BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA)
STN	125820
CBER Received Date	17 June 2024
PDUFA Goal Date	14 February 2025
Division / Office	Division of Clinical and Toxicology Review (DCTR)/Office of Vaccines Research and Review (OVRR)
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Judith Anesi, MD MSCE, Primary Reviewer Sixun Yang, MD PhD, Secondary Reviewer
Review Completion Date / Stamped Date	20 December 2024 / 11 February 2025
Supervisory Concurrence	Sheral Patel, MD, Team Leader Andrea Hulse, MD, Branch Chief
Applicant	Bavarian Nordic A/S
Established Name	Chikungunya Vaccine, Recombinant
(Proposed) Trade Name	Vimkunya
Pharmacologic Class	Prophylactic Vaccine
Formulation(s), including Adjuvants, etc.	40 µg of chikungunya virus virus-like particles adsorbed on aluminum hydroxide (approximately 300 µg aluminum) in a 0.8 mL dose
Dosage Form(s) and Route(s) of Administration	Sterile suspension for intramuscular injection
Dosing Regimen	A single dose (0.8 mL)
Indication(s) and Intended Population(s)	For the prevention of disease caused by chikungunya virus in individuals 12 years of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BLA	Biologics License Application
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CHIK	chikungunya
CHIKV	chikungunya virus
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COVID-19	Coronavirus disease of 2019
CVA	cerebrovascular accident
DART	developmental and reproductive toxicology
DHT	Digital Health Technology
ECSA	East/Central/South African
eCTD	electronic common technical document
FDA	Food and Drug Administration
FRNT	focus reduction neutralization test
GCP	Good Clinical Practice
GMT	geometric mean titer
ICH	International Council for Harmonisation
IEP	immunogenicity evaluable population
IM	intramuscular
IND	investigational new drug
IP	investigational product
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IR	information request
LB	lower bound
LLOD	lower limit of detection
LLOQ	lower limit of quantitation
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NHP	nonhuman primate
OBPV	Office of Biostatistics and Pharmacovigilance
PeRC	Pediatric Research Committee
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PSP	pediatric study plan
PT	preferred term
RWE	Real-World Evidence
SAE	serious adverse event
SD	standard deviation
SMQ	Standard Medical Dictionary for Regulatory Activities Query
SNA	serum neutralizing antibody
SOC	system organ class

ULOQ	upper limit of quantitation
USAMRIID	US Army Medical Research Institute of Infectious Diseases
USPI	United States Prescribing Information
VEEV	Venezuelan equine encephalitis virus
VLP	virus-like particle
WRAIR	Walter Reed Army Institute of Research

1. EXECUTIVE SUMMARY

Bavarian Nordic A/S (the Applicant) submitted a Biologics License Application (BLA) on June 17, 2024, to support licensure via the accelerated approval pathway of PXVX0317 (Chikungunya Vaccine, Recombinant), a virus-like particle (VLP) vaccine for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 12 years of age and older. Throughout development, the investigational product (IP) was referred to as PXVX0317, CHIKV VLP, or Chikungunya Vaccine, Recombinant. In this memo, the IP will be referred to as PXVX0317, which is synonymous with CHIKV VLP and Chikungunya Vaccine, Recombinant.

CHIKV is a mosquito-borne virus that has been identified in over 110 countries in Asia, Africa, Europe, and the Americas. Approximately 5 million cases of CHIKV infection were reported during the past 15 years. Symptomatic CHIKV infections typically present with fever and arthralgia, with some patients experiencing severe, recurrent, and/or persistent joint pain lasting for months to years following infection. As no specific antiviral treatments are available, the treatment of chikungunya (CHIK) is supportive and includes fluids and medications for pain and fever. One vaccine is currently licensed in the U.S. to prevent CHIK, but its clinical benefit has not yet been verified.

The BLA includes data from five clinical studies evaluating the safety and immunogenicity of PXVX0317: (1) a phase 2 dose-escalation study (PXVX-CV-317-001, referred to as Study 001); (2) a pivotal phase 3 safety, effectiveness, and lot consistency study in individuals 12 to <65 years of age (EBSI-CV-317-004 or Study 004); (3) a pivotal phase 3 safety and effectiveness study in individuals 65 years of age and older (EBSI-CV-317-005 or Study 005); (4) a phase 2 study evaluating the impact of prior alphavirus vaccination on safety and effectiveness of PXVX0317 (EBSI-CV-317-002 or Study 002); and (5) a phase 2 study performed to collect plasma and serum samples for nonhuman primate (NHP) studies (EBSI-CV-317-010 or Study 010). Immunogenicity data from the two phase 3 studies were analyzed separately and also pooled with data from phase 2 Studies 002 and 010 in the integrated summary of effectiveness (ISE) analyses. Safety data from all five studies were pooled for the integrated summary of safety (ISS) analyses as all five studies used similar definitions of adverse events (AEs), AE collection tools, and durations of follow-up.

In the first pivotal phase 3 study (Study 004), participants ages 12 to <65 years were enrolled at 47 sites in the U.S. and randomized 2:2:2:1 to one of three lots of PXVX0317 or placebo. The primary immunogenicity endpoint was a CHIKV-specific serum neutralizing antibody (SNA) titer ≥100 as determined by CHIKV-luciferase assay at Day 22 postvaccination. The CHIKV SNA 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 supported the use of the CHIKV SNA titer of ≥100 as a surrogate endpoint that is reasonably likely to predict a clinical benefit and serves as the basis for approval of the vaccine under the accelerated approval pathway. All participants in the Immunogenicity Evaluable Population (IEP) had a CHIKV SNA titer <15 at baseline. At Day 22, 98% (2503/2559) of participants in the PXVX0317 group and 1% (5/424) of participants in the placebo group had a CHIKV SNA titer ≥100, resulting in a seroresponse rate difference of 97% (95% CI: 95, 98). The results met the pre-specified success criterion of a lower bound (LB) of the 95% confidence interval (CI) of ≥70%.

A nested lot-to-lot consistency substudy was also performed in Study 004 among adults 18 to <46 years of age. The results of this substudy demonstrated that the 95% CIs of the CHIKV

SNA 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.

The second pivotal phase 3 study (Study 005) enrolled participants 65 years of age and older at 10 sites in the U.S. and randomized participants 1:1 to PXVX0317 or placebo. The primary immunogenicity endpoint and IEP were defined in the same fashion as in Study 004. At Day 22, 87% (165/189) of participants in the PXVX0317 group and 1% (2/183) of participants in the placebo group had a CHIKV SNA titer ≥100, resulting in a seroresponse rate difference of 86% (95% CI: 80, 90). The results met the pre-specified success criterion of a LB of the 95% CI of ≥70%.

The integrated effectiveness analyses, which pooled immunogenicity data from Studies 004, 005, 002, and 010 (with 2,829 participants receiving PXVX0317 and 607 receiving placebo), showed a seroresponse rate difference of 96% (95% CI: 95, 97) 21 days postvaccination, consistent with the seroresponse rate difference observed in Study 004.

The immunogenicity results from Studies 004, 005, and the ISE indicate that in the majority of recipients, PXVX0317 elicits a seroresponse, a surrogate endpoint that is reasonably likely to predict clinical benefit. As the seroresponse cutoff (CHIKV SNA titer ≥100) was estimated based on the results from an NHP study, an adequate and well-controlled postmarketing study will be needed to confirm clinical benefit in humans. The Applicant has submitted a protocol (EBSI-CV-317-007) for a randomized, placebo-controlled, event-driven trial to evaluate the effectiveness of PXVX0317 in preventing laboratory-confirmed acute CHIKV disease in up to 6,144 participants in the arbovirus-endemic regions of Thailand and the Philippines.

In safety analyses from Study 004, solicited adverse reactions (ARs) were reported by 38% (1059/2790) of PXVX0317 recipients and 27% (124/464) of placebo recipients. Systemic solicited ARs were reported by 891 (32%) PXVX0317 recipients and 114 (25%) placebo recipients. The most common systemic solicited ARs in PXVX0317 recipients were fatigue (20% PXVX0317, 17% placebo), headache (18% PXVX0317, 17% placebo), and myalgia (18% PXVX0317, 10% placebo). Local solicited ARs were reported by 662 (24%) PXVX0317 recipients and 49 (11%) placebo recipients, with the most common being injection site pain (24% PXVX0317, 11% placebo).

In Study 005, solicited ARs were reported by 12% (25/206) of PXVX0317 recipients and 14% (28/207) of placebo recipients. Systemic solicited ARs were reported by 22 (11%) PXVX0317 and 27 (14%) placebo recipients. The most common systemic solicited ARs in PXVX0317 recipients were fatigue (6% PXVX0317, 6% placebo), myalgia (6% PXVX0317, 7% placebo), and headache (4% PXVX0317, 8% placebo). Local solicited ARs were reported by 11 (5%) PXVX0317 recipients and 4 (2%) placebo recipients, with the most common being injection site pain (5% PXVX0317, 2% placebo).

