results for both Studies EBSI-CV-317-004 and EBSI-CV-317-005 are summarized below:

EBSI-CV-317-004

EBSI-CV-317-004 was a Phase 3, safety, immunogenicity, and lot-consistency trial of PXVX0317 in healthy adults and adolescents 12 to <65 YOA. Subjects were randomized in a 2:2:2:1 allocation ratio to receive one of three consecutively manufactured lots of PXVX0317 (b) (4) or placebo on Day 1, stratified by age category (i.e., 12 to <18 years, 18 to <46 years, or 46 to <65 years).

There were two co-primary immunogenicity objectives:

1. Demonstration of superiority for anti-CHIKV SNA titers for CHIKV VLP pooled across lots (pooled CHIKV VLP group) versus the placebo group on Day 22.
2. Demonstration of lot-consistency for anti-CHIKV SNA titers on Day 22 among the three CHIKV VLP lot groups.

For the first co-primary immunogenicity objective, superiority was to be demonstrated in terms of both the geometric mean titer (GMT) and seroresponse rate (SRR), where seroresponse rate was defined as the percentage of participants achieving anti-CHIKV SNA titer ≥100. The success criterion was that the lower bounds of the 2-sided confidence intervals (CIs) for GMT ratio (pooled CHIKV VLP group divided by placebo group) and SRR difference (pooled CHIKV VLP group minus placebo group) were > 1 and > 70%, respectively.

For the second co-primary immunogenicity objective, lot-consistency was to be demonstrated in terms of GMT only. The success criterion was that for each pairwise comparison of CHIKV VLP lot groups, the 95% CI of GMT ratio was within the interval of (0.67, 1.5).

The success criterion for the trial was that both success criteria for the two co-primary immunogenicity objectives were met.

If the success criterion for the trial was met, a key secondary immunogenicity objective of demonstrating superiority for anti-CHIKV SNA titers for CHIKV VLP pooled across lots (pooled CHIKV VLP group) versus the placebo group on Days 15, 183, and 8 was to be evaluated (i.e., following a Fixed-Sequence Method).

For the key secondary immunogenicity objective, superiority was to be demonstrated in terms of the SRR only. For Days 15, 183, and 8, the success criterion was that the lower bounds of the 2-sided CIs for the SRR differences (pooled CHIKV VLP group minus placebo group) were > 70%, > 0%, and > 0%, respectively. Days 15, 183, and 8 were to be tested in order (i.e., following a Fixed-Sequence Method).

Of note, in the original CSRs for Studies EBSI-CV-317-004 and EBSI-CV-317-005, the Chikungunya Luciferase Neutralization Assay was used to quantitate anti-CHIKV SNA titer for both the primary and key secondary immunogenicity objectives. The upper limit of quantitation (ULOQ) was set at 99599.9 in an assay validation report addendum which examined intermediate precision but not dilutional linearity. No formal ULOQ was established in the original assay validation report. As the ULOQ of 99599.9 was not considered to be adequately validated by CBER, in response to an information request (IR), an ULOQ of 10794.8 was established based on all available intermediate precision and dilutional linearity results from the original assay validation report.

As SRR was defined based on a threshold of anti-CHIKV SNA titer ≥ 100, the immunogenicity analyses of SRR difference did not change regardless of the ULOQ. Only the immunogenicity analyses of GMT ratio were impacted by the ULOQ.

For both the original and additional immunogenicity analyses of GMT ratio which used the ULOQs of 99599.9 and 10794.8, respectively, for the Chikungunya Luciferase Neutralization Assay, the success criteria were met. The success criterion for the trial and the success criteria for the key secondary immunogenicity objective on Days 15, 183 and 8 were met. Of note, the immunogenicity analyses of GMT ratio presented in the Executive Summary used a ULOQ of 10794.8.

For the first co-primary immunogenicity objective, adjusting for site, the GMT ratio was 203.29 with 95% CI (181.08, 228.23). The SRR difference was 96.6% with 95% CI (95.0%, 97.5%).

For the second co-primary immunogenicity objective, adjusting for site, the GMT ratios between (b) (4) were 0.99

with 95% CI (0.86, 1.13), 0.97 with 95% CI (0.84, 1.12), and 0.96 with 95% CI (0.83, 1.10), respectively.

For the key secondary immunogenicity objective, the SRR differences on Days 15, 183, and 8 were 96.0% with 95% CI (94.3%, 96.8%), 84.0% with 95% CI (81.7%, 85.6%), and 46.1% with 95% CI (43.8%, 48.1%), respectively.

For safety, solicited adverse reactions (ARs) were collected through Day 8. Unsolicited adverse events (AEs) were collected through Day 29. Adverse Events of Special Interest (AESIs), Medically Attended Adverse Events (MAAEs), and Serious Adverse Events (SAEs) were collected through Day 183. AESI was defined as new onset or worsening arthralgia that is medically attended, as indicated on the case report form (CRF).

The percentages of subjects reporting solicited local and systemic reactions were generally higher in the pooled CHIKV VLP group than the placebo group. For both the pooled CHIKV VLP group and placebo group, the most frequently reported solicited local reaction was pain, while the most frequently reported solicited systemic reaction was fatigue.

Within 28 days following vaccination, regardless of relationship to study vaccination, there were similar percentages of unsolicited AEs between the pooled CHIKV VLP group and placebo group. There were also similar percentages of unsolicited AEs considered by the investigator to be related to study vaccination between both groups.

Within six months following vaccination, one death was reported in the pooled CHIKV VLP group and it was not considered to be related to the study vaccination by the investigator. No deaths were reported in the placebo group. One SAE (retinal detachment) considered by the investigator to be related to study vaccination was reported in the pooled CHIKV VLP group while none were reported in the placebo group. The SAE was later assessed by the Applicant and independent Safety Monitoring Committee (SMC) chair as unrelated due to prior medical history. Two related AESIs were reported in the pooled CHIKV VLP group while none were reported in the placebo group. A total of 0.5% of subjects reported related MAAEs in the pooled CHIKV VLP group while none were reported in the placebo group.

EBSI-CV-317-005

EBSI-CV-317-005 was a Phase 3, safety, and immunogenicity trial of PXVX0317 in adults ≥65 YOA. Subjects were randomized in a 1:1 allocation ratio to receive either PXVX0317 or placebo on Day 1, stratified by age category (i.e., ≥65 to <75 or ≥75 YOA).

The primary immunogenicity objective was demonstration of superiority for anti-CHIKV SNA titers for the CHIKV VLP group versus the placebo group on Day 22.

Superiority was to be demonstrated in terms of both GMT and SRR. The success criterion — also the success criterion for the trial — was that the lower bounds of the 2-sided CIs for GMT ratio (CHIKV VLP group divided by placebo group) and SRR difference (CHIKV VLP group minus placebo group) were > 1 and > 70%, respectively.

If the success criterion for the trial was met, a key secondary immunogenicity objective of demonstrating superiority for anti-CHIKV SNA titers for the CHIKV VLP group versus the placebo group on Days 15 and 183 was to be evaluated (i.e., following a Fixed-Sequence Method).

For the key secondary immunogenicity objective, superiority was to be demonstrated in terms of the SRR only. For Days 15 and 183, the success criterion was that the lower bounds of the 2-sided CIs for the SRR differences (CHIKV VLP group minus placebo group) were > 0%, and > 0%, respectively. Days 15 and 183 were to be tested in order (i.e., following a Fixed-Sequence Method).

For both the original and additional immunogenicity analyses of GMT ratio which used the ULOQs of 99599.9 and 10794.8, respectively, for the Chikungunya Luciferase Neutralization Assay, the success criteria were met. The success criterion for the trial and the success criteria for the key secondary immunogenicity objective on Days 15 and 183 were met.

For the primary immunogenicity objective, adjusting for site, the GMT ratio was 89.18 with 95% CI (68.35, 116.36). The SRR difference was 86.2% with 95% CI (80.0%, 90.3%).

For the key secondary immunogenicity objective, the SRR differences on Days 15 and 183 were 79.5% with 95% CI (72.3%, 84.6%) and 74.4% with 95% CI (67.1%, 80.1%), respectively.

For safety, solicited ARs were collected through Day 8. Unsolicited AEs were collected through Day 29. AESIs, MAAEs, and SAEs were collected through Day 183.

The percentages of subjects reporting solicited local and systemic reactions were generally higher in the CHIKV VLP group than the placebo group. For both the CHIKV VLP group and placebo group, the most frequently reported solicited local reaction was pain. The most frequently reported solicited systemic reactions were fatigue and myalgia in the CHIKV VLP group and headache in the placebo group.

Within 28 days following vaccination, regardless of relationship to study vaccination, there were similar percentages of unsolicited AEs between the CHIKV VLP group and placebo group. There were also similar percentages of unsolicited AEs considered by the investigator to be related to study vaccination between both groups.

Within six months following vaccination, one death each was reported in the CHIKV VLP group and the placebo group and neither was considered to be related to the study

vaccination by the investigator. One MAAE considered by the investigator to be related to study vaccination was reported in the CHIKV VLP group while none were reported in the placebo group. No related AESIs or related SAEs were reported.

Overall, the immunogenicity data appear to support the effectiveness of the CHIKV VLP vaccine in individuals 12 YOA and older. I defer to the clinical reviewer with respect to the overall safety assessment.

2. Clinical and Regulatory Background

Bavarian Nordic, Inc. submitted this BLA to seek licensure of the CHIKV VLP vaccine (PXVX0317) intended to prevent disease caused by chikungunya virus infection in individuals 12 YOA and older. The rolling submission was completed on 17 June 2024. The Priority Review of this BLA was granted. The BLA is supported primarily by immunogenicity and safety data from two Phase 3 clinical studies, EBSI-CV-317-004 and EBSI-CV-317-005.

Prior to initiating Studies EBSI-CV-317-004 and EBSI-CV-317-005, FDA agreed that anti-CHIKV SNA may be used as a surrogate endpoint to support licensure through the accelerated approval pathway provided that an SNA titer that is able to prevent viremia following wild-type CHIKV challenge in the human anti-CHIKV IgG passive transfer NHP model is identified. Subsequently, based on both the immunogenicity and efficacy results of NHPs in Study PAS-NHP-CHIK-003, it was agreed with FDA that an anti-CHIKV SNA titer ≥100 would be reasonably likely to predict protection from CHIKV disease.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

During the BLA review process, some inconsistencies were identified among the Study Data Tabulation Model (SDTM) datasets (e.g., flags, dates, etc.) for the safety analyses of the two Phase 3 clinical studies, EBSI-CV-317-004 and EBSI-CV-317-005, as well as the Phase 2 clinical study, PXVX-CV-317-001. The updated safety analyses and SDTM datasets were submitted in Response to IR 17.

This BLA review memo focuses on the updated safety analyses of Studies EBSI-CV-317-004 and EBSI-CV-317-005. Updated tables for the Integrated Summary of Safety (ISS) were submitted in Response to IR 29.

3.2 Compliance With Good Clinical Practice and Data Integrity

No data integrity issues were identified during the review.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to reviews of other review disciplines.

5. Sources of Clinical Data and Other Information Considered

5.1 Review Strategy

This review memo focuses on the two Phase 3 clinical studies, EBSI-CV-317-004 and EBSI-CV-317-005, supporting the licensure of the CHIKV VLP vaccine. An ISS was also submitted. Safety data from three Phase 2 clinical studies, PXVX-CV-317-001, EBSI-CV-317-002, and EBSI-CV-317-010, were included in the ISS — hence, this review memo also includes both the ISS and brief descriptions of the experimental designs of the three Phase 2 clinical studies.

5.2 BLA Documents That Serve as the Basis for the Statistical Review

The following documents submitted to the BLA are reviewed:

STN 125820/0.1 (submitted on 6/10/2024)
1. Module 5. Clinical Study Reports
   - EBSI-CV-317-004 Clinical Study Report
   - EBSI-CV-317-004 Trial Protocol
   - EBSI-CV-317-004 Statistical Analysis Plan
   - EBSI-CV-317-005 Clinical Study Report
   - EBSI-CV-317-005 Trial Protocol
   - EBSI-CV-317-005 Statistical Analysis Plan
   - PXVX-CV-317-001 Clinical Study Report
   - EBSI-CV-317-002 Clinical Study Report
   - EBSI-CV-317-010 Clinical Study Report
   - Integrated Summary of Safety

STN 125820/0.13 (submitted on 8/30/2024)
1. Module 1. Information Amendments
   - Response to IR 13

STN 125820/0.20 (submitted on 9/20/2024)
1. Module 1. Information Amendments
   - Response to IR 12

STN 125820/0.28 (submitted on 10/11/2024)
1. Module 1. Information Amendments
   - Response to IR 17
2. Module 5. Clinical Study Reports
   - Updated Tables for Safety Analyses of Studies EBSI-CV-317-004 and EBSI-CV-317-005

STN 125820/0.35 (submitted on 11/01/2024)

1. Module 1. Information Amendments
   - Response to IR 29
2. Module 5. Clinical Study Reports
   - Updated Tables for Integrated Summary of Safety

5.3 Table of Studies/Clinical Trials

Two Phase 3 clinical studies, EBSI-CV-317-004 and EBSI-CV-317-005, were conducted to support licensure of the CHIKV VLP vaccine. Safety data from three Phase 2 clinical studies, PXVX-CV-317-001, EBSI-CV-317-002, and EBSI-CV-317-010, were included in the ISS. All five studies are summarized in Table 1.

Table 1: Clinical Studies Supporting the BLA

Study	N	Age	Description
EBSI-CV-317-004	3258	12 to <65 YOA	Phase 3, randomized, double-blind, multi-center, immunogenicity, lot-consistency, and safety study with four parallel groups (i.e., three CHIKV VLP groups and one placebo group).
EBSI-CV-317-005	413	≥65 YOA	Phase 3, randomized, double-blind, multi-center, immunogenicity, and safety study with two parallel groups (i.e., one CHIKV VLP group and one placebo group).
PXVX-CV-317-001	445	12 to <46 YOA	Phase 2, randomized, double-blind, multi-center, immunogenicity, and safety study with ten parallel groups for different combinations of CHIKV VLP (varying by dose level, number of doses, and unadjuvanted or alum-adjuvanted) and placebo.
EBSI-CV-317-002	60	18 to <66 YOA	Phase 2, open-label, multi-center, immunuogenicity, and safety study with CHIKV VLP administered to two parallel groups (i.e., prior recipients of other alphavirus vaccines and alphavirus naïve controls).
EBSI-CV-317-010	25	12 to <46 YOA	Phase 2, open-label, single-center, immunogenicity, and safety study with one CHIKV VLP group.

N = number of enrolled subjects.
Source: Adapted from EBSI-CV-317-004, EBSI-CV-317-005, PXVX-CV-317-001, EBSI-CV-317-002, and EBSI-CV-317-010 Clinical Study Reports.

6. Discussion of Individual Studies/Clinical Trials

6.1 Clinical Study EBSI-CV-317-004

Title of Study: A Phase 3 safety, immunogenicity, and lot-consistency trial of the VLP-based Chikungunya vaccine PXVX0317 in healthy adults and adolescents.

Dates:
1. Study start date (first participant enrolled): 29 September 2021
2. Study end date (last participant completed): 3 April 2023

6.1.1 Objectives

Co-Primary Immunogenicity Objectives:

1. To compare the anti-CHIKV SNA response to CHIKV VLP vaccine and placebo at Day 22, as measured by GMT and clinically relevant difference in seroresponse rate[a] (CHIKV VLP vaccine minus placebo).
2. To demonstrate the consistency of the anti-CHIKV SNA response across three consecutively manufactured lots of CHIKV VLP vaccine at Day 22 as measured by GMT.

[a]Seroresponse rate is defined as the percentage of participants who achieve an anti-CHIKV SNA titer ≥ 100.

Safety Objective:

1. To evaluate the safety of CHIKV VLP vaccine in healthy adult and adolescent participants 12 to <65 YOA.

Key Secondary Immunogenicity Objective:

1. To compare the anti-CHIKV SNA response to CHIKV VLP vaccine and placebo at Day 15, Day 183, and Day 8, as measured by seroresponse rate.

6.1.2 Design Overview

Approximately 3150 subjects were randomized in a 2:2:2:1 allocation ratio to receive one of three consecutively manufactured lots of CHIKV VLP vaccine(b) (4) (b) (4) or placebo on Day 1, stratified by age category (i.e., 12 to <18 years, 18 to <46 years, or 46 to <65 years).

For immunogenicity assessment, for all subjects, blood samples were collected at pre-Dose 1 (Day 1), Day 8, Day 15, Day 22, and Day 183. For safety assessment, for all subjects, solicited ARs were collected through Day 8. Unsolicited AEs were collected through Day 29. AESIs, MAAEs, and SAEs were collected through Day 183. AESI was defined as new onset or worsening arthralgia that is medically attended, as indicated on the CRF.

6.1.3 Population

Subjects 12 to <65 YOA were enrolled.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The CHIKV VLP vaccine was a sterile aqueous buffered suspension comprised of 40 µg CHIKV VLP adsorbed on 300 µg aluminum hydroxide adjuvant and formulation buffer supplied as a single dose in a pre-filled 1 mL glass syringe with a 0.8 mL deliverable volume.

Placebo (formulation buffer) was supplied as a single dose of 0.8 mL in a pre-filled syringe.

6.1.6 Sites and Centers

A total of 47 sites in the U.S. participated in this clinical trial.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Study Success Criteria

Co-Primary Immunogenicity Endpoints:

1a. Anti-CHIKV SNA GMT at Day 22 for CHIKV VLP vaccine and placebo.
- Success criterion: The LL of the 2-sided CI for the GMT ratio is > 1.

1b. Anti-CHIKV SNA seroresponse rate (CHIKV VLP vaccine minus placebo) at Day 22.
- Success criterion: The LL of the 2-sided CI for the SRR difference is > 70%.

2. Anti-CHIKV SNA GMT ratio between all three pairs of CHIKV VLP vaccine lots (b) (4) (subjects 18 to <46 YOA) at Day 22.
- Success criterion: For each of the three pairwise GMT ratios, both the LL and UL of the 2-sided CI for the GMT ratio are within the bounds of (0.67, 1.5).

Safety Endpoints:

1. In all participants:
- Incidence of solicited ARs through Day 8 for CHIKV VLP vaccine and placebo.
- Incidence of unsolicited AEs through Day 29 for CHIKV VLP vaccine and placebo.
- Incidence of AESIs, MAAEs, and SAEs through Day 183 for CHIKV VLP vaccine and placebo.

Key Secondary Immunogenicity Endpoints:

1a. Anti-CHIKV SNA seroresponse rate (CHIKV VLP vaccine minus placebo) at Day 15.
- Success criterion: The LL of the 2-sided CI for the SRR difference is > 70%.

1b. Anti-CHIKV SNA seroresponse rate (CHIKV VLP vaccine minus placebo) at Day 183.
- Success criterion: The LL of the 2-sided CI for the SRR difference is > 0%.

1c. Anti-CHIKV SNA seroresponse rate (CHIKV VLP vaccine minus placebo) at Day 8.
- Success criterion: The LL of the 2-sided CI for the SRR difference is > 0%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

For both primary immunogenicity endpoints 1a and 2, GMT ratio was estimated via an analysis of covariance (ANCOVA) model using Day 22 log_{10}-transformed titers as the dependent variable and both vaccine group and study site as the independent variables. Missing data were not replaced. Titers < lower limit of quantitation (LLOQ) were replaced by half the LLOQ. Titers > ULOQ were replaced by the ULOQ. For primary immunogenicity endpoint 2, immunogenicity analyses were limited to subjects 18 to <46 YOA.

For primary immunogenicity endpoint 1b and key secondary immunogenicity endpoints 1a, 1b, and 1c, the 95% CI for the SRR difference was estimated via the Newcombe hybrid score method.

All immunogenicity analyses were performed on the Immunogenicity Evaluable Population (IEP), which was a subset of the Modified Intent-to-Treat Population (mITTP), which was a subset of the Randomized Population (RP). All three analysis sets were defined as follows:

- RP: All screened participants who provided informed consent and provided demographic and other screening measurements and were randomized.
- mITTP: Participants in the RP who were vaccinated and had at least one post-injection anti-CHIKV SNA NT80 result. Participants were counted in the group to which they were randomized.
- IEP: Participants in the mITTP who:
  - Provided evaluable serum sample results for the relevant post-vaccination time points, and within the required time frames:
    - Day 22: Day 19 through Day 27, inclusive.
  - Had no measurable anti-CHIKV SNA at Day 1 (baseline).
  - Had no major protocol deviation or other reason to be excluded as defined prior to unblinding.

Analysis of Safety

All safety data were summarized descriptively. Safety analyses were performed on the Safety Population (SP), which is a subset of the RP. The SP was defined as:

- SP: Participants in the RP who received the investigational product and who provided safety assessment data. Participants were analyzed as treated (i.e., according to the treatment a participant received, rather than the treatment to which the participant may have been randomized).

Multiplicity Adjustment

The success criterion of the trial was the rejection of all three null hypotheses corresponding to the three co-primary immunogenicity endpoints (i.e., 1a, 1b, and 2). If all three were rejected, the null hypotheses corresponding to the key secondary

immunogenicity endpoints (i.e., 1a, 1b, and 1c) were to be tested in order (i.e., following a Fixed-Sequence Method).

Sample Size Determination

The sample size was determined based on power calculations for both primary immunogenicity endpoints 1b and 2.

For primary immunogenicity endpoint 1b, assuming an SRR of 90% for CHIKV VLP pooled across lots (pooled CHIKV VLP group) and < 5% in the placebo group and a dropout rate of 10%, a sample size of 2700 subjects in the pooled CHIKV VLP group (900 per lot) and 450 subjects in the placebo group (3150 total subjects) was calculated to yield > 99.9% power for demonstrating superiority with a 70% margin for CHIKV VLP compared to placebo.