The integrated safety analyses, which pooled data from Studies 004, 005, 001, 002, and 010, evaluated a total of 3,522 PXVX0317 and 675 placebo recipients (of which 3,141 PXVX0317 recipients received the to-be-licensed dose). The study populations among the five studies were generally similar except that Study 004 enrolled those 12 to <65 years of age and Study 005 enrolled those 65 years of age and older. The incidence of solicited ARs in the ISS was similar to that reported in Study 004.

Due to the concern that a VLP vaccine might be able to 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, 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 symptoms was performed: 14 (0.4%) participants in the PXVX0317 group and 2 (0.3%) in the placebo group met criteria for CHIK-like ARs.

Serious adverse events (SAEs) were reported by 31 (1%) PXVX0317 and 4 (0.6%) placebo recipients. None of the SAEs were considered related to PXVX0317.

In conclusion, the immunogenicity data from Studies 004 and 005 indicate that a single intramuscular (IM) injection of PXVX0317 is likely effective in preventing disease caused by CHIKV based on the surrogate endpoint of seroresponse rate; however, a postmarketing confirmatory study will be needed to confirm clinical benefit. The overall reactogenicity profile of the to-be-licensed dose of PXVX0317 is acceptable. The available data support accelerated approval of PXVX0317 for use in individuals 12 years of age and older. Mitigation of the observed risks will be accomplished through labeling and the pharmacovigilance plan, and an adequate and well-controlled trial will be conducted to confirm clinical benefit.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1 summarizes the demographic characteristics of study participants who enrolled in pivotal Studies 004 and 005 and were randomized to PXVX0317 or placebo. A total of 3,667 participants were randomized and treated in the studies, including 2,996 participants in the PXVX0317 group and 671 participants in the placebo group.

Table 1. Demographic Characteristics, Randomized Population, Studies 004 and 005

Characteristic	PXVX0317 (N=2996)	Placebo (N=671)	Total (N=3667)
Age (years)	-	-	-
Mean (SD)	40.9 (16.14)	48.6 (19.25)	41.0 (12, 95)
Median (min, max)	39.0 (12, 95)	50.0 (12, 84)	42.3 (17.01)
Age group, n[a] (%)	-	-	-
Age 12 to <18 years	217 (7.2)	37 (5.5)	254 (6.9)
Age 18 to 65 years	2593 (86.5)	445 (66.3)	3038 (82.8)
Age >65 years	186 (6.2)	189 (28.2)	375 (10.2)
Sex, n[a] (%)	-	-	-
Female	1560 (52.1)	348 (51.9)	1908 (52.0)
Male	1436 (47.9)	323 (48.1)	1759 (48.0)
Race, n[a] (%)	-	-	-
American Indian/Alaska Native	31 (1.0)	3 (0.4)	34 (0.9)
Asian	83 (2.8)	17 (2.5)	100 (2.7)
Black/African American	553 (18.5)	118 (17.6)	671 (18.3)
Multiracial	82 (2.7)	13 (1.9)	95 (2.6)
Native Hawaiian	6 (0.2)	4 (0.6)	10 (0.3)
Unknown/Not Reported	25 (0.8)	7 (1.0)	32 (0.9)
White	2216 (74.0)	509 (75.9)	2725 (74.3)

Characteristic	PXVX0317 (N=2996)	Placebo (N=671)	Total (N=3667)
Ethnicity, n[a] (%)	-	-	-
Hispanic or Latino	598 (20.0)	161 (24.0)	759 (20.7)
Not Hispanic or Latino	2335 (77.9)	495 (73.8)	2830 (77.2)
Unknown/Not Reported	63 (2.1)	15 (2.2)	78 (2.1)

Source: Reviewer generated table
Abbreviations: max=maximum; min=minimum; SD=standard deviation
[a]n (%) of each treatment group are provided except where otherwise specified.

Clinical Reviewer Comment: *The median age of participants in the placebo group (49 years) is greater than that of the PXVX0317 group (41 years) due to the different randomization ratios used in Studies 004 and 005. Specifically, in Study 004 (which enrolled individuals 12 to <65 years of age), the randomization ratio was 6:1, while in Study 005 (which enrolled those 65 years of age and older), the randomization ratio was 1:1. Thus, the PXVX0317 group contains more participants from Study 004, which enrolled younger adults. The implications of this difference in the median age of the pooled PXVX0317 and placebo groups are discussed in section 8.3.*

Effectiveness Analyses by Age, Sex, Race, and Ethnicity

The IEP was used for primary immunogenicity analyses (see sections 6.1.10 and 6.2.10) and includes 2,748 participants exposed to PXVX0317 in pivotal Studies 004 and 005. The majorities of the IEP were female (52%), White (75%), and not Hispanic or Latino (79%); 7% of the IEP was 12 to <18 years of age, 83% was 18 to <65 years of age, and 10% was ≥65 years of age.

Subgroup analyses did not indicate meaningful differences in seroresponse rates by sex, race, or ethnicity. The seroresponse rate difference (PXVX0317 minus placebo) was higher among those 12 to <65 years of age (97% [95% CI: 95, 98]) than among those ≥65 years of age (86% [95% CI: 80, 90]); the clinical significance of the difference is unknown.

Safety Analyses by Age, Sex, Race, and Ethnicity

The safety database includes 2,996 participants exposed to PXVX0317 in Studies 004 and 005, as well as 526 participants from the phase 2 studies. Among the PXVX0317 recipients in the safety population from Studies 004 and 005, 7% were 12 to <18 years of age, 87% were 18 to <65 years of age, and 6% were ≥65 years of age. The majorities were female (52%), White (74%), and Not Hispanic or Latino (80%).

The incidence of solicited ARs following PXVX0317 was higher in younger participants (38% among 12 to <65 years of age subgroup) than older participants (12% among ≥65 years of age subgroup). As compared with their counterparts, solicited ARs were more commonly reported by female, White, and Not Hispanic or Latino participants. No clinically meaningful differences in the occurrence of unsolicited AEs or SAEs were observed by age group, sex, race, or ethnicity.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

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 may be symptomatic (CDC, 2024) though estimates vary, with another study showing more than 80% of CHIKV infected individuals are asymptomatic (Yoon, 2020). Recent evidence suggests rates of symptomatic infection may be lineage dependent (Bustos Carrillo, 2019).

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 climate change, 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 incidence.

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, 2025).

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 present with fever, transient

maculopapular rash, and mild to severe arthralgia/arthritis. This is followed by a subacute stage and then chronic stage of disease that may lead to impaired quality of life in some people due to arthritic symptoms that may persist months or years after infection (Simon, 2015; Suhrbier, 2012). Depending on the study report, approximately 2% to 57% of patients developed chronic or recurrent arthralgia (Suhrbier, 2012). A study of 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). Mortality due to CHIKV infection is low with an estimated rate of 0.07%. 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).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

On November 9, 2023, Ixchiq (Chikungunya Vaccine, Live) was approved via accelerated approval for the prevention of CHIK in individuals 18 years of age and older who are at increased risk of exposure to CHIKV. No CHIK-specific treatments are currently available. Treatment of CHIK is supportive and includes adequate fluid intake and medications for relief of fever and pain during the acute, subacute, and chronic phases of infection.

2.3 Safety and Efficacy of Pharmacologically Related Products

Immunogenicity data from pivotal studies indicate that a single IM injection of Ixchiq is likely effective in preventing disease caused by CHIKV based on a surrogate endpoint of seroresponse rate; however, postmarketing studies are still needed to confirm clinical benefit. The reactogenicity profile of Ixchiq was acceptable for the indication of use. However, 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) restricting the indication of the vaccine to individuals at increased risk of CHIKV exposure; (2) a warning in the label regarding the risk of severe or prolonged CHIK-like illness; (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 postmarketing requirement (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.

2.4 Previous Human Experience With the Product (Including Foreign Experience)

No previous human experience exists with the product outside of the prelicensure studies reviewed in this memo.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

2.5.1 Pre-submission regulatory activities

Clinical development of PXVX0317 was conducted under IND 17998. Table 2 summarizes key regulatory activities related to the clinical development program.

Table 2. Key Regulatory Activities During Clinical Development Program

Date	Regulatory Activity	Comments
2017 Apr 13	(b) (4) Pre-IND meeting	None
2018 Feb 26	IND 17998 submitted	None
2018 Apr 26	Fast Track Designation granted	None
2019 Apr 29	Type C Meeting	Discussed proposed CMC development plan for manufacture of phase 3 vaccine material.
2019 Sep 11	Type C Meeting	Discussed new surrogate endpoint for approval under accelerated approval.
2019 Nov 8	VRBPAC meeting to discuss pathways for development and licensure of CHIK vaccines	VRBPAC recommended using a CHIKV SNA titer that completely prevented viremia and fever in a NHP adaptive transfer model as a surrogate endpoint to support licensure via accelerated approval. During VRBPAC discussions, CHIKV vaccine developers expressed concern about including fever as a component of the endpoints in NHP studies because fever is not consistently observed in NHPs after CHIKV challenge. CBER agreed to not include fever in the endpoints in NHP studies.
2019 Dec 17	End of Phase 2 Type B Meeting	Discussed data from the phase 2 study PXVX-CV-317-001 and the draft protocol for the phase 3 study EBSI-CV-317-004.
2020 Oct 16	Breakthrough Therapy Designation granted	Designation granted based on results of (1) a passive transfer and challenge study (PAS-NHP-CHIK-002) that showed all three dose levels of IgG from plasma of vaccinated participants protected NHPs from viremia as measured by plaque assay; (2) an active vaccination and challenge study (PAS-NHP-CHIK-001) that showed all three dose levels of the vaccine protected NHPs from viremia as measured by plaque assay.
2020 Sep 30	Agreement on iPSP	Deferral for children 0 to <12 years of age.
2022 Feb 03	Reached agreement with FDA on surrogate endpoint (CHIKV SNA titer threshold) for use in pivotal phase 3 trials	CBER and Applicant agreed on a CHIKV SNA titer threshold of ≥100 to be reasonably likely to predict clinical benefit.
2023 Oct 06	Type B pre-BLA Meeting	Discussed the proposed format and content of the nonclinical and clinical sections of the BLA.
2023 Nov 07	Type B pre-BLA Meeting	Discussed the proposed format and content of the CMC section of the BLA.

Source: Reviewer generated table
Abbreviations: CBER=Center for Biologics Evaluation and Research; CHIKV=chikungunya virus; CMC=chemistry, manufacturing, and controls; IND=investigational new drug application; iPSP=initial pediatric study plan; NHP=nonhuman primate; SNA=serum neutralizing antibody; VRBPAC=Vaccines and Related Biological Products Advisory Committee

2.5.2 Post-Submission Regulatory Activities

Table 3 summarizes requests that were critical for the clinical review of this BLA.

Table 3. Key Information Requests for Clinical Review

Information Request Number	Date Sent	Amendment Response Number[a]	Date Response Received	Topic
4	2024-07-24	6	2024-07-26	EBSI-CV-317-004 ADAE dataset.

Information Request Number	Date Sent	Amendment Response Number[a]	Date Response Received	Topic
6	2024-07-25	8	2024-07-30	Financial disclosure information; case narrative for AE dropout in PXVX-CV-317-001; MedDRA versions across studies.
8	2024-08-01	9	2024-08-06	PXVX-CV-317-001 MedDRA version and define file.
12	2024-08-21	20	2024-09-20	Sent by Statistical Reviewer regarding ULOQ of CHIKV SNA assay validation.
13	2024-08-23	13, 51	2024-08-30	Tabulation of solicited ARs; immunogenicity data against multiple CHIKV genotypes; placebo recipients with a seroresponse; case narrative for a participant with CHIK-like AR.
14	2024-08-26	14	2024-09-03	Sent by DHT Reviewer regarding the eDiary.
16	2024-09-09	19	2024-09-16	Program codes for PXVX-CV-317-001 and EBSI-CV-317-002; missing data for solicited ARs; DHT comment regarding eDiary; prior alphavirus vaccinations in EBSI-CV-317-002; case narrative for participant with anaphylaxis in EBSI-CV-317-010.
17	2024-09-10	23, 28	2024-10-11	Data standards for EBSI-CV-317-004, EBSI-CV-317-005, and PXVX-CV-317-001.
18	2024-09-18	21	2024-09-25	iPSP timeline.
22	2024-09-20	22	2024-09-27	Sent by Pharmacovigilance Reviewer regarding duration of arthralgia AEs.
24	2024-10-01	26, 29, 43	2024-10-14	Sent by Pharmacovigilance Reviewer requesting case narratives for participants with prolonged arthralgia AEs.
25	2024-10-11	30	2024-10-15	Immunogenicity data for Venezuelan equine encephalitis virus in EBSI-CV-317-002; program code for table in PXVX-CV-317-001; case narrative for related grade 3 AE in EBSI-CV-317-004.
29	2024-10-21	35	2024-11-01	Updates to ISS datasets and tables based on data standards revisions for individual studies
32	2024-11-05	39	2024-11-14	Sent by Toxicology Reviewer regarding rabbit DART study results.
34	2024-11-07	40	2024-11-15	Sent by Pharmacovigilance Reviewer regarding pregnancy registry outcomes, internal control, and study sites.
39	2024-11-21	47	2024-12-03	Sent by Pharmacovigilance Reviewer regarding pregnancy registry target enrollment.

Information Request Number	Date Sent	Amendment Response Number[a]	Date Response Received	Topic
44	2024-12-10	50	2024-12-13	Clarification of updated AESI incidence in EBSI-CV-317-004.
48	2024-12-17	55	2024-12-20	Clarification of AESI incidence involving solicited ARs in EBSI-CV-317-004 and EBSI-CV-317-005.
52	2025-01-03	59, 66	2025-01-31	Request to repeat Day 22 SNA titers for placebo recipients with seroresponse in EBSI-CV-317-004 and EBSI-CV-317-005.

Source: Reviewer generated table
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; CHIK=chikungunya; CHIKV=chikungunya virus; DART=developmental and reproductive toxicology; DHT=Digital Health Technology; iPSP=initial pediatric study plan; ISS=integrated summary of safety; MedDRA=medical dictionary for regulatory activities; SNA=serum neutralizing antibody; ULOQ=upper limit of quantitation; USPI=United States prescribing information
[a]All responses were acceptable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This BLA was submitted in electronic common technical document (eCTD) format. Data sources include protocols, reporting and analysis plans, study reports, the integrated summaries of efficacy and safety, and datasets (in both Study Data Tabulation Model and Analysis Data Model formats). The submission was adequately organized and integrated to allow clinical review.

3.2 Compliance With Good Clinical Practices and Submission Integrity

In Section 1.3.4 of the Clinical Overview, the Applicant states, “Studies were conducted in accordance with the study protocols, clinical research guidelines established by the Basic Principles defined in the US 21 Code of Federal Regulations Parts 50, 54, 56, and 312, the principles enunciated in the latest version of The Declaration of Helsinki, the International Council for Harmonization (ICH) guideline Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2), and other applicable federal and local regulatory requirements and laws governing the conduct of human clinical trials.” Specific statements regarding adherence to ICH guidelines and GCP were identified in the clinical study reports for Studies 004, 005, 001, 002, and 010.

Additionally, the Clinical Reviewers Guide Appendix Tables 3 and 4 provide a plan for in-study GCP audits and summaries of the audit findings for pivotal Studies 004 and 005. Two enrollment sites for Study 004 had critical findings, and only one took corrective actions. The investigator at study site 0091, who enrolled 47 participants, failed to delegate study conduct duties to qualified personnel. This resulted in a permanent enrollment hold, and the site was not considered for future studies. Study site 0020, which enrolled 166 participants, failed to adequately consent study subjects. Corrective and preventative action plans were executed at study site 0020 to ensure adequate resolution of the critical finding; these actions were ultimately deemed suitable to ensure compliance.

Clinical Reviewer Comment*: Study site 0091 enrolled 47 participants before it was closed, and those participants were included in the safety and effectiveness analyses in this BLA. Given the small number of participants (47/3258 [1.4%]), it is unlikely that conclusions regarding safety or*

effectiveness for Study 004 would be substantially impacted by irregularities at this site. However, the clinical and statistical reviewers performed sensitivity analyses in which participants enrolled at site 0091 were excluded, and the safety and immunogenicity results were not significantly impacted; see section 6.1.6 for details.

3.3 Financial Disclosures

A total of 585 investigators participated in the two pivotal phase 3 studies, Study 004 (464 investigators) and Study 005 (119 investigators); none of the investigators were employees of the Applicant or had disclosable financial interests/arrangements. Certification of due diligence was submitted for one sub-investigator, a Pharmacy Designee for Study 005 (site 0095) who was no longer a staff member at the site during the study. No financial disclosure information was collected for three sub-investigators because it was confirmed that they did not perform any work on the study: two sub-investigators for Study 004 (site 0070) and one sub-investigator for Study 005 (site 0009).

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

4.1 Chemistry, Manufacturing, and Controls

The product reviewer did not identify any significant issues with chemistry, manufacturing, and controls (CMC). Please refer to the CMC review for details.

4.2 Assay Validation

The assay validation reviewer did not identify any significant issues. The statistical reviewer noted that the upper limit of quantitation (ULOQ) for the SNA assay was not properly validated (see section 4.5). Please refer to the assay validation review and statistical review for details.

4.3 Nonclinical Pharmacology/Toxicology

The toxicology reviewer identified an issue with one developmental and reproductive toxicology (DART) study (*A Fertility and Postnatal Development Toxicity Study of PXVX0317 Vaccine by Intramuscular Injection in Female Rabbits*), which demonstrated decreased viability of rabbit kits in the vaccine group (69% survival in controls as compared to 42% survival in the vaccine group at postnatal day 28). The cause of death in the kits was not assessed. This information will be included in the United States Prescribing Information (USPI) section 8.1, and a postmarketing commitment (PMC) pregnancy registry will be recommended based on this information (see section 11.6). Please refer to the Center for Biologics Evaluation and Research (CBER) toxicology review for details.