For primary immunogenicity endpoint 2, assuming a between-group mean difference of 0 and a standard deviation of 0.455 for $\log_{10}$-transformed titers, a sample size of 207 subjects for each of the three CHIKV VLP groups was calculated to yield 95% power for demonstrating lot-to-lot consistency using the (0.67, 1.5) equivalence margin for a single pairwise comparison. To account for dropouts, ≥ 300 subjects for each of the three CHIKV VLP groups were enrolled.

6.1.10 Study Population and Disposition

Table 2 displays a summary of analysis set by vaccine group. Totals of 919, 948, 927, and 464 participants were randomized to the PXVX0317 Lot (b) (4) group, PXVX0317 Lot (b) (4) group, PXVX0317 Lot (b) (4) group, and placebo group, respectively. Totals of 841, 860, 858, and 424 participants in the PXVX0317 Lot (b) (4) group, PXVX0317 Lot (b) (4) group, PXVX0317 Lot (b) (4) group, and placebo group, respectively, were included in the IEP.

Table 3 displays the distributions of demographic characteristics for the RP by vaccine group. No major imbalances in baseline characteristics were observed among the vaccine groups. Demographic characteristics were generally similar in both the IEP and SP.

Table 4 displays the dispositions of the RP by vaccine group, including the percentages of participants who completed each study visit and the study itself.

Table 2: Summary of All Enrolled Participants by Study Analysis Sets

Analysis Set	**PXVX0317 (b) (4) n (%)**	**PXVX0317 (b) (4) n (%)**	**PXVX0317 (b) (4) n (%)**	**Pooled PXVX0317 Group n (%)**	**Placebo Group n (%)**	**Total n (%)**
Randomized Population	919	948	927	2794	464	3258
Safety Population	918 (99.9)	945 (99.7)	927 (100)	2790 (99.9)	464 (100)	3254 (99.9)
mITT Population	905 (98.5)	938 (98.9)	920 (99.2)	2763 (98.9)	459 (98.9)	3222 (98.9)
Immunogenicity Evaluable Population	841 (91.5)	860 (90.7)	858 (92.6)	2559 (91.6)	424 (91.4)	2983 (91.6)

Source: Table 10 from EBSI-CV-317-004 Clinical Study Report.

Table 3: Summary of Study Population Demographics by Vaccine Group – RP

-	**PXVX0317 (b) (4) (N=919) n (%)**	**PXVX0317 (b) (4) (N=948) n (%)**	**PXVX0317 (b) (4) (N=927) n (%)**	**Pooled PXVX0317 Group (N=2794) n (%)**	**Placebo Group (N=464) n (%)**	**Total (N=3258) n (%)**
Age (years)	-	-	-	-	-	-
Mean (SD)	39 (14.4)	38 (14.3)	39 (14.0)	39 (14.3)	39 (14.4)	39 (14.3)
Median	38	38	38	38	38	38
Min, Max	12, 64	12, 64	12, 64	12, 64	12, 64	12, 64
Sex, n (%)	-	-	-	-	-	-
Male	467 (50.8)	442 (46.6)	449 (48.4)	1358 (48.6)	233 (50.2)	1591 (48.8)
Female	452 (49.2)	506 (53.4)	478 (51.6)	1436 (51.4)	231 (49.8)	1667 (51.2)
Child Bearing Potential[a]	253 (56.0)	305 (60.3)	288 (60.3)	846 (58.9)	136 (58.9)	982 (58.9)
Age, n (%)	-	-	-	-	-	-
12 to <18 years	67 (7.3)	76 (8.0)	74 (8.0)	217 (7.8)	37 (8.0)	254 (7.8)
18 to <46 years	541 (58.9)	552 (58.2)	543 (58.6)	1636 (58.6)	270 (58.2)	1906 (58.5)
46 to <65 years	311 (33.8)	320 (33.8)	310 (33.4)	941 (33.7)	157 (33.8)	1098 (33.7)
Race, n (%)	-	-	-	-	-	-
White	663 (72.1)	693 (73.1)	687 (74.1)	2043 (73.1)	341 (73.5)	2384 (73.2)
American Indian or Alaska Native	11 (1.2)	6 (0.6)	13 (1.4)	30 (1.1)	2 (0.4)	32 (1.0)
Asian	26 (2.8)	30 (3.2)	23 (2.5)	79 (2.8)	16 (3.4)	95 (2.9)
Black or African American	190 (20.7)	175 (18.5)	169 (18.2)	534 (19.1)	89 (19.2)	623 (19.1)
Native Hawaiian or Other Pacific Islander	2 (0.2)	4 (0.4)	0	6 (0.2)	4 (0.9)	10 (0.3)
Multiracial	23 (2.5)	32 (3.4)	23 (2.5)	78 (2.8)	8 (1.7)	86 (2.6)
Not reported	4 (0.4)	8 (0.8)	12 (1.3)	24 (0.9)	4 (0.9)	28 (0.9)
Ethnicity, n (%)	-	-	-	-	-	-
Hispanic or Latino	165 (18.0)	166 (17.5)	175 (18.9)	506 (18.1)	71 (15.3)	577 (17.7)
Not Hispanic or Latino	735 (80.0)	760 (80.2)	731 (78.9)	2226 (79.7)	379 (81.7)	2605 (80.0)
Not reported	18 (2.0)	22 (2.3)	21 (2.3)	61 (2.2)	14 (3.0)	75 (2.3)
Unknown	1 (0.1)	0	0	1 (<0.1)	0	1 (<0.1)
Height (cm)	-	-	-	-	-	-
Mean (SD)	171.4 (10.03)	170.4 (9.55)	170.7 (10.02)	170.8 (9.87)	171.2 (9.97)	170.9 (9.89)
Median	170.7	170.2	170.4	170.2	170.8	170.2
Min, Max	142.2, 201.9	146.3, 198.1	133.4, 203.2	133.4, 203.2	141.2, 201.2	133.4, 203.2

Table 3: Summary of Study Population Demographics by Vaccine Group – RP (continued)

-	**PXVX0317 (b) (4) (N=919) n (%)**	**PXVX0317 (b) (4) (N=948) n (%)**	**PXVX0317 (b) (4) (N=927) n (%)**	**Pooled PXVX0317 Group (N=2794) n (%)**	**Placebo Group (N=464) n (%)**	**Total (N=3258) n (%)**
Weight (kg)	-	-	-	-	-	-
Mean (SD)	78.5 (16.50)	78.4 (16.08)	78.3 (16.42)	78.4 (16.33)	77.6 (16.42)	78.3 (16.34)
Median	77.6	77.9	78.2	77.8	76.0	77.5
Min, Max	30.8, 132.6	35.7, 125.6	32.5, 130.2	30.8, 132.6	35.8, 128.2	30.8, 132.6
BMI (kg/m^2)	-	-	-	-	-	-
Mean (SD)	26.63 (4.579)	26.89 (4.480)	26.73 (4.499)	26.75 (4.519)	26.38 (4.570)	26.70 (4.527)
Median	26.78	26.90	26.71	26.77	26.26	26.71
Min, Max	13.06, 35.39	14.84, 34.95	14.90, 34.92	13.06, 35.39	15.66, 34.93	13.06, 35.39
Baseline Anti-CHIKV SNA Serostatus, n (%)	-	-	-	-	-	-
Negative (<LLOQ)	894 (97.3)	925 (97.6)	906 (97.7)	2725 (97.5)	458 (98.7)	3183 (97.7)
Positive (≥LLOQ)	24 (2.6)	18 (1.9)	21 (2.3)	63 (2.3)	6 (1.3)	69 (2.1)
Missing	1 (0.1)	5 (0.5)	0	6 (0.2)	0	6 (0.2)

[a]For the percentages of females of child-bearing potential, the denominator (N) is the number of females.
Source: Table 11 from EBSI-CV-317-004 Clinical Study Report.

Table 4: Summary of Participant Disposition

Disposition	**PXVX0317 (b) (4) n (%)**	**PXVX0317 (b) (4) n (%)**	**PXVX0317 (b) (4) n (%)**	**Pooled PXVX0317 Group n (%)**	**Placebo Group n (%)**	**Total n (%)**
Randomized	919	948	927	2794	464	3258
Treated	918 (99.9)	945 (99.7)	927 (100)	2790 (99.9)	464 (100.0)	3254 (99.9)
Completed study	803 (87.4)	837 (88.3)	832 (89.8)	2472 (88.5)	430 (92.7)	2902 (89.1)
Primary reason for not completing study:	-	-	-	-	-	-
Death	0	0	1 (0.1)	1 (<0.1)	0	0
Lost to follow up	65 (7.1)	70 (7.4)	58 (6.3)	193 (6.9)	23 (5.0)	216 (6.6)
Physician decision	2 (0.2)	1 (0.1)	1 (0.1)	4 (0.1)	0	4 (0.1)
Applicant decision	0	1 (0.1)	0	1 (<0.1)	0	1 (<0.1)
Withdrawn by participant	45 (4.9)	30 (3.2)	27 (2.9)	102 (3.7)	7 (1.5)	109 (3.3)
Other[a]	4 (0.4)	9 (0.9)	8 (0.9)	21 (0.8)	4 (0.9)	25 (0.8)
Study visit completion:	-	-	-	-	-	-
Day 1	919 (100)	948 (100)	927 (100)	2794 (100)	464 (100)	3258 (100)
Day 8	895 (97.4)	928 (97.9)	908 (98.0)	2731 (97.7)	456 (98.3)	3187 (97.8)
Day 15	879 (95.6)	914 (96.4)	891 (96.1)	2684 (96.1)	449 (96.8)	3133 (96.2)
Day 22	878 (95.5)	904 (95.4)	904 (97.5)	2686 (96.1)	443 (95.5)	3129 (96.0)
Day 29	879 (95.6)	910 (96.0)	904 (97.5)	2693 (96.4)	445 (95.9)	3138 (96.3)
Day 92	861 (93.7)	897 (94.6)	882 (95.1)	2640 (94.5)	442 (95.3)	3082 (94.6)
Day 183	803 (87.4)	837 (88.3)	832 (89.8)	2472 (88.5)	431 (92.9)	2903 (89.1)

[a]Examples of "other" withdrawals include the participant moving, deployed, incarcerated.

Source: Table 8 from EBSI-CV-317-004 Clinical Study Report.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Co-Primary Immunogenicity Endpoints

Table 5 displays the Day 22 adjusted GMTs and SRRs for co-primary immunogenicity endpoints 1a and 1b, respectively, in the IEP pooled across CHIKV VLP vaccine lots versus placebo. Adjusting for site, the GMT ratio was 206.12 with 95% CI (183.17, 231.95). The SRR difference was 96.6% with 95% CI (95.0%, 97.5%). As the LLs of the 2-sided CIs for GMT ratio and SRR difference were > 1 and > 70%, respectively, the success criteria for co-primary immunogenicity endpoints 1a and 1b were met.