A passive transfer study was performed in NHPs using human anti-CHIKV immune sera collected from participants in two phase 2 studies (Studies 001 and 002) who received a single dose of a vaccine formulation containing the same VLP used in PXVX0317. Sera obtained on Day 22 after vaccination were pooled to generate a serum pool with a 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 six 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. Of note, fever and arthritis-related endpoints (e.g., joint pathology or CHIKV viral loads in joints) were not evaluated in the NHP passive transfer study, since the NHP model of CHIK does not consistently exhibit fever or arthritis. Potential limitations of this surrogate endpoint are discussed in section 11.2.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

PXVX0317 elicits CHIKV-specific neutralizing antibody responses, which are thought to mediate the immune responses that protect humans against CHIK, though the exact mechanism of protection is unknown.

4.5 Statistical

The statistical reviewer noted that the ULOQ for the SNA assay was not properly validated. As a result, the ULOQ was modified, and updated GMT analyses were submitted by the Applicant (see the response to IR #12). Otherwise, the statistical reviewer verified the key results of the Applicant's analyses of the immunogenicity and safety data. Please refer to the statistical review for details.

4.6 Pharmacovigilance

The pharmacovigilance reviewer did not identify any important risks in the pharmacovigilance plan but has requested that CHIK-like illness including vaccine-associated arthralgia be included as a potential risk. The pharmacovigilance reviewer has also requested a PMC pregnancy registry (see section 11.6). Please refer to the pharmacovigilance review for details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The Applicant submitted five clinical studies evaluating the safety and immunogenicity of PXVX0317: (1) a phase 2 dose-escalation study (Study 001); (2) a pivotal phase 3 safety, effectiveness, and lot consistency study in individuals 12 to <65 years of age (Study 004); (3) a pivotal phase 3 safety and effectiveness study in individuals 65 years of age and older (Study 005); (4) a phase 2 study evaluating the impact of prior alphavirus vaccination on the safety and effectiveness of PXVX0317 (Study 002); and (5) a phase 2 study performed to collect plasma and serum samples for NHP studies (Study 010). Studies 004 and 005 are considered essential to support the proposed indication and are reviewed in sections 6.1 and 6.2, respectively. Studies 001, 002, and 010 are supportive and are summarized in the Appendix (A1.1, A1.2, and A1.3, respectively).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

This clinical review considered the following documents submitted to the BLA STN 125820, as listed by eCTD module:

Table 4. Documents That Serve as the Basis for the Clinical Review

Module	Sequence	Documents
1.14	3	Labeling
1.2	2	Reviewer Guide Clinical, Reviewer Guide Clinical Appendix
1.3.4	2	Financial Certification and Disclosure
1.3.6	3	Tropical Disease Priority Review Voucher
1.9.4	2	Initial Pediatric Study Plan, Revised Proposal for Planned Deferred Pediatric Studies
2.2	1	Introduction
2.5	2	Clinical Overview
2.7.3	2	Summary of Clinical Efficacy
2.7.4	2	Summary of Clinical Safety
5.2	2	Tabular Listing of All Clinical Studies
5.3.5.1	2	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication – PXVX-CV-317-001, EBSI-CV-317-004, EBSI-CV-317-005
5.3.5.2	2	Study Reports of Uncontrolled Clinical Studies – EBSI-CV-317-002, EBSI-CV-317-010
5.3.5.3	2	Reports of Analyses of Data from More than One Study – Integrated Summary of Safety, Integrated Summary of Effectiveness

Source: Reviewer generated table

5.3 Table of Studies/Clinical Trials

Table 5. 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: Adapted from Tabular Listing of All Clinical Studies (page 1)

5.4 Consultations

No external consults or collaborations were sought.

5.5 Literature Reviewed

Alvarez, M. F. et al (2017). Cardiovascular involvement and manifestations of systemic Chikungunya virus infection: A systematic review. F1000Research, 6, 390. https://doi.org/10.12688/f1000research.11078.2

Anderson, G. F. (2005) Medicare and Chronic Conditions. The New England Journal of Medicine, 353:305-309. https://www.nejm.org/doi/full/10.1056/NEJMsb044133

Burt, F. et al (2014). Chikungunya virus and arthritic disease. *The Lancet. Infectious Diseases, 14*(9), 789–790. https://doi.org/10.1016/S1473-3099(14)70869-2

Bustos Carrillo, F et al. (2019). Epidemiological Evidence for Lineage-Specific Differences in the Risk of Inapparent Chikungunya Virus Infection. *Journal of virology, 93*(4), e01622-18. https://doi.org/10.1128/JVI.01622-18

Centers for Disease Control and Prevention (2024) Chikungunya Virus. CDC Yellow Book | CDC https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/chikungunya

Centers for Disease Control and Prevention (2025) Chikungunya Virus. Chikungunya in the US | Chikungunya virus | CDC https://www.cdc.gov/chikungunya/data-maps/chikungunya-us.html

Cotella, J. I. et al (2021). Chikungunya and the Heart. Cardiology, 146(3), 324–334. https://doi.org/10.1159/000514206

de Lima Cavalcanti T.Y.V. et al (2022) A Review on Chikungunya Virus Epidemiology, Pathogenesis and Current Vaccine Development. Viruses, 14(5):969. https://doi.org/10.3390/v14050969

Hawman, D. W. et al (2013). Chronic joint disease caused by persistent Chikungunya virus infection is controlled by the adaptive immune response. *Journal of Virology, 87*(24), 13878–13888. https://doi.org/10.1128/JVI.02666-13

Langsjoen, R. M. et al (2016). Molecular Virologic and Clinical Characteristics of a Chikungunya Fever Outbreak in La Romana, Dominican Republic, 2014. *PLoS Neglected Tropical Diseases, 10*(12), e0005189. https://doi.org/10.1371/journal.pntd.0005189

Pal, P. et al (2014). Chikungunya viruses that escape monoclonal antibody therapy are clinically attenuated, stable, and not purified in mosquitoes. *Journal of Virology, 88*(15), 8213–8226. https://doi.org/10.1128/JVI.01032-14

Raju, S. et al. (2023) A chikungunya virus-like particle vaccine induces broadly neutralizing and protective antibodies against alphaviruses in humans. Sci Transl Med. 2023 May 17;15(696):eade8273. doi: 10.1126/scitranslmed.ade8273. Epub 2023 May 17. PMID: 37196061; PMCID: PMC10562830.

Simon, F. et al (2015). Chikungunya Virus Infections. The New England Journal of Medicine, 373(1), 93–94. https://doi.org/10.1056/NEJMc1505501

Sissoko, D. et al (2009). Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. PLoS neglected tropical diseases, 3(3), e389. https://doi.org/10.1371/journal.pntd.0000389

Suhrbier, A. et al (2012). Arthritogenic alphaviruses-an overview. Nature Reviews. Rheumatology, 8(7), 420–429. https://doi.org/10.1038/nrrheum.2012.64

Traverse, E. M. et al (2021). Cardiomyopathy and Death Following Chikungunya Infection: An Increasingly Common Outcome. Tropical Medicine and Infectious Disease, 6(3), 108. https://doi.org/10.3390/tropicalmed6030108

United States Census Bureau (2024) Quick Facts https://www.census.gov/quickfacts/fact/table/US/PST045223

Vairo, F. et al (2019). Chikungunya: Epidemiology, Pathogenesis, Clinical Features, Management, and Prevention. *Infectious Disease Clinics of North America, 33*(4), 1003–1025. https://doi.org/10.1016/j.idc.2019.08.006

Yoon, I. K et al (2015). High rate of subclinical chikungunya virus infection and association of neutralizing antibody with protection in a prospective cohort in the Philippines. *PLoS Neglected Tropical Diseases, 9*(5), e0003764. https://doi.org/10.1371/journal.pntd.0003764

Yoon, I. K. et al (2020). Pre-existing chikungunya virus neutralizing antibodies correlate with risk of symptomatic infection and subclinical seroconversion in a Philippine cohort. International Journal of Infectious Diseases: IJID : Official Publication of the International Society for Infectious Diseases, 95, 167–173. https://doi.org/10.1016/j.ijid.2020.03.073

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

NCT05072080
EBSI-CV-317-004: A Phase 3 Safety, Immunogenicity, and Lot-consistency Trial of the VLP-based Chikungunya Vaccine PXVX0317 in Healthy Adults and Adolescents

6.1.1 Objectives

Primary Objectives

1. To evaluate the safety of PXVX0317 in healthy adult and adolescent participants 12 to <65 years of age.
2. To compare the anti-CHIKV SNA response to PXVX0317 and placebo at Day 22 in healthy adult and adolescent participants 12 to <65 years of age.
3. To demonstrate the consistency of the anti-CHIKV SNA GMT across three consecutively manufactured lots of PXVX0317 at Day 22 in participants 18 to <46 years of age.

Key Secondary Objective

1. To compare the anti-CHIKV SNA response to PXVX0317 and placebo at Day 15, Day 183, and Day 8, as measured by GMT and seroresponse rate.

Clinical Reviewer Comment*: Additional secondary and exploratory objectives were defined but are not discussed in this memo since they did not contribute significantly to the benefit-risk assessment.*

6.1.2 Design Overview

Study 004 was a phase 3, randomized, placebo-controlled, double-blind, parallel-group study with four treatment groups. 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, with a target enrollment of 3,150 participants. A nested lot consistency substudy was planned for 1,050 adult participants 18 to <46 years of age in the PXVX0317 treatment group (b) (4) The planned study duration was 12 months.