Table 6 displays the Day 22 adjusted GMTs for each CHIKV VLP vaccine lot (b) (4) (b) (4) for co-primary immunogenicity endpoint 2 in the IEP. Adjusting for site, the GMT ratios between (b) (4) (b) (4) were 0.98 with 95% CI (0.85, 1.14), 0.97 with 95% CI (0.84, 1.12), and 0.95 with 95% CI (0.82, 1.10), respectively, among subjects 18 to <46 YOA. Because each pair of LLs and ULs of the 95% CIs was within the pre-defined equivalence margins of (0.67, 1.5), the success criterion for co-primary immunogenicity endpoint 2 was met.

As the success criteria for all three co-primary immunogenicity endpoints were met, the success criterion for the trial was met and $\alpha = 0.05$ (2-sided) was propagated to the evaluation of the key secondary immunogenicity endpoints.

Table 5: Day 22 Anti-CHIKV SNA GMT Ratio and Anti-CHIKV SNA SRR Difference – IEP

-	**Pooled PXVX0317 Group**	**Placebo Group**
N	2559	424
GMT (95% CI)[a]	1618.05 (1522.11, 1720.04)	7.85 (6.98, 8.83)
GMT Ratio (95% CI)[a]	206.12 (183.17, 231.95)	-
Seroresponse Rate, % (95% CI)[b]	2503/2559 97.8 (97.2, 98.3)	5/424 1.2 (0.5, 2.7)
SRR Difference, % (95% CI)[c]	96.6 (95.0, 97.5)	-

[a]GMT estimates, together with their 95% CIs, are derived from an ANCOVA model that includes site and vaccine group as fixed effects, assuming normality of the $\log_{10}$-transformed titers. GMTs, GMT ratio, and corresponding 95% CIs are all derived from the same model.
[b]95% CIs of seroresponse rates are based on the Wilson method.
[c]95% CIs are based on the Newcombe hybrid score method.
Source: Adapted from both Tables 14 and 15 from EBSI-CV-317-004 Clinical Study Report.

Table 6: Day 22 Pairwise Lot Comparison of Anti-CHIKV SNA GMT Ratio Among Subjects 18 to <46 YOA – IEP

-	**PXVX0317** (b) (4)	**PXVX0317** (b) (4)	**PXVX0317** (b) (4)
N	488	498	494
GMT (95% CI)[a]	1856.97 (1641.36, 2100.90)	1887.29 (1671.99, 2130.32)	1950.47 (1723.63, 2207.15)
GMT Ratio (b) (4) (95% CI)[a]	0.98 (0.85, 1.14)	-	-
GMT Ratio (b) (4) (95% CI)[a]	0.97 (0.84, 1.12)	-	-
GMT Ratio (b) (4) (95% CI)[a]	0.95 (0.82, 1.10)	-	-

[a]GMT estimates, together with their 95% CIs, are derived from an ANCOVA model that includes site and product lot as fixed effects, assuming normality of the $\log_{10}$-transformed titers. GMTs, GMT ratios, and corresponding 95% CIs are all derived from the same model.
Source: Table 16 from EBSI-CV-317-004 Clinical Study Report.

Reviewer's Comments:

- *Five placebo participants recorded positive seroresponse on Day 22. In Response to IR 13, the Applicant noted that Day 22 was the only time point where these placebo participants had an anti-CHIKV SNA titer ≥ 100, except for one participant for whom there was no Day 183 data available. The Applicant stated that "This observation suggests that natural CHIKV infection is unlikely, as the expectation in that case would be positive titers above the LLOQ at subsequent study immunogenicity time points (i.e., Day 183) and this was not observed. An assay error is unlikely based on the frequency and pattern of errors. These single seropositive titer values on Day 22 only are considered anomalous with a possible root cause of human error with sample management, either at the clinical sites or during processing of samples."*

- *In the original CSRs for Studies EBSI-CV-317-004 and EBSI-CV-317-005, the Chikungunya Luciferase Neutralization Assay was used to quantitate anti-CHIKV SNA titer for both the primary and key secondary immunogenicity objectives. The ULOQ was set at 99599.9 in an assay validation report addendum which examined intermediate precision but not dilutional linearity. No formal ULOQ was established in the original assay validation report. As the ULOQ of 99599.9 was not considered to be adequately validated by CBER, in response to an IR, an ULOQ of 10794.8 was established based on all available intermediate precision and dilutional linearity results from the original assay validation report.*

  Additional analyses of immunogenicity were conducted using the ULOQ of 10794.8. As SRR was defined based on a threshold of anti-CHIKV SNA titer ≥ 100, the immunogenicity analyses of SRR difference did not change regardless of the ULOQ. For Study EBSI-CV-317-004, additional analyses of GMT ratio for both co-primary immunogenicity endpoints 1a and 2 are displayed in both Tables 7 and 8,

respectively. The results of the additional analyses were similar to the original analysis results and met the success criteria.

Table 7: Additional Analyses of Day 22 Anti-CHIKV SNA GMT Ratio – IEP

-	**Pooled PXVX0317 Group**	**Placebo Group**
N	2559	424
GMT (95% CI)[a]	1596.98 (1504.11, 1695.57)	7.86 (7.00, 8.81)
GMT Ratio (95% CI)[a]	203.29 (181.08, 228.23)	-

[a]GMT estimates, together with their 95% CIs, are derived from an ANCOVA model that includes site and vaccine group as fixed effects, assuming normality of the log_{10}-transformed titers. GMTs, GMT ratio, and corresponding 95% CIs are all derived from the same model.
Source: Adapted from Table 14.2.2.1.1 from Response to IR 12.

Table 8: Additional Analyses of Day 22 Pairwise Lot Comparison of Anti-CHIKV SNA GMT Ratio Among Subjects 18 to <46 YOA – IEP

-	**PXVX0317** (b) (4)	**PXVX0317** (b) (4)	**PXVX0317** (b) (4)
N	488	498	494
GMT (95% CI)[a]	1832.96 (1624.87, 2067.71)	1860.37 (1652.85, 2093.94)	1913.95 (1696.30, 2159.53)
GMT Ratio (b) (4) (95% CI)[a]	0.99 (0.86, 1.13)	-	-
GMT Ratio (b) (4) (95% CI)[a]	0.97 (0.84, 1.12)	-	-
GMT Ratio (b) (4) (95% CI)[a]	0.96 (0.83, 1.10)	-	-

[a]GMT estimates, together with their 95% CIs, are derived from an ANCOVA model that includes site and product lot as fixed effects, assuming normality of the log_{10}-transformed titers. GMTs, GMT ratios, and corresponding 95% CIs are all derived from the same model.
Source: Adapted from Table 14.2.3.1 from Response to IR 12.

6.1.11.2 Analyses of Key Secondary Immunogenicity Endpoints

Table 9 displays the Day 15, Day 183, and Day 8 SRR analyses for key secondary immunogenicity endpoints 1a, 1b, and 1c, respectively, in the IEP pooled across CHIKV VLP vaccine lots versus placebo.

For key secondary immunogenicity endpoint 1a, the SRR difference was 96.0% with 95% CI (94.3%, 96.8%). As the LL of the 2-sided CI for SRR difference was > 70%, the success criterion for key secondary immunogenicity endpoint 1a was met and $\alpha = 0.05$ (2-sided) was propagated to the evaluation of key secondary immunogenicity endpoint 1b.

For key secondary immunogenicity endpoint 1b, the SRR difference was 84.0% with 95% CI (81.7%, 85.6%). As the LL of the 2-sided CI for SRR difference was > 0%, the success criterion for key secondary immunogenicity endpoint 1b was met and $\alpha = 0.05$

(2-sided) was propagated to the evaluation of key secondary immunogenicity endpoint 1c.

For key secondary immunogenicity endpoint 1c, the SRR difference was 46.1% with 95% CI (43.8%, 48.1%). As the LL of the 2-sided CI for SRR difference was > 0%, the success criterion for key secondary immunogenicity endpoint 1c was met.

Table 9: Days 15, 183, and 8 Anti-CHIKV SNA SRR Difference – IEP

-	**Pooled PXVX0317 Group**	**Placebo Group**
N	2559	424
Day 15 Seroresponse Rate, % (95% CI)[a]	2355/2434 96.8 (96.0, 97.4)	3/395 0.8 (0.3, 2.2)
Day 15 SRR Difference, % (95% CI)[b]	96.0 (94.3, 96.8)	-
Day 183 Seroresponse Rate, % (95% CI)[a]	1967/2301 85.5 (84.0, 86.9)	6/401 1.5 (0.7, 3.2)
Day 183 SRR Difference, % (95% CI)[b]	84.0 (81.7, 85.6)	-
Day 8 Seroresponse Rate, % (95% CI)[a]	1169/2510 46.6 (44.6, 48.5)	2/419 0.5 (0.1, 1.7)
Day 8 SRR Difference, % (95% CI)[b]	46.1 (43.8, 48.1)	-

[a]95% CIs of seroresponse rates are based on the Wilson method.
[b]95% CIs are based on the Newcombe hybrid score method.
Source: Adapted from Table 17 from EBSI-CV-317-004 Clinical Study Report.

6.1.12 Safety Analyses

Solicited ARs

Table 10 displays the percentages of subjects reporting solicited local and systemic reactions within 7 days following vaccination in the SP pooled across CHIKV VLP vaccine lots versus placebo. The percentages of subjects reporting solicited local and systemic reactions were generally higher in the pooled CHIKV VLP group than the placebo group. For both the pooled CHIKV VLP group and placebo group, the most frequently reported solicited local reaction was pain (23.7% and 10.7%, respectively), while the most frequently reported solicited systemic reaction was fatigue (19.9% and 17.0%, respectively).

One grade 4 systemic solicited AE of 105ºF fever was reported by a CHIKV VLP vaccine recipient, but the site deemed this entry an error.

Unsolicited AEs

Table 11 displays the percentages of subjects reporting unsolicited AEs within 28 days following vaccination as well as the percentages of subjects reporting AESIs, MAAEs, and SAEs within six months following vaccination in the SP pooled across CHIKV VLP vaccine lots versus placebo.

Within 28 days following vaccination, regardless of relationship to study vaccination, there were similar percentages of unsolicited AEs between the pooled CHIKV VLP

group and placebo group. There were also similar percentages of unsolicited AEs considered by the investigator to be related to study vaccination between both groups.

Within six months following vaccination, regardless of relationship to study vaccination, there were similar percentages of MAAEs between both groups. A total of 0.8% and 0.2% of subjects reported SAEs in the pooled CHIKV VLP group and placebo group, respectively. Five AESIs were reported in the pooled CHIKV VLP group, while none were reported in the placebo group. Two unsolicited AEs leading to study discontinuation were reported in the pooled CHIKV VLP group, while none were reported in the placebo group. One death was reported in the pooled CHIKV VLP group and it was not considered to be related to the study vaccination by the investigator. No deaths were reported in the placebo group.

Within six months following vaccination, one SAE (retinal detachment) considered by the investigator to be related to study vaccination was reported in the pooled CHIKV VLP group while none were reported in the placebo group. The SAE was later assessed by the Applicant and independent SMC chair as unrelated due to prior medical history. Two related AESIs were reported in the pooled CHIKV VLP group while none were reported in the placebo group. A total of 0.5% of subjects reported related MAAEs in the pooled CHIKV VLP group while none were reported in the placebo group.