6.1.3 Population

Individuals who were 12 to <65 years of age and generally healthy were eligible for enrollment. Women of childbearing potential were eligible if they had negative pregnancy testing at the screening and randomization visits and used contraception for the duration of participation. Individuals were excluded from participation if they were pregnant, lactating, had a history of a congenital or acquired immunodeficiency, received or anticipated use of systemic immunomodulatory or immunosuppressive medications during the six months prior to screening, or had previously received an investigational CHIKV vaccine/product.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Single dose of PXVX0317 or placebo:

1. *PXVX0317*: 0.8 mL IM injection supplied in a prefilled syringe containing CHIKV VLP (40µg), aluminum hydroxide (b) (4) adjuvant (300µg), and formulation buffer. Three lots were used: (b) (4)

2. *Placebo:* 0.8 mL IM injection of formulation buffer in a pre-filled syringe.

6.1.5 Directions for Use

PXVX0317 or placebo was administered IM into the deltoid muscle as a single injection on Day 1 (Visit 2).

6.1.6 Sites and Centers

The study was conducted at 47 investigational sites in the U.S.

Clinical Reviewer Comment*: Site 0091, which enrolled 47 participants, had three minor, two major, and one critical GCP finding at the time of audit, including failing to delegate study conduct duties to qualified personnel. Per the Applicant, an enrollment hold was implemented and ultimately maintained due to these findings. Study results submitted by the Applicant include the 47 participants enrolled at this site. The clinical and statistical reviewers evaluated safety and efficacy results, respectively, after excluding Site 0091. The reviewers found that safety and efficacy results for Study 004 were not meaningfully altered by excluding participants from Site 0091. As such, the tables and results in this memo include the 47 participants from Site 0091, consistent with the Applicant's approach. A second site for Study 004 (Site 0020) enrolled 166 participants and also had one critical GCP finding, as well as two minor findings. However, the Applicant notes that a Corrective and Preventative Action plan was executed at the site level which was deemed suitable to ensure compliance. Due to the critical GCP finding, Site 0020 was inspected by BIMO, with no significant irregularities noted.*

6.1.7 Surveillance/Monitoring

Solicited ARs, unsolicited AEs, AESIs, medically attended AEs (MAAEs), AEs leading to withdrawal from the study, and serious AEs (SAEs) were assessed. The following ARs and AEs were documented and monitored:

Solicited Systemic and Local ARs

Solicited ARs were collected via eDiary for 7 days post-vaccination. Solicited systemic ARs included arthralgia, myalgia, fever, chills, fatigue, headache, and nausea. Local ARs included injection site pain, redness, swelling, and reaction size. The day of onset and duration of solicited ARs were recorded.

Clinical Reviewer Comment*: Initially, solicited ARs that continued past Day 8 were also reported as an unsolicited AE and the maximum duration of solicited ARs was set at 8 days. In response to Information Requests (IRs) #3 and 17, the Applicant removed solicited ARs that lasted more than 8 days from unsolicited AEs (as was recommended by the Data Standards Reviewer) and updated the duration of solicited ARs to be the entire duration of the AR, rather than the imputed maximum duration of 8 days. The solicited AR data presented in this memo use the updated approach.*

Unsolicited AEs

Unsolicited AEs were collected between Day 1 (Visit 2) and Day 29 (Visit 6). Solicited ARs (collected Day 1 to Day 8) that were AESIs or serious, SAEs, and MAAEs were also recorded as unsolicited AEs. All unsolicited AEs were documented in the respective AE section of the electronic case report form during the applicable study visit.

AESIs

Participants were monitored for new onset or worsening arthralgia that was medically attended from Day 1 (Visit 2) through the end of study (Day 183, Visit 8). Medically attended visits included hospital, emergency room, urgent care clinic, or other visits to or from medical personnel. Of note, arthralgia that was reported as an unsolicited AE was ultimately listed under the preferred term (PT) that captured the final diagnosis or etiology of the arthralgia (e.g., arthralgia due to osteoarthritis would be listed under the PT of osteoarthritis but would still be assessed for qualification as an AESI).

SAEs and MAAEs

Participants were monitored for SAEs and MAAEs from Day 1 (Visit 2) through the end of study (Day 183, Visit 8). For SAEs, death was considered an outcome rather than an event; the condition leading to death was the event.

Safety Monitoring Committee

An independent Safety Monitoring Committee reviewed aggregated, blinded safety data after the 300th enrolled participant passed Day 29 and again after the last enrolled participant passed Day 29. The Applicant's Medical Monitor also reviewed safety data on an ongoing basis.

Clinical Reviewer Comment*: No safety signals were identified at the planned Safety Monitoring Committee meetings.*

6.1.8 Endpoints and Criteria for Study Success

6.1.8.1 Primary Endpoints

Safety Endpoints

1. Incidence of solicited ARs through Day 8 for PXVX0317 and placebo.
2. Incidence of unsolicited AEs through Day 29 for PXVX0317 and placebo.
3. Incidence of AESIs, MAAEs, and SAEs through Day 183 for PXVX0317 and placebo.

Coprimary Immunogenicity Endpoints and Success *Criteria*

1. Difference in anti-CHIKV SNA seroresponse rate (PXVX0317 minus placebo) and associated 95% CI at Day 22.
   a. Note: Seroresponse rate was defined as the percentage of participants who achieved a CHIKV SNA titer ≥100.
   b. Success criteria: Statistical superiority to placebo and LB of the two-sided 95% CI ≥70%.
2. Anti-CHIKV SNA GMT and associated 95% CIs at Day 22 for PXVX0317 and placebo.
   a. Success criterion: Significant difference between PXVX0317 and placebo.
3. Anti-CHIKV SNA GMT ratio between all three pairs of PXVX0317 lots (b) (4) among adults 18 to <46 years of age at Day 22.
   a. Success criteria: Pairwise GMT ratios (b) (4) each with a two-sided 95% CI within [0.667, 1.5].

6.1.8.2. Key Secondary Endpoints

1. Difference in anti-CHIKV SNA seroresponse rate (PXVX0317 minus placebo) with associated 95% CIs at Day 15, Day 183, and Day 8, in that order.
    a. Success criteria: Statistical superiority to placebo, and at Day 15 only, LB of the two-sided 95% CI ≥70%
2. Anti-CHIKV SNA GMTs and associated 95% CIs at Day 8, Day 15, and Day 183 for PXVX0317 and placebo.
    a. No success criteria specified.

6.1.9 Statistical Considerations & Statistical Analysis Plan

6.1.9.1 Study Hypotheses and Analyses of Primary Endpoints

Anti-CHIKV seroresponse rate difference at Day 22: The seroresponse rate was defined as the percentage of participants in the IEP with a CHIKV-luc assay anti-CHIKV SNA NT80 ≥100 at Day 22. The null hypothesis H0 was the LB of the 95% CI of seroresponse rate difference (PXVX0317 minus placebo) <70% and the alternative hypothesis H1 was LB of 95% CI of seroresponse rate difference ≥70%.

Anti-CHIKV GMT at Day 22: GMTs for the IEP were analyzed via a linear model based on an alpha of 0.05. The primary model was an analysis of variance, with logarithmically transformed anti-CHIKV SNA titers (log10) as the dependent variable and treatment group and study site as the fixed effects in the model. The adjusted least square means and their 95% CIs calculated based on the analysis of variance were back transformed and reported as the group GMT values.

Lot equivalency at Day 22: Lot equivalency was measured by calculating anti-CHIKV SNA GMT ratios and their 95% CIs between all three pairs of consecutively manufactured PXVX0317 lots (b) (4) in the IEP 18 to <46 years of age stratum. GMTs were calculated as described above for coprimary endpoint #2.

There was no adjustment for multiplicity for any of the above analyses, but a family-wise error rate was fixed at a two-sided alpha of 0.05 by the requirement that all coprimary endpoint hypotheses must be met for a successful outcome (Day 22 seroresponse, Day 22 GMT, and lot consistency pairwise GMT ratios). This family-wise error rate was prespecified to reduce type I error in the setting of multiple comparisons.

6.1.9.2 Sample Size Calculation

The sample size was guided by the following considerations:

1. Predicted difference in seroresponse rates between PXVX0317 and placebo groups: Based on data from Study 001, the seroresponse rate for PXVX0317 was expected to be approximately 90% compared with <5% for placebo. With an assumed 10% rate of non-evaluable participants, the power to show superiority over placebo with 2,430 PXVX0317 and 405 placebo evaluable participants was >99.9% and the width of a two-sided 95% CI was ±1.2%. The difference in seroresponse rate would need to be above 72% for the LB of the 95% CI to be ≥70%.
2. Lot consistency evaluation: The study was powered at 95% to reject the null hypothesis that the difference in mean titers between lots is below -0.176 or above 0.176 in favor of an alternative hypothesis of equivalence when the expected difference in log10 means was 0,

the common standard deviation (SD) was 0.455, each test was at the 2.5% level, and the sample size in each lot was 207.

3. Size of the safety database: With 2,700 participants receiving any lot of PXVX0317, the study was estimated to be 93.3% likely to detect at least one AE with a true frequency of ≥0.1%.