Table 10: Summary of Participants with Solicited Events by Vaccine Group and Highest Reported Severity – SP

Local Adverse Reactions	**Pooled PXVX0317 Group (N=2790) n (%)**	**Placebo Group (N=464) n (%)**
Pain	656/2764 (23.7)	49/458 (10.7)
Pain, Grade 3	4/2764 (0.1)	0/458
Redness	13/2764 (0.5)	0/458
Redness, Grade 3	1/2764 (<0.1)	0/458
Swelling	10/2764 (0.4)	0/458
Swelling, Grade 3	0/2764	0/458
Systemic Adverse Reactions	-	-
Fever	25/2760 (0.9)	1/457 (0.2)
Fever, Grade 3	6/2760 (0.2)	0/457
Fever, Grade 4	1/2760 (<0.1)	0/457
Chills	238/2764 (8.6)	15/458 (3.3)
Chills, Grade 3	4/2764 (0.1)	0/458
Fatigue	551/2764 (19.9)	78/458 (17.0)
Fatigue, Grade 3	19/2764 (0.7)	1/458 (0.2)
Headache	498/2765 (18.0)	76/458 (16.6)
Headache, Grade 3	9/2765 (0.3)	2/458 (0.4)
Myalgia	486/2764 (17.6)	44/458 (9.6)
Myalgia, Grade 3	11/2764 (0.4)	2/458 (0.4)
Arthralgia	214/2764 (7.7)	33/458 (7.2)
Arthralgia, Grade 3	7/2764 (0.3)	1/458 (0.2)
Nausea	208/2764 (7.5)	30/458 (6.6)
Nausea, Grade 3	12/2764 (0.4)	0/458

N = The number of participants in the SP. For each solicited event, the denominator is the number of participants who completed the diary card for that solicited event following vaccination.
n/% = number/percentage of participants presenting at least one type of event.
Grade 3 pain, chills, fatigue, headache, myalgia, arthralgia, nausea: defined as significant, prevents daily activity.
Redness and swelling defined as ≥ 25 mm; Grade 3 redness and swelling defined as > 100 mm.
Fever defined as ≥ 38.0°C/100.4°F; Grade 3 fever defined as ≥ 39.0°C/102.2°F. Grade 4 fever defined as > 40.0°C/104°F.
Source: Adapted from Table 14.3.2.2.1 from Response to IR 17.

Table 11: Summary of Unsolicited Adverse Events – SP

-	**PXVX0317 (b) (4) (N=918) n (%)**	**PXVX0317 (b) (4) (N=945) n (%)**	**PXVX0317 (b) (4) (N=927) n (%)**	**Pooled PXVX0317 Group (N=2790) n (%)**	**Placebo Group (N=464) n (%)**
Regardless of relationship to study vaccination	-	-	-	-	-
Unsolicited AEs	138 (15.0)	143 (15.1)	152 (16.4)	433 (15.5)	59 (12.7)
Grade 3 or higher	12 (1.3)	9 (1.0)	10 (1.1)	31 (1.1)	1 (0.2)
SAE	10 (1.1)	7 (0.7)	6 (0.6)	23 (0.8)	1 (0.2)
Discontinued study due to unsolicited AE	0	1 (0.1)	1 (0.1)	2 (0.1)	0
Fatal AE	0	0	1 (0.1)	1 (<0.1)	0
AESI	2 (0.2)	2 (0.2)	1 (0.1)	5 (0.2)	0
MAAE	81 (8.8)	83 (8.8)	85 (9.2)	249 (8.9)	41 (8.8)
Related to study vaccination	-	-	-	-	-
Unsolicited AEs	15 (1.6)	16 (1.7)	22 (2.4)	53 (1.9)	3 (0.6)
Grade 3 or higher	0	0	1 (0.1)	1 (<0.1)	0
SAE	0	1 (0.1)	0	1 (<0.1)	0
AESI	0	1 (0.1)	1 (0.1)	2 (<0.1)	0
MAAE	5 (0.5)	5 (0.5)	4 (0.4)	14 (0.5)	0

Unsolicited AEs (including Grade 3 or higher) were collected through Day 29. All other AEs were collected through Day 183.
Source: Adapted from Table 14.3.2.1 from Response to IR 17; the related AESIs and related MAAEs were derived by the reviewer from the SDTM datasets.

6.2 Clinical Study EBSI-CV-317-005

Title of Study: A Phase 3 safety and immunogenicity trial of the VLP-based Chikungunya virus vaccine PXVX0317 in adults ≥65 YOA.

Dates:
1. Study start date (first participant enrolled): 12 May 2022
2. Study end date (last participant completed): 5 June 2023

6.2.1 Objectives

Primary Immunogenicity Objective:

1. To compare the anti-CHIKV SNA response to CHIKV VLP vaccine and placebo at Day 22, as measured by GMT and clinically relevant difference in seroresponse rate[a] (CHIKV VLP vaccine minus placebo) in adults ≥65 YOA.

[a]Seroresponse rate is defined as the percentage of participants who achieve an anti-CHIKV SNA titer ≥ 100.

Safety Objective:

1. To evaluate the safety of CHIKV VLP vaccine in adults ≥65 YOA.

Key Secondary Immunogenicity Objective:

1. To compare the anti-CHIKV SNA response to CHIKV VLP vaccine and placebo at Day 15 and Day 183, as measured by seroresponse rate.

6.2.2 Design Overview

Approximately 400 subjects were randomized in a 1:1 allocation ratio to receive either CHIKV VLP vaccine or placebo on Day 1, stratified by age category (i.e., ≥65 to <75 or ≥75 YOA).

For immunogenicity assessment, for all subjects, blood samples were collected at pre-Dose 1 (Day 1), Day 15, Day 22, and Day 183. For safety assessment, for all subjects, solicited ARs were collected through Day 8. Unsolicited AEs were collected through Day 29. AESIs, MAAEs, and SAEs were collected through Day 183. AESI was defined as new onset or worsening arthralgia that is medically attended, as indicated on the CRF.

6.2.3 Population

Subjects ≥65 YOA were enrolled.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The CHIKV VLP vaccine was a sterile aqueous buffered suspension comprised of 40 µg CHIKV VLP adsorbed on 300 µg aluminum hydroxide adjuvant and formulation buffer supplied as a single dose in a pre-filled 1 mL glass syringe with a 0.8 mL deliverable volume.

Placebo (formulation buffer) was supplied as a single dose of 0.8 mL in a pre-filled syringe.

6.2.6 Sites and Centers

A total of 10 sites in the U.S. participated in this clinical trial.

6.2.7 Surveillance/Monitoring

Please refer to the clinical review.

6.2.8 Endpoints and Study Success Criteria

Co-Primary Immunogenicity Endpoints:

1a. Anti-CHIKV SNA GMT at Day 22 for CHIKV VLP vaccine and placebo.
- Success criterion: The LL of the 2-sided 95% CI for the GMT ratio is > 1.

1b. Anti-CHIKV SNA seroresponse rate (CHIKV VLP vaccine minus placebo) at Day 22.
- Success criterion: The LL of the 2-sided 95% CI for the SRR difference is > 70%.

Safety Endpoints:

1. In all participants:
   - Incidence of solicited ARs through Day 8 for CHIKV VLP vaccine and placebo.
   - Incidence of unsolicited AEs through Day 29 for CHIKV VLP vaccine and placebo.
   - Incidence of AESIs, MAAEs, and SAEs through Day 183 for CHIKV VLP vaccine and placebo.

Key Secondary Immunogenicity Endpoints:

1a. Anti-CHIKV SNA seroresponse rate (CHIKV VLP vaccine minus placebo) at Day 15.
- Success criterion: The LL of the 2-sided 95% CI for the SRR difference is > 0%.

1b. Anti-CHIKV SNA seroresponse rate (CHIKV VLP vaccine minus placebo) at Day 183.
- Success criterion: The LL of the 2-sided 95% CI for the SRR difference is > 0%.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

The statistical analyses for both the GMT endpoint and SRR endpoints were the same as the statistical analyses for both the GMT endpoints and SRR endpoints for Study EBSI-CV-317-004 as described in Section 6.1.9.

All immunogenicity analyses were performed on the same analysis set (i.e., the IEP) as defined in Section 6.1.9.

Analysis of Safety

All safety data were summarized descriptively and were performed on the same analysis set (i.e., the SP) as defined in Section 6.1.9.

Multiplicity Adjustment

The success criterion of the trial was the rejection of both null hypotheses corresponding to the two co-primary immunogenicity endpoints (i.e., 1a, and 1b). If both were rejected, the null hypotheses corresponding to the key secondary immunogenicity endpoints (i.e., 1a and 1b) were to be tested in order (i.e., following a Fixed-Sequence Method).

Sample Size Determination

The sample size was determined based on a power calculation for primary immunogenicity endpoint 1b only. Assuming an SRR of 90% in the CHIKV VLP group and < 5% in the placebo group and a dropout rate of 10%, a sample size of 400 (200 per group) subjects was calculated to yield > 99.9% power for demonstrating superiority under a 70% margin for CHIKV VLP compared to placebo.

6.2.10 Study Population and Disposition

Table 12 displays the sample size in each analysis set by vaccine group. Totals of 206 and 207 participants were randomized to the PXVX0317 group and placebo group, respectively. Totals of 189 and 183 participants in the PXVX0317 group and placebo group, respectively, were included in the IEP.

Table 13 displays the distributions of demographic characteristics for the RP by vaccine group. No major imbalances in baseline characteristics were observed between the vaccine groups. Demographic characteristics were generally similar in both the IEP and SP.

Table 14 displays the dispositions of the RP by vaccine group, including the percentages of participants who completed each study visit and the study itself.

Table 12: Summary of All Enrolled Participants by Study Analysis Sets

Analysis Set	**PXVX0317 Group n (%)**	**Placebo Group n (%)**	**Total n (%)**
Randomized Population	206	207	413
Safety Population	206 (100)	207 (100)	413 (100)
mITT Population	205 (99.5)	205 (99.0)	410 (99.3)
Immunogenicity Evaluable Population	189 (91.7)	183 (88.4)	372 (90.1)

Source: Table 10 from EBSI-CV-317-005 Clinical Study Report.

Table 13: Summary of Study Population Demographics by Vaccine Group – RP

-	**PXVX0317 Group (N=206) n (%)**	**Placebo Group (N=207) n (%)**	**Total (N=413) n (%)**
Age (years)	-	-	-
Mean (SD)	71 (5.3)	71 (4.5)	71 (4.9)
Median	70	70	70
Min, Max	65, 95	65, 84	65, 95
Sex, n (%)	-	-	-
Male	81 (39.3)	90 (43.5)	171 (41.4)
Female	125 (60.7)	117 (56.5)	242 (58.6)
Age, n (%)	-	-	-
≥65 to <75 years	159 (77.2)	159 (76.8)	318 (77.0)
≥75 years	47 (22.8)	48 (23.2)	95 (23.0)
Race, n (%)	-	-	-
White	176 (85.4)	168 (81.2)	344 (83.3)
American Indian or Alaska Native	1 (0.5)	1 (0.5)	2 (0.5)
Asian	4 (1.9)	1 (0.5)	5 (1.2)
Black or African American	20 (9.7)	29 (14.0)	49 (11.9)
Multiracial	4 (1.9)	5 (2.4)	9 (2.2)
Not reported	1 (0.5)	3 (1.4)	4 (1.0)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	93 (45.1)	90 (43.5)	183 (44.3)
Not Hispanic or Latino	112 (54.4)	116 (56.0)	228 (55.2)
Not reported	1 (0.5)	1 (0.5)	2 (0.5)
Height (cm)	-	-	-
Mean (SD)	166.4 (9.42)	167.1 (9.84)	166.8 (9.63)
Median	165.1	167.6	166.6
Min, Max	144.8, 195.6	142.2, 190.5	142.2, 195.6
Weight (kg)	-	-	-
Mean (SD)	75.8 (13.61)	77.2 (13.29)	76.5 (13.45)
Median	76.2	75.4	76.2
Min, Max	47.2, 110.2	44.9, 111.6	44.9, 111.6
BMI (kg/m^2)	-	-	-
Mean (SD)	27.3 (3.98)	27.6 (3.90)	27.5 (3.94)
Median	27.5	27.5	27.5
Min, Max	17.5, 34.8	19.3, 34.9	17.5, 34.9
Baseline Anti-CHIKV SNA Serostatus, n (%)	-	-	-
Negative (<LLOQ)	201 (97.6)	196 (94.7)	397 (96.1)
Positive (≥LLOQ)	5 (2.4)	10 (4.8)	15 (3.6)
Missing	0	1 (0.5)	1 (0.2)

Source: Table 11 from EBSI-CV-317-005 Clinical Study Report.

Table 14: Summary of Participant Disposition

-	**PXVX0317 Group n (%)**	**Placebo Group n (%)**	**Total n (%)**
Randomized	206	207	413
Treated/Exposed	206 (100)	207 (100)	413 (100)
Completed study	200 (97.1)	188 (90.8)	388 (93.9)
Primary reason for not completing study:	-	-	-
Death	1 (0.5)	1 (0.5)	2 (0.5)
Lost to follow up	3 (1.5)	8 (3.9)	11 (2.7)
Withdrawn by participant	2 (1.0)	10 (4.8)	12 (2.9)
Study visit completion (based on database visit):	-	-	-
Day 1	206 (100)	207 (100)	413 (100)
Day 15	197 (95.6)	198 (95.7)	395 (95.6)
Day 22	199 (96.6)	195 (94.2)	394 (95.4)
Day 29	203 (98.5)	203 (98.1)	406 (98.3)
Day 92	200 (97.1)	196 (94.7)	396 (95.9)
Day 183	200 (97.1)	188 (90.8)	388 (93.9)

Source: Table 8 from EBSI-CV-317-005 Clinical Study Report.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Co-Primary Immunogenicity Endpoints

Table 15 displays the Day 22 adjusted GMTs and SRRs for both co-primary immunogenicity endpoints 1a and 1b, respectively, in the IEP for CHIKV VLP vaccine versus placebo. Adjusting for site, the GMT ratio was 89.64 with 95% CI (68.62,117.10). The SRR difference was 86.2% with 95% CI (80.0%, 90.3%). As the LLs of the 2-sided CIs for GMT ratio and SRR difference were > 1 and > 70%, respectively, the success criteria for both co-primary immunogenicity endpoints 1a and 1b were met.

As the success criteria for both co-primary immunogenicity endpoints were met, the success criterion for the trial was met and $\alpha = 0.05$ (2-sided) was propagated to the evaluation of the key secondary immunogenicity endpoints.

Table 15: Day 22 Anti-CHIKV SNA GMT Ratio and Anti-CHIKV SNA SRR Difference – IEP

-	**PXVX0317 Group**	**Placebo Group**
N	189	183
GMT (95% CI)[a]	723.93 (584.13, 897.20)	8.08 (6.50, 10.04)
GMT Ratio (95% CI)[a]	89.64 (68.62,117.10)	-
Seroresponse Rate, % (95% CI)[b]	165/189 87.3 (81.8, 91.3)	2/183 1.1 (0.3, 3.9)
SRR Difference, % (95% CI)[c]	86.2 (80.0, 90.3)	-

[a]GMT estimates, together with their 95% CIs, are derived from an ANCOVA model that includes site and vaccine group as fixed effects, assuming normality of the $\log_{10}$-transformed titers. GMTs, GMT ratio, and corresponding 95% CIs are all derived from the same model.
[b]95% CIs of seroresponse rates are based on the Wilson method.
[c]95% CIs are based on the Newcombe hybrid score method.
Source: Adapted from Tables 14 and 15 from EBSI-CV-317-005 Clinical Study Report.

Reviewer's Comments:

- *Two placebo participants recorded positive seroresponse on Day 22. In Response to IR 13, the Applicant noted that Day 22 was the only time point where these placebo participants had an anti-CHIKV SNA titer ≥ 100. Per the Reviewer's Comment from Section 6.1.11.1, for Study EBSI-CV-317-005, the same rationale of human error was provided by the Applicant for why these placebo participants recorded positive seroresponse on Day 22.*

- *Per the Reviewer's Comment from Section 6.1.11.1, for Study EBSI-CV-317-005, additional analyses of GMT ratio for co-primary immunogenicity endpoint 1a which used the ULOQ of 10794.8 are displayed in Table 16. The results of the additional analyses met the success criterion.*

Table 16: Additional Analyses of Day 22 Anti-CHIKV SNA GMT Ratio – IEP

-	**PXVX0317 Group**	**Placebo Group**
N	189	183
GMT (95% CI)[a]	720.98 (582.33, 892.65)	8.08 (6.51, 10.04)
GMT Ratio (95% CI)[a]	89.18 (68.35, 116.36)	-

[a]GMT estimates, together with their 95% CIs, are derived from an ANCOVA model that includes site and vaccine group as fixed effects, assuming normality of the $\log_{10}$-transformed titers. GMTs, GMT ratio, and corresponding 95% CIs are all derived from the same model.
Source: Adapted from Table 14.2.2.1.1 from Response to IR 12.

6.2.11.2 Analyses of Key Secondary Immunogenicity Endpoints

Table 17 displays both the Day 15 and Day 183 SRRs for both key secondary immunogenicity endpoints 1a and 1b, respectively, in the IEP for CHIKV VLP vaccine versus placebo.

For key secondary immunogenicity endpoint 1a, the SRR difference was 79.5% with 95% CI (72.3%, 84.6%). As the LL of the 2-sided CI for SRR difference was > 0%, the success criterion for key secondary immunogenicity endpoint 1a was met and $\alpha = 0.05$ (2-sided) was propagated to the evaluation of key secondary immunogenicity endpoint 1b.

For key secondary immunogenicity endpoint 1b, the SRR difference was 74.4% with 95% CI (67.1%, 80.1%). As the LL of the 2-sided CI for SRR difference was > 0%, the success criterion for key secondary immunogenicity endpoint 1b was met.

Table 17: Days 15 and 183 Anti-CHIKV SNA SRR Difference – IEP

-	**PXVX0317 Group**	**Placebo Group**
N	189	183
Day 15 Seroresponse Rate, % (95% CI)[a]	149/181 82.3 (76.1, 87.2)	5/176 2.8 (1.2, 6.5)
Day 15 SRR Difference, % (95% CI)[b]	79.5 (72.3, 84.6)	-
Day 183 Seroresponse Rate, % (95% CI)[a]	139/184 75.5 (68.9, 81.2)	2/173 1.2 (0.3, 4.1)
Day 183 SRR Difference, % (95% CI)[b]	74.4 (67.1, 80.1)	-

[a]95% CIs of seroresponse rates are based on the Wilson method.
[b]95% CIs are based on the Newcombe hybrid score method.
Source: Adapted from Table 16 from EBSI-CV-317-005 Clinical Study Report.

6.2.12 Safety Analyses

Solicited ARs

Table 18 displays the percentages of subjects reporting solicited local and systemic reactions within 7 days following vaccination in the SP for CHIKV VLP vaccine versus placebo. The percentages of subjects reporting solicited local and systemic reactions were generally higher in the CHIKV VLP group than the placebo group. For both the CHIKV VLP group and placebo group, the most frequently reported solicited local reaction was pain (5.4% and 1.5%, respectively). The most frequently reported solicited systemic reactions were both fatigue and myalgia in the CHIKV VLP group (each at 6.3%) and headache in the placebo group (7.5%).

Unsolicited AEs

Table 19 displays the percentages of subjects reporting unsolicited AEs within 28 days following vaccination as well as the percentages of subjects reporting AESIs, MAAEs, and SAEs within six months following vaccination in the SP for CHIKV VLP vaccine versus placebo.

Within 28 days following vaccination, regardless of relationship to study vaccination, there were similar percentages of unsolicited AEs between the CHIKV VLP group and placebo group. There were also similar percentages of unsolicited AEs considered by the investigator to be related to study vaccination between both groups.

Within six months following vaccination, regardless of relationship to study vaccination, there were similar percentages of MAAEs and SAEs between both groups. One unsolicited AE leading to study discontinuation each was reported in the CHIKV VLP group and the placebo group. One AESI was reported in the placebo group while none were reported in the CHIKV VLP group. One death was each reported in the CHIKV VLP group and the placebo group and neither was considered to be related to the study vaccination by the investigator.

Within six months following vaccination, one MAAE considered by the investigator to be related to study vaccination was reported in the CHIKV VLP group while none were reported in the placebo group. No related AESIs or related SAEs were reported.

Table 18: Summary of Participants with Solicited Events by Vaccine Group and Highest Reported Severity – SP

Local Adverse Reactions	**PXVX0317 Group (N=205) n (%)**	**Placebo Group (N=200) n (%)**
Pain	11 (5.4)	3 (1.5)
Pain, Grade 3	0	0
Redness	0	1 (0.5)
Redness, Grade 3	0	0
Swelling	0	0
Swelling, Grade 3	0	0
Systemic Adverse Reactions	-	-
Fever	0	2 (1.0)
Fever, Grade 3	0	0
Chills	6 (2.9)	6 (3.0)
Chills, Grade 3	0	0
Fatigue	13 (6.3)	12 (6.0)
Fatigue, Grade 3	1 (0.5)	0
Headache	9 (4.4)	15 (7.5)
Headache, Grade 3	1 (0.5)	0
Myalgia	13 (6.3)	13 (6.5)
Myalgia, Grade 3	0	0
Arthralgia	6 (2.9)	8 (4.0)
Arthralgia, Grade 3	0	0
Nausea	6 (2.9)	3 (1.5)
Nausea, Grade 3	0	0

N = The number of participants who completed the diary card following vaccination.
n/% = number/percentage of participants presenting at least one type of event.
Grade 3 pain, chills, fatigue, headache, myalgia, arthralgia, nausea: defined as significant, prevents daily activity.
Redness and swelling defined as ≥ 25 mm; Grade 3 redness and swelling defined as > 100 mm.
Fever defined as ≥ 38.0°C/100.4°F; Grade 3 fever defined as ≥ 39.0°C/102.2°F.
Source: Adapted from Table 14.3.2.2.1 from Response to IR 17.