6.1.9.3 Methods of Handling Missing Data

Participants with missing immunogenicity data at Days 8, 15, 22, or 183 were excluded from the corresponding analysis; missing immunogenicity data was not imputed. Human SNA assay values below the lower limit of quantitation (LLOQ) were replaced by LLOQ/2 in the immunogenicity analyses. Participants missing solicited AR data were excluded from the corresponding analysis; missing solicited AR data was not imputed. Imputation rules for partial or missing dates are described in the study statistical analysis plan.

6.1.9.4 Interim Analysis

No interim analyses of immunogenicity were planned or conducted.

6.1.9.5 Safety Analyses

The incidence of adverse events (solicited ARs, unsolicited AEs, SAEs, AESIs, MAAEs) in the PXVX0317 group (with the three lots combined) were compared with the placebo group using the safety population. The number and percentage of participants, plus the number of events in each category, were presented.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 24.1. When summarized, AEs were counted by participant, not by event, and participants were only counted once within each system organ class (SOC) or PT. Where AEs were presented by severity, participants with multiple events within a particular SOC or PT were counted once under the category of their most severe event within that SOC or PT. When AEs were categorized by relationship to the IP, AEs with a causality reported as probable or possible were considered related to the product. Participants with multiple events within a particular SOC or PT were counted under the category of their most treatment-related event within that SOC or PT.

No statistical hypothesis testing was performed using the safety data.

No clinical safety laboratory data was collected in this study.

Clinical Reviewer Comment*: Please see the statistical review for further details about the statistical methods used for the immunogenicity and safety analyses.*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Participants enrolled and analyzed are presented in Table 6.

Table 6. Analysis Sets, Randomized Participants, Study 004

Population	PXVX0317 (b) (4) (N=919) n (%)	PXVX0317 (b) (4) (N=948) n (%)	PXVX0317 (b) (4) (N=927) n (%)	Pooled PXVX0317 (N=2794) n (%)	Placebo (N=464) n (%)	Total (N=3258) n (%)
Randomized	919 (100.0)	948 (100.0)	927 (100.0)	2794 (100.0)	464 (100.0)	3258 (100.0)
Exposed[a]	918 (99.9)	945 (99.7)	927 (100.0)	2790 (99.9)	464 (100.0)	3254 (99.9)
Safety[b]	918 (99.9)	945 (99.7)	927 (100.0)	2790 (99.9)	464 (100.0)	3254 (99.9)
mITT[c]	905 (98.5)	938 (98.9)	920 (99.2)	2763 (98.9)	459 (98.9)	3222 (98.9)
Immunogenicity Evaluable[d]	841 (91.5)	860 (90.7)	858 (92.6)	2559 (91.6)	424 (91.4)	2983 (91.6)

Source: Adapted from ESBI-CV-317-004 Clinical Study Report Table 10
Abbreviations: %=n/N*100; mITT=modified intention to treatintent-to-treat; N=number of enrolled participants in the study; n=number of participants per parameter; SNA=serum neutralizing antibody
[a]Exposed Population = Randomized participants who received study vaccination.
[b]Safety Population = Exposed participants who provided safety assessment data.
[c]mITT Population = Exposed participants who had at least one post-injection anti-CHIKV SNA result.
[d]Immunogenicity evaluable population = mITT population participants who had no measurable anti-CHIKV SNA at Day 1 (<LLOQ), had an evaluable Day 22 serum sample result within window (Day 19 through Day 27, inclusive), and had no important protocol deviation deemed exclusionary or other reason for exclusion as defined prior to unblinding.

***Clinical Reviewer Comment**: The percentage of randomized participants included in the IEP and Safety Population were comparable between treatment groups.*

For inclusion in the IEP, the Applicant required a Day 1 CHIKV SNA titer <LLOQ and referred to any participant with a Day 1 CHIKV SNA titer ≥LLOQ as "baseline seropositive." For the CHIKV SNA assay used in this study, the LLOQ is 15 while the lower limit of detection (LLOD) is 10. Although the Applicant does not state their rationale for using the LLOQ for this cutoff (rather than a different threshold, such as the LLOD), this approach is acceptable per the CMC Reviewer. Using the LLOQ rather than a lower threshold (such as the LLOD or LLOQ/2) may result in participants being included in the IEP who have a low level of serum neutralizing antibodies against CHIKV, but this should be a small number and distributed evenly between the PXVX0317 and placebo groups. As such, using the LLOQ rather than a lower threshold should not have a significant impact on the interpretation of immunogenicity results.

6.1.10.1.1 Demographic Characteristics

As shown in Table 7, demographic and baseline characteristics were generally balanced between the treatment groups (differences in categorical variables were <3%). Overall, the median age was 38 years (range 12-64 years), and 51% of participants were female. The majority of participants were White (73%) and not Hispanic or Latino (80%). At baseline, 2% of participants were seropositive for anti-CHIKV SNA. Among the pediatric participants (ages 12 to <18 years [N=254]), 56% were male, 82% were White, 77% were not Hispanic or Latino, and 0.8% were seropositive at baseline.

Table 7. Demographic and Baseline Characteristics, Randomized Participants, Study 004

Characteristic	PXVX0317 (b) (4) (N=919)	PXVX0317 (b) (4) (N=948)	PXVX0317 (b) (4) (N=927)	Pooled PXVX0317 (N=2794)	Placebo (N=464)	All Participants (N=3258)
Sex, n (%)	-	-	-	-	-	-
Female	452 (49.2)	506 (53.4)	478 (51.6)	1436 (51.4)	231 (49.8)	1667 (51.2)
Male	467 (50.8)	442 (46.6)	449 (48.4)	1358 (48.6)	233 (50.2)	1591 (48.8)
Age (years)	-	-	-	-	-	-
Mean (SD)	38.9 (14.4)	38.3 (14.3)	38.6 (14.0)	38.6 (14.3)	38.7 (14.4)	38.6 (14.3)
Median	38.0	37.5	38.0	38.0	38.0	38.0
(Min, Max)	(12, 64)	(12, 64)	(12, 64)	(12, 64)	(12, 64)	(12, 64)
Age group, n (%)	-	-	-	-	-	-
12 to <18 years of age	67 (7.3)	76 (8.0)	74 (8.0)	217 (7.8)	37 (8.0)	254 (7.8)
18 to <46 years of age	541 (58.9)	552 (58.2)	543 (58.6)	1636 (58.6)	270 (58.2)	1906 (58.5)
46 to <65 years of age	311 (33.8)	320 (33.8)	310 (33.4)	941 (33.7)	157 (33.8)	1098 (33.7)
Race, n (%)	-	-	-	-	-	-
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)
Multiple	23 (2.5)	32 (3.4)	23 (2.5)	78 (2.8)	8 (1.7)	86 (2.6)
Native Hawaiian or Other Pacific Islander	2 (0.2)	4 (0.4)	0	6 (0.2)	4 (0.9)	10 (0.3)
Not reported	4 (0.4)	8 (0.8)	12 (1.3)	24 (0.9)	4 (0.9)	28 (0.9)
White	663 (72.1)	693 (73.1)	687 (74.1)	2043 (73.1)	341 (73.5)	2384 (73.2)
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)
Childbearing Potential at Screening[a], n (%)	-	-	-	-	-	-
No	199 (21.7)	201 (21.2)	190 (20.5)	590 (21.1)	95 (20.5)	685 (21.0)
Yes	253 (27.5)	305 (32.2)	288 (31.1)	846 (30.3)	136 (29.3)	982 (30.1)
Height (cm)	-	-	-	-	-	-
Mean (SD)	171.4 (10.0)	170.4 (9.6)	170.7 (10.0)	170.8 (9.9)	171.2 (10.0)	170.9 (9.9)
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)
Weight[b] (kg)	-	-	-	-	-	-
Mean (SD)	78.5 (16.5)	78.4 (16.1)	78.3 (16.4)	78.4 (16.3)	77.6 (16.4)	78.3 (16.3)
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)
Body Mass Index[b] (kg/m^2)	-	-	-	-	-	-
Mean (SD)	26.6 (4.6)	26.9 (4.5)	26.7 (4.5)	26.8 (4.5)	26.4 (4.6)	26.7 (4.5)
Median	26.8	26.9	26.7	26.8	26.3	26.7
(Min, Max)	(13.1, 35.4)	(14.8, 35.0)	(14.9, 34.9)	(13.1, 35.4)	(15.7, 34.9)	(13.1, 35.4)

Characteristic	PXVX0317 (b) (4) (N=919)	PXVX0317 (b) (4) (N=948)	PXVX0317 (b) (4) (N=927)	Pooled PXVX0317 (N=2794)	Placebo (N=464)	All Participants (N=3258)
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)

Source: Adapted from ESBI-CV-317-004 Clinical Study Report Table 11
Abbreviations: %=n/N*100; BMI = body mass index; LLOQ=lower limit of quantitation; max=maximum; min=minimum; N=number of participants per group; n=number of participants per parameter; SD=standard deviation; SNA=serum neutralizing antibody
[a]The percentages for childbearing potential are based on the number of female participants.
[b]Weight and body mass index from screening visit.