Table 19: Summary of Unsolicited Adverse Events – SP

-	PXVX0317 Group (N=206) n (%)	Placebo Group (N=207) n (%)
Regardless of relationship to study vaccination	-	-
Unsolicited AEs	26 (12.6)	32 (15.5)
Grade 3 or higher	3 (1.9)	3 (1.4)
SAEs	4 (1.9)	3 (1.4)
Discontinued study due to unsolicited AE	1 (0.5)	1 (0.5)
Fatal AE	1 (0.5)	1 (0.5)
AESI	0	1 (0.5)
MAAE	19 (9.2)	23 (11.1)
Related to study vaccination	-	-
Unsolicited AEs	3 (1.5)	3 (1.4)
Grade 3 or higher	0	0
MAAE	1 (0.5)	0

Unsolicited AEs (including Grade 3 or higher) were collected through Day 29. All other AEs were collected through Day 183.
Source: Adapted from Table 14.3.2.1 from Response to IR 17; the related MAAEs were derived by the reviewer from the SDTM datasets.

7. Integrated Overview of Efficacy

An Integrated Summary of Efficacy (ISE) was submitted, in which immunogenicity data were presented by individual study. No pooled immunogenicity analyses across studies were conducted. Therefore, all immunogenicity analyses were reviewed for the individual studies in Section 6 and no additional review of the ISE is performed.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

Both solicited ARs and unsolicited AEs were summarized descriptively by the vaccine groups defined below.

1. PXVX0317 single dose group: Subjects who received a single dose of 40 µg CHIKV VLP with 300 µg adjuvant in either Study EBSI-CV-317-004, EBSI-CV-317-005, EBSI-CV-317-002, EBSI-CV-317-010, or PXVX-CV-317-001 Groups 8 and 10.
   - N = 3141.

2. PXVX0317 other dose group: Subjects who received a dose of 6, 10, or 20 µg CHIKV VLP with or without 300 µg adjuvant administered twice separated by 14 or 28 days in Study PXVX-CV-317-001 Groups 1 – 7 and 9.
   - N = 381.
   - Solicited ARs were only included after the first dose.

3. Pooled PXVX0317 group: Both the PXVX0317 single dose group and PXVX0317 other dose group combined.

- N = 3522.

4. Pooled placebo group: Subjects who received a single dose of placebo in either Study EBSI-CV-317-004, EBSI-CV-317-005, or PXVX-CV-317-001.
   - N = 675.
   - Four subjects who only received placebo in Study PXVX-CV-317-001 were included. For these four subjects, solicited ARs were only included after the first dose.

For all five studies, the safety analysis set was the SP as defined in Section 6.1.9.

8.2 Safety Database

Safety data from Studies EBSI-CV-317-004, EBSI-CV-317-005, PXVX-CV-317-001, EBSI-CV-317-002, and EBSI-CV-317-010 were included for analyses of both solicited ARs and unsolicited AEs. Phase 3 Studies EBSI-CV-317-004 and EBSI-CV-317-005 are individually reviewed in Section 6; brief descriptions of the experimental designs of the three Phase 2 clinical studies are included in Sections 8.2.1 to 8.2.3.

8.2.1 Clinical Study PXVX-CV-317-001

Title of Study: A Phase 2 parallel-group, randomized, double-blind study to assess the safety and immunogenicity of PXVX0317 (Chikungunya virus virus-like particle vaccine [CHIKV VLP], unadjuvanted or alum-adjuvanted).

As safety data from PXVX-CV-317-001 were only submitted to support the ISS, a full review of PXVX-CV-317-001 is not provided in this review memo. Instead, a summary of the design of PXVX-CV-317-001 is provided.

PXVX-CV-317-001 was a randomized, double-blind study to evaluate both the immunogenicity and safety of PXVX0317 administered according to different dose levels, number of doses, and unadjuvanted or alum-adjuvanted versus placebo in subjects 18 to <46 YOA. A total of 445 subjects were enrolled in 10 parallel groups with dosing schedules displayed in Table 20.

Table 20: Study Treatment Groups

Treatment	N	Day 1	Day 15	Day 29	Day 547
Group 1	53	20/unadjuvanted	Placebo	20/unadjuvanted	N/A
Group 2	52	6/300	Placebo	6/300	N/A
Group 3	51	10/300	Placebo	10/300	N/A
Group 4	50	20/300	Placebo	20/300	40/300
Group 5	53	Placebo	6/300	6/300	N/A
Group 6	53	Placebo	10/300	10/300	N/A
Group 7	51	Placebo	20/300	20/300	N/A
Group 8	52	Placebo	Placebo	40/300	N/A
Group 9[a]	20	20/300	N/A	20/300	N/A
Group 10[a]	10	40/300	N/A	N/A	N/A

Intramuscular Administered Dose of VLP in µg/(b) (4) in µg or Diluent Placebo Control.
N = number of enrolled subjects; N/A = not applicable.
[a]Open label group.
Source: Adapted from both Tables 6 and 14 from PXVX-CV-317-001 Clinical Study Report.

Safety data from all 445 subjects were included in the ISS.

8.2.2 Clinical Study EBSI-CV-317-002

Title of Study: A Phase 2 open-label study to assess the safety and immunogenicity of an alum-adjuvanted Chikungunya virus-like particle vaccine (PXVX0317) in prior recipients of other alphavirus vaccines versus alphavirus naïve controls.

As safety data from EBSI-CV-317-002 were only submitted to support the ISS, a full review of EBSI-CV-317-002 is not provided in this review memo. Instead, a summary of the design of EBSI-CV-317-002 is provided.

EBSI-CV-317-002 was an open-label study to evaluate both the immunogenicity and safety of PXVX0317 administered as a single dose in subjects 18 to <66 YOA who previously did or did not receive an alphavirus vaccine. A total of 60 subjects were enrolled, where 30 subjects previously received an investigational heterologous alphavirus vaccine with 30 age- and gender-matched subjects who did not. Safety data from all 60 subjects were included in the ISS.

8.2.3 Clinical Study EBSI-CV-317-010

Title of Study: A Phase 2 open-label study to assess the safety and immunogenicity of PXVX0317 (Chikungunya virus virus-like particle vaccine [CHIKV VLP], alum-adjuvanted).

As safety data from EBSI-CV-317-010 were only submitted to support the ISS, a full review of EBSI-CV-317-010 is not provided in this review memo. Instead, a summary of the design of EBSI-CV-317-010 is provided.

EBSI-CV-317-002 was an open-label study to evaluate both the immunogenicity and safety of PXVX0317 administered as a single dose in subjects 18 to <46 YOA. A total of 25 subjects were enrolled in a single arm. Safety data from all 25 subjects were included in the ISS.

8.3 Pooling of Data Across Studies/Clinical Trials

One pooled dataset was generated for both the solicited ARs and unsolicited AEs including all subjects in Study EBSI-CV-317-004, EBSI-CV-317-005, EBSI-CV-317-002, EBSI-CV-317-010, or PXVX-CV-317-001 who met the criteria for the SP.

8.4 Safety Results

Solicited ARs

Table 21 displays the percentages of subjects reporting solicited local and systemic reactions within 7 days following vaccination in the SP pooled across all five studies by vaccine group. Across studies, the occurrence of both solicited local and systemic reactions was largely consistent between the PXVX0317 single dose group and PXVX0317 other dose group. The percentages of subjects reporting solicited local and systemic reactions were generally higher in the pooled CHIKV VLP group than the pooled placebo group.

For both the pooled CHIKV VLP group and pooled placebo group, the most frequently reported solicited local reaction was pain (24.0% and 7.9%, respectively). The most frequently reported solicited systemic reaction was fatigue in the pooled CHIKV VLP group (17.8%) and headache in the pooled placebo group (13.9%).

In Study EBSI-CV-317-004, one grade 4 systemic solicited AE of 105ºF fever was reported by a CHIKV VLP vaccine recipient, but the site deemed this entry an error.

Unsolicited AEs

Table 22 displays the percentages of subjects reporting unsolicited AEs within 28 days following vaccination as well as the percentages of subjects reporting AESIs, MAAEs, and SAEs within six months following vaccination in the SP pooled across all five studies by vaccine group.

Within 28 days following vaccination, regardless of relationship to study vaccination, there were slightly smaller percentages of unsolicited AEs in the PXVX0317 single dose group than the PXVX0317 other dose group. There were similar percentages of unsolicited AEs between the pooled CHIKV VLP group and pooled placebo group. A total of 2.0% and 4.5% of subjects reported related unsolicited AEs in the PXVX0317 single dose group and PXVX0317 other dose group, respectively. A total of 2.2% and 0.9% of subjects reported related unsolicited AEs in the pooled CHIKV VLP group and pooled placebo group, respectively.

Within six months following vaccination, regardless of relationship to study vaccination, there were similar percentages of SAEs and unsolicited AEs leading to study discontinuation between the PXVX0317 single dose group and the PXVX0317 other dose group. There were also similar percentages of unsolicited AEs leading to study discontinuation between the pooled CHIKV VLP group and pooled placebo group. A total of 1.1% and 0.6% of subjects reported SAEs in the pooled CHIKV VLP group and pooled placebo group, respectively. One SAE (retinal detachment) considered by the investigator to be related to study vaccination was reported in the PXVX0317 single dose group while none were reported in the PXVX0317 other dose group. This SAE was later

assessed by the Applicant and independent SMC chair as unrelated due to prior medical history. No related SAEs were reported in the pooled placebo group.

Two deaths were reported in the PXVX0317 single dose group while none were reported in the PXVX0317 other dose group, neither of which were considered to be related to the study vaccination by the investigator. One death was reported in the pooled placebo group which was not considered to be related.

AESIs and MAAEs were only collected in Studies EBSI-CV-317-004, EBSI-CV-317-005, and EBSI-CV-317-010, corresponding to the PXVX0317 single dose group and pooled placebo group. Regardless of relationship to study vaccination, there were similar percentages of AESIs and MAAEs between the PXVX0317 single dose group and the pooled placebo group. Two related AESIs were reported in the PXVX0317 single dose group while none were reported in the pooled placebo group. A total of 0.5% of subjects reported related MAAEs in the PXVX0317 single dose group while none were reported in the pooled placebo group.