Clinical Reviewer Comment*: The demographics of the enrolled population generally reflect those of the U.S. population (which is the target population for PXVX0317), except for a relatively small difference in the average body mass index (BMI) (Study 004 average BMI: 26.7; U.S. population average BMI: 29.2) (US Census, 2024). The U.S. baseline seropositivity rate for CHIKV is unknown, so it is unknown whether Study 004 is representative of the U.S. population regarding baseline seropositivity. Of note, among the participants who were seropositive at baseline (n=69), 16 (23%) are Hispanic or Latino, suggesting that Hispanic or Latino participants are overrepresented in the baseline seropositive subgroup.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The percentage of participants with any medical history was similar between the two groups (84% PXVX0317, 83% placebo), including medical history of arthritis (1.0% PXVX0317, 1.5% placebo), myalgia (0.5% PXVX0317, 0.6% placebo), and fibromyalgia (0.5% PXVX0317, 0.6% placebo). The placebo group had a higher percentage of participants with prior arthralgia than the PXVX0317 group (3.5% PXVX0317, 5.0% placebo).

Most participants (70% among PXVX0317, 67% among placebo recipients) received prior and/or concomitant medications. The most common concomitant medications were selective serotonin reuptake inhibitors (13% PXVX0317, 14% placebo). Corticosteroids were used by 11 (0.4%) participants in the PXVX0317 group and 1 (0.2%) in the placebo group prior to IP administration.

Clinical Reviewer Comment*: A slightly higher percentage of participants in the placebo group had a history of arthralgia compared with the PXVX0317 group (difference of 1.5%); this is unlikely to have a significant impact on the interpretation of AEs given the small difference. Further, since the AESI definition captured worsening arthralgia, the placebo group participants with a prior history of arthralgia would still be counted as experiencing an AESI if their pre-existing arthralgia worsened post-vaccination.*

Although the details of prior corticosteroid use among participants are not provided in the Applicant's submission (e.g., minimal information is provided about the dosing, route, or duration of exposure), prior corticosteroid use among study participants is unlikely to impact the safety or immunogenicity results significantly since the percentage of participants with prior corticosteroid exposure is small (<1%).

6.1.10.1.3 Subject Disposition

The disposition of participants is provided in Table 8. A similar percentage of participants completed the study in the PXVX0317 (89%) and placebo (93%) groups.

Table 8. Disposition of Randomized Participants, Study 004

Disposition	PXVX0317 (b) (4) (N=919) n (%)	PXVX0317 (b) (4) (N=948) n (%)	PXVX0317 (b) (4) (N=927) n (%)	Pooled PXVX0317 (N=2794) n (%)	Placebo (N=464) n (%)	Total (N=3258) n (%)
Randomized	919 (100.0)	948 (100.0)	927 (100.0)	2794 (100.0)	464 (100.0)	3258 (100.0)
Treated	918 (99.9)	945 (99.7)	927 (100.0)	2790 (99.9)	464 (100.0)	3254 (99.9)
Completed study[a]	803 (87.4)	837 (88.3)	832 (89.8)	2472 (88.5)	430 (92.7)	2902 (89.1)
Reason for discontinuation	-	-	-	-	-	-
Death	0	0	1 (0.1)	1 (0.0)	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)
Sponsor request	0	1 (0.1)	0	1 (0.0)	0	1 (0.0)
Participant withdrawal	45 (4.9)	30 (3.2)	27 (2.9	102 (3.7)	7 (1.5)	109 (3.3)
Other[b]	4 (0.4)	9 (0.9)	8 (0.9)	21 (0.8)	4 (0.9)	25 (0.8)
Completed study visit	-	-	-	-	-	-
Day 1	919 (100.0)	948 (100.0)	927 (100.0)	2794 (100.0)	464 (100.0)	3258 (100.0)
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)

Source: Adapted from ESBI-CV-317-004 Clinical Study Report Table 8
Abbreviations: %=n/N*100; N=number of participants in the treatment group; n=number of participants with parameter
[a]An individual participant was considered completed based on the Day 183 visit and any required safety follow-up.
[b]Examples of "other" reasons for discontinuation from the study included the participant moving, being deployed, or being incarcerated.

Clinical Reviewer Comment*: A total of 71 participants (2%) did not complete the Day 8 study visit, and 120 participants (4%) did not complete the Day 29 visit. The participants who did not complete the Day 8 study visit were primarily lost to follow-up (30 [64%]) and were enrolled at 27 different study sites with no single study site driving the dropouts. The participants who did not complete the Day 29 study visit were also primarily lost to follow-up (50 [61%]) and enrolled at 34 sites, again with no single study site driving the dropouts. Similarly, at each timepoint, the early dropouts do not appear to be driven by a single lot of PXVX0317 or study group. As described in sections 6.1.11.4 and 6.1.12.6, the early discontinuations do not appear to have had a deleterious impact on immunogenicity or safety analyses.*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

6.1.11.1.1 Coprimary Endpoint #1: Day 22 Anti-CHIKV Seroresponse Rate

The seroresponse rate in the IEP at Day 22 was 98% (2503/2559 participants) in the pooled PXVX0317 group and 1% (5/424 participants) in the placebo group (Table 9). The difference in seroresponse rates was thus 97% (95% CI: 95, 98). The LB of the 95% CI is ≥70% and the seroresponse rate was significantly higher in PXVX0317 than placebo recipients, so the success criteria were met. Similar results were observed in the mITT population where the seroresponse rate (%) difference was 96% (95% CI: 94, 97).

Clinical Reviewer Comment*: The Statistical Reviewer performed a sensitivity analysis in which participants enrolled at Site 0091 were excluded; this resulted in a seroresponse rate (%)*

difference of 97% (95% CI: 95, 97), which is similar to the results obtained when Site 0091 was included.

*Five placebo recipients (1%) developed a seroresponse at Day 22 despite the lack of circulating CHIKV in the U.S. at the time of trial completion (CDC, 2025) and the requirement for a baseline Day 1 SNA <LLOQ (LLOQ=15). Per the CMC reviewer, variability in assay performance could account for variation within 2*LLOQ, but these five placebo recipients had SNA levels ≥100, suggesting their seroresponse was not due to assay variability. In response to IR #13, the Applicant reports that Day 22 was the only timepoint where these placebo recipients had a CHIKV SNA titer ≥100. For all other timepoints, these placebo recipients had CHIKV SNA titers below the LLOQ, except for one participant for whom there was no Day 183 data available. The Applicant states in response to IR #13 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 Response to IR #52, the Applicant reported that on repeat testing, two of the placebo recipients who originally had CHIKV SNA titers ≥100 at Day 22 had CHIKV SNA titers <15 on the repeat testing. The Applicant attributed the anomalous results to "sampling handling errors." In light of these findings and because SNA titers were <100 at time points prior to and after Day 22, this reviewer agrees that these five placebo recipients likely had false-positive CHIKV SNA titers on Day 22. Further, this small number of anomalous CHIKV SNA titers (1%) do not change the overall conclusions of the immunogenicity results, since the LB of the 95% CI around the seroresponse rate difference is more than 1% above the cutoff of 70%.*

6.1.11.1.2 Coprimary Endpoint #2: Day 22 Anti-CHIKV SNA GMT

The Day 22 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) (Table 9).

***Clinical Reviewer Comment**: The provided GMT and GMT ratio values were computed using the updated ULOQ that was provided by the Applicant in response to IR #12.*

The success criteria for the first two coprimary immunogenicity endpoints were met, suggesting PXVX0317 is effective at neutralizing CHIKV at a significantly higher rate than placebo.

Table 9. Day 22 CHIKV SNA GMT, GMT Ratios, Seroresponse Rates, and Seroresponse Rate Differences, IEP, Study 004

Parameter	Pooled PXVX0317 (N=2559)	Placebo (N=424)
GMT (95% CI)[a]	1596.98 (1504.11, 1695.57)	7.86 (7.00, 8.81)
GMT Ratio (95% CI)[a,d]	203.29 (181.08, 228.23)	-
Seroresponse Rate, n/N % (95% CI)[b]	2503/2559 97.8 (97.2, 98.3)	5/424 1.2 (0.5, 2.7)
Seroresponse Rate Difference, % (95% CI)[c,e]	96.6 (95.0, 97.5)	-

Source: Adapted from EBSI-CV-317-004 Clinical Study Report Tables 14 and 15 and from Response to IR #12 (Sequence 0021) Table 14.2.2.1.1
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP= immunogenicity evaluable population; N=number of participants in treatment group; n=number of participants with parameter; SNA=serum neutralizing antibodies
[a]GMT estimates, together with their 95% CIs, are derived from an ANOVA model that includes site and vaccine group as fixed effects, assuming normality of the log titers. GMT ratios and 95% CIs are derived from the same model. Of note, the provided GMT values were computed using the updated ULOQ (10,794) from IR #12.
[b]95% CIs of seroresponse rates are based on the Wilson method.
[c]95% CIs of seroresponse rate differences are based on the Newcombe hybrid score method.
[d]Success criterion: lower bound of the 95% CI for GMT ratio > 1
[e]Success criteria: statistical superiority to placebo and lower bound of the two-sided 95% CI ≥70%

6.1.11.1.3 Coprimary Endpoint #3: Lot Comparison of GMT Ratio at Day 22

Pairwise lot comparison of 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 (b) (4) 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. Subpopulations were not evaluated for this endpoint.