Reviewer's Comment:

- *All immunogenicity and safety analyses were verified based on data submitted in the SDTM format, and the results were consistent with those reported by the Applicant.*

Table 21: Summary of Participants with Solicited Events by Vaccine Group and Highest Reported Severity Across All Five Studies – SP

Local Adverse Reactions	**PXVX0317 Single Dose Group (N=3141) n (%)**	**PXVX0317 Other Dose Group (N=381) n (%)**	**Pooled PXVX0317 Group (N=3522) n (%)**	**Pooled Placebo Group (N=675) n (%)**
Pain	725/3114 (23.3)	112/379 (29.6)	837/3493 (24.0)	52/661 (7.9)
Pain, Grade 3	5/3114 (0.2)	0/379	5/3493 (0.1)	0/661
Redness	13/3114 (0.4)	1/379 (0.3)	14/3493 (0.3)	1/661 (0.2)
Redness, Grade 3	1/3114 (<0.1)	0/379	1/3493 (<0.1)	0/661
Swelling	10/3114 (0.3)	1/379 (0.3)	11/3493 (0.3)	0/661
Swelling, Grade 3	0/3114	0/379	0/3493	0/661
Systemic Adverse Reactions	-	-	-	-
Fever	26/3109 (0.8)	1/379 (0.3)	27/3488 (0.8)	3/660 (0.5)
Fever, Grade 3	6/3109 (0.2)	0/379	6/3488 (0.2)	0/660
Fever, Grade 4	1/3109 (<0.1)	0/379	1/3488 (<0.1)	0/660
Chills	246/3114 (7.9)	12/379 (3.2)	258/3493 (7.4)	21/661 (3.2)
Chills, Grade 3	5/3114 (0.2)	3/379 (0.8)	8/3493 (0.2)	0/661
Fatigue	582/3114 (18.7)	41/379 (10.8)	623/3493 (17.8)	90/661 (13.6)
Fatigue, Grade 3	23/3114 (0.7)	4/379 (1.1)	27/3493 (0.8)	1/661 (0.2)
Headache	530/3115 (17.0)	52/379 (13.7)	582/3494 (16.7)	92/661 (13.9)
Headache, Grade 3	12/3115 (0.4)	2/379 (0.5)	14/3494 (0.4)	2/661 (0.3)
Myalgia	523/3114 (16.8)	52/379 (13.7)	575/3493 (16.5)	58/661 (8.8)
Myalgia, Grade 3	13/3114 (0.4)	5/379 (1.3)	18/3493 (0.5)	3/661 (0.5)
Arthralgia	230/3114 (7.4)	25/379 (6.6)	255/3493 (7.3)	41/661 (6.2)
Arthralgia, Grade 3	7/3114 (0.2)	3/379 (0.8)	10/3493 (0.3)	1/661 (0.2)
Nausea	219/3114 (7.0)	21/379 (5.5)	240/3493 (6.9)	34/661 (5.1)
Nausea, Grade 3	12/3114 (0.4)	1/379 (0.3)	13/3493 (0.4)	0/661
Malaise[a]	7/120 (5.8)	28/379 (7.4)	35/499 (7.0)	0/3
Malaise[a], Grade 3	0/120	3/379 (0.8)	3/499 (0.6)	0/3

N = The number of participants in the SP. For each solicited event, the denominator is the number of participants who completed the diary card for that solicited event following vaccination.
n/% = number/percentage of participants presenting at least one type of event.
Grade 3 pain, chills, fatigue, headache, myalgia, arthralgia, nausea: defined as significant, prevents daily activity.
Redness and swelling defined as ≥ 25 mm; Grade 3 redness and swelling defined as > 100 mm.
Fever defined as ≥ 38.0°C/100.4°F; Grade 3 fever defined as ≥ 39.0°C/102.2°F. Grade 4 fever defined as > 40.0°C/104°F.
[a]Malaise was assessed in both Studies PXVX-CV-317-001 and EBSI-CV-317-002 only.
Source: Table 13.1.1 from Response to IR 29.

Table 22: Summary of Unsolicited Adverse Events by Vaccine Group Across All Five Studies – SP

-	PXVX0317 Single Dose Group (N=3141) n (%)	PXVX0317 Other Dose Group (N=381) n (%)	Pooled PXVX0317 Group (N=3522) n (%)	Pooled Placebo Group (N=675) n (%)
Regardless of relationship to study vaccination	-	-	-	-
Unsolicited AEs	485 (15.4)	83 (21.8)	568 (16.1)	92 (13.6)
Grade 3 or higher	40 (1.3)	12 (3.2)	52 (1.5)	4 (0.6)
SAE	31 (1.0)	6 (1.6)	37 (1.1)	4 (0.6)
Discontinued study due to unsolicited AE	3 (0.1)	1 (0.3)	4 (0.1)	1 (0.1)
Fatal AE	2 (0.1)	0	2 (0.1)	1 (0.1)
AESI[a]	5/3021 (0.2)	-	-	1/671 (0.2)
MAAE[a]	272/3021 (9.0)	-	-	64/671 (9.5)
Related to study vaccination	-	-	-	-
Unsolicited AEs	62 (2.0)	17 (4.5)	79 (2.2)	6 (0.9)
Grade 3 or higher	1 (<0.1)	0	1 (<0.1)	0
SAE	1 (<0.1)	0	1 (<0.1)	0
AESI[a]	2/3021 (0.1)	-	-	0/3021
MAAE[a]	15/3021 (0.5)	-	-	0/3021

Unsolicited AEs (including Grade 3 or higher) were collected through Day 29. All other AEs were collected through Day 183.
[a]AESIs and MAAEs were only collected in Studies EBSI-CV-317-004, EBSI-CV-317-005, and EBSI-CV-317-010.
Source: Adapted from Tables 3.1.1, 5.1.1, 7.1.1, 8.1.1, 10.1.1, 11.1.1, and 12.1.1 from Response to IR 29; the unsolicited AEs leading to study discontinuation, related AESIs, and related MAAEs were derived by the reviewer from the SDTM datasets.

8.5 Additional Safety Evaluations

Not applicable.

8.6 Safety Conclusions

Across studies, the occurrence of both solicited local and systemic reactions was largely consistent between the PXVX0317 single dose group and PXVX0317 other dose group. The percentages of subjects reporting solicited local and systemic reactions were generally higher in the pooled CHIKV VLP group than the pooled placebo group.

Within 28 days following vaccination, a total of 2.0% and 4.5% of subjects reported related unsolicited AEs in the PXVX0317 single dose group and PXVX0317 other dose group, respectively. A total of 2.2% and 0.9% of subjects reported related unsolicited AEs in the pooled CHIKV VLP group and pooled placebo group, respectively.

Within six months following vaccination, one SAE (retinal detachment) considered by the investigator to be related to study vaccination was reported in the PXVX0317 single dose group while none were reported in the PXVX0317 other dose group. The SAE was later assessed by the Applicant and independent SMC chair as unrelated due to prior medical history. No related SAEs were reported in the pooled placebo group. No related deaths were reported.

AESIs and MAAEs were only collected in Studies EBSI-CV-317-004, EBSI-CV-317-005, and EBSI-CV-317-010, corresponding to the PXVX0317 single dose group and pooled placebo group. Two related AESIs were reported in the PXVX0317 single dose group while none were reported in the pooled placebo group. A total of 0.5% of subjects reported related MAAEs in the PXVX0317 single dose group while none were reported in the pooled placebo group.

The ISS did not identify any novel safety concerns.

9. Additional Statistical Issues

There are no additional statistical issues.

10. Conclusions

10.1 Statistical Issues and Collective Evidence

This BLA is primarily supported by immunogenicity and safety data from two Phase 3 clinical studies, EBSI-CV-317-004 and EBSI-CV-317-005. The immunogenicity analyses of both Studies EBSI-CV-317-004 and EBSI-CV-317-005 met the superiority criteria for all immunogenicity objectives, demonstrating that CHIKV VLP vaccine induces superior immune response compared to placebo in individuals 12 YOA and older. The main immunogenicity (using the corrected ULOQ of 10794.8) and safety results for the two studies are summarized below:

Study EBSI-CV-317-004

For the first co-primary immunogenicity objective, adjusting for site, the GMT ratio was 203.29 with 95% CI (181.08, 228.23). The SRR difference was 96.6% with 95% CI (95.0%, 97.5%).

For the second co-primary immunogenicity objective, adjusting for site, the GMT ratios between (b) (4) were 0.99 with 95% CI (0.86, 1.13), 0.97 with 95% CI (0.84, 1.12), and 0.96 with 95% CI (0.83, 1.10), respectively.

For the key secondary immunogenicity objective, the SRR differences on Days 15, 183, and 8 were 96.0% with 95% CI (94.3%, 96.8%), 84.0% with 95% CI (81.7%, 85.6%), and 46.1% with 95% CI (43.8%, 48.1%), respectively.

For safety, the percentages of subjects reporting solicited local and systemic reactions were generally higher in the pooled CHIKV VLP group than the placebo group. For both the pooled CHIKV VLP group and placebo group, the most frequently reported solicited local reaction was pain, while the most frequently reported solicited systemic reaction was fatigue.

Within 28 days following vaccination, regardless of relationship to study vaccination, there were similar percentages of unsolicited AEs between the pooled CHIKV VLP group and placebo group. There were also similar percentages of unsolicited AEs considered by the investigator to be related to study vaccination between both groups.

Within six months following vaccination, one death was reported in the pooled CHIKV VLP group and it was not considered to be related to the study vaccination by the investigator. No deaths were reported in the placebo group. One SAE (retinal detachment) considered by the investigator to be related to study vaccination was reported in the pooled CHIKV VLP group while none were reported in the placebo group. This SAE was later assessed by the Applicant and independent SMC chair as unrelated due to prior medical history. Two related AESIs were reported in the pooled CHIKV VLP group while none were reported in the placebo group. A total of 0.5% of subjects reported related MAAEs in the pooled CHIKV VLP group while none were reported in the placebo group.

Study EBSI-CV-317-005

For the primary immunogenicity objective, adjusting for site, the GMT ratio was 89.18 with 95% CI (68.35, 116.36). The SRR difference was 86.2% with 95% CI (80.0%, 90.3%).

For the key secondary immunogenicity objective, the SRR differences on Days 15 and 183 were 79.5% with 95% CI (72.3%, 84.6%) and 74.4% with 95% CI (67.1%, 80.1%), respectively.

For safety, the percentages of subjects reporting solicited local and systemic reactions were generally higher in the CHIKV VLP group than the placebo group. For both the CHIKV VLP group and placebo group, the most frequently reported solicited local reaction was pain. The most frequently reported solicited systemic reactions were fatigue and myalgia in the CHIKV VLP group and headache in the placebo group.

Within 28 days following vaccination, regardless of relationship to study vaccination, there were similar percentages of unsolicited AEs between the CHIKV VLP group and placebo group. There were also similar percentages of unsolicited AEs considered by the investigator to be related to study vaccination between both groups.

Within six months following vaccination, one death was each reported in the CHIKV VLP group and the placebo group and neither was considered to be related to the study

vaccination by the investigator. One MAAE considered by the investigator to be related to study vaccination was reported in the CHIKV VLP group while none were reported in the placebo group. No related AESIs or related SAEs were reported.

10.2 Conclusions and Recommendations

No major statistical issues have been identified. All success criteria for the pre-specified immunogenicity objectives of both Studies EBSI-CV-317-004 and EBSI-CV-317-005 were met. Overall, the immunogenicity results appear to support the effectiveness of the CHIKV VLP vaccine in individuals 12 YOA and older. I defer to the clinical reviewer with respect to the overall safety assessment.