Clinical Reviewer Comment*: The success criterion for the third coprimary immunogenicity endpoint was met, suggesting different lots of PXVX0317 elicit comparable CHIKV SNA titers.*

Table 10. Pairwise Lot Comparison of Anti-CHIKV SNA GMT Ratio on Day 22, IEP, Adults 18 to < 46 Years, Study 004

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

Source: Adapted from Response to IR #12 Table 14.2.3.1
Abbreviations: CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP=immunogenicity evaluable population; SNA=serum neutralizing antibody
[a]GMT estimates, together with their 95% CIs, are derived from an ANOVA model that includes site and product lot as fixed effects, assuming normality of the log titers. GMT ratios and 95% CIs are derived from the same model. Of note, the provided GMT values were computed using the updated ULOQ (10,794) from IR #12.

6.1.11.2 Analyses of Secondary Endpoints: Day 8, 15, 183 Difference in Anti-CHIKV SNA Seroresponse Rate and Anti-CHIKV SNA GMT

Seroresponse rates and GMT in the IEP at Days 8, 15, and 183 are displayed in Table 11. At each time point, PXVX0317 recipients had a higher seroresponse rate and GMT compared with placebo.

Table 11. Days 8, 15, and 183 Anti-CHIKV SNA GMT, GMT Ratios, Seroresponse Rates, and Seroresponse Rate Differences, IEP, Study 004

Day	Pooled PXVX0317 (N=2559)	Placebo (N=424)
Day 8 N	2510	419
Day 8 GMT[a] (95% CI)	93.12 (86.98, 99.69)	7.40 (6.49, 8.43)
Day 8 GMT ratio[a] (95% CI)	12.59 (11.04, 14.36)	-
Day 8 Seroresponse Rate[b], n/N, % (95% CI)	1169/2510 46.6 (44.6, 48.5)	2/419 0.5 (0.1, 1.7)
Day 8 Seroresponse Rate Difference[c], % (95% CI)	46.1 (43.8, 48.1)	-
Day 15 N	2434	395
Day 15 GMT[a] (95% CI)	1087.83 (1022.63, 1157.20)	7.62 (6.77, 8.58)
Day 15 GMT ratio[a] (95% CI)	142.78 (126.82, 160.74)	-
Day 15 Seroresponse Rate[b], n/N, % (95% CI)	2355/2434 96.8 (96.0, 97.4)	3/395 0.8 (0.3, 2.2)
Day 15 Seroresponse Rate Difference[c], % (95% CI)	96.0 (94.3, 96.8)	-
Day 183 N	2301	401
Day 183 GMT[a] (95% CI)	337.73 (318.27, 358.37)	8.19 (7.33, 9.14)
Day 183 GMT ratio[a] (95% CI)	41.26 (36.95, 46.07)	-
Day 183 Seroresponse Rate[b], n/N, % (95% CI)	1967/2301 85.5 (84.0, 86.9)	6/401 1.5 (0.7, 3.2)
Day 183 Seroresponse Rate Difference[c], % (95% CI)	84.0 (81.7, 85.6)	-

Source: Adapted from EBSI-CV-317-004 Clinical Study Report Tables 17 and 18
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP=immunogenicity evaluable population; N=number of participants per treatment group; n=number of participants with parameter; SNA=serum neutralizing antibody
[a]GMT estimates, together with their 95% CIs, are derived from an ANOVA model that includes site and vaccine group as fixed effects, assuming normality of the log titers. GMTs, GMT ratios, and corresponding 95% CIs are all derived from the same model. The updated ULOQ (=10794.8) was used as per IR #12.
[b]95% CIs are based on the Wilson method.
[c]95% CIs are based on the Newcombe hybrid score method.

Clinical Reviewer Comment: *Secondary analyses suggest a notable increase in CHIKV SNA titers (≥100) as early as Day 15 after PXVX0317 administration in 97% of participants. The immune response persists through Day 183 in the majority of participants (86%) though there is some waning of the antibody response.*

The placebo recipients who had evidence of a seroresponse at Days 8, 15, and 183 each had only one timepoint postvaccination when their CHIKV SNA titer was ≥100, suggesting these may have been false-positive results. See the clinical reviewer comment in section 7.1.4 for details.

6.1.11.3 Subpopulation Analyses

Day 22 differences in seroresponse rate (PXVX0317 minus placebo) did not vary substantially by demographic subgroups, including sex, race, ethnicity, and age (Table 12).

Table 12. Day 22 CHIKV SNA Seroresponse Rate and Seroresponse Rate Differences by Subgroup, IEP, Study 004

Subgroup	Pooled PXVX0317 Seroresponse Rate[a], n/N % (95% CI)	Placebo Seroresponse Rate[a], n/N % (95% CI)	Seroresponse Rate Difference[b], n/N % (95% CI)
All IEP	2503/2559 97.8 (97.2, 98.3)	5/424 1.2 (0.5, 2.7)	96.6 (95.0, 97.5)
Sex	-	-	-
Male	1208/1241 97.3 (96.3, 98.1)	3/210 1.4 (0.5, 4.1)	95.9 (93.0, 97.1)
Female	1295/1318 98.3 (97.4, 98.8)	2/214 0.9 (0.3, 3.3)	97.3 (94.8, 98.2)
Race	-	-	-
White	1847/1887 97.9 (97.1, 98.4)	2/315 0.6 (0.2, 2.3)	97.2 (95.4, 98.0)
Non-White	636/652 97.5 (96.1, 98.5)	3/105 2.9 (1.0, 8.1)	94.7 (89.3, 96.8)
Ethnicity	-	-	-
Hispanic or Latino	447/457 97.8 (96.0, 98.8)	0/65 0 (0, 5.6)	97.8 (92.0, 98.8)
Not Hispanic or Latino	2004/2049 97.8 (97.1, 98.4)	5/347 1.4 (0.1, 3.3)	96.4 (94.3, 97.4)
Age group	-	-	-
12 to <18 years	195/201 97.0 (93.6, 98.6)	1/33 3.0 (0.5, 15.3)	94.0 (81.2, 97.0)
18 to <46 years	1455/1480 98.3 (97.5, 98.9)	4/245 1.6 (0.6, 4.1)	96.7 (94.1, 97.8)
46 to <65 years	853/878 97.2 (95.8, 98.1)	0/146 0 (0, 2.6)	97.2 (94.3, 98.1)

Source: Adapted from EBSI-CV-317-004 Clinical Study Report Table 14 and from Response to IR #12 Table 14.2.1.1.1
Abbreviations: CHIKV=chikungunya virus; CI=confidence interval; IEP= immunogenicity evaluable population; N=number of participants in the specified subgroup and treatment group; n=number of participants with parameter; SNA=serum neutralizing antibody
[a]95% CIs are based on the Wilson method.
[b]95% CIs are based on the Newcombe hybrid score method.

Day 22 CHIKV SNA GMTs were numerically higher in female participants and the 12 to <18 years of age group (Table 13).

Table 13. CHIKV SNA GMT, GMT Ratios on Day 22 by Subgroup, IEP, Study 004

Subgroup	Pooled PXVX0317 N GMT (95% CI)[a,b]	Placebo N GMT (95% CI)[a,b]	GMT Ratio (95% CI)[a,b]
All IEP	2559 1596.98 (1504.11, 1695.57)	424 7.86 (7.00, 8.81)	203.29 (181.08, 228.23)
Sex	-	-	-
Male	1241 1327.06 (1216.33, 1447.88)	210 7.94 (6.72, 9.38)	167.13 (141.24, 197.77)
Female	1318 1937.90 (1775.04, 2115.70)	214 8.06 (6.85, 9.48)	240.44 (205.06, 281.92)
Race	-	-	-
White	1887 1586.61 (1466.54, 1716.51)	315 7.34 (6.40, 8.41)	216.25 (189.54, 246.71)
Non-White	652 1602.98 (1381.35, 1860.17)	105 9.62 (7.38, 12.53)	166.71 (129.49, 214.62)

Subgroup	Pooled PXVX0317 N GMT (95% CI)[a,b]	Placebo N GMT (95% CI)[a,b]	GMT Ratio (95% CI)[a,b]
Ethnicity	-	-	-
Hispanic or Latino	457 1735.22 (1438.91, 2092.54)	65 7.31 (5.22, 10.22)	237.53 (173.05, 326.04)
Not Hispanic/Latino	2049 1580.87 (1469.87, 1700.25)	347 7.90 (6.94, 9.00)	199.99 (176.03, 227.21)
Age group	-	-	-
12 to <18 years	201 2459.65 (1829.77, 3306.37)	33 9.24 (5.53, 15.44)	266.12 (161.86, 437.54)
18 to <46 years	1480 1849.09 (1704.17, 2006.32)	245 8.23 (7.11, 9.53)	224.67 (194.58, 259.42)
46 to <65 years	878 1166.16 (1044.83, 1301.58)	146 7.20 (5.91, 8.79)	161.86 (132.65, 197.51)

Source: Adapted from EBSI-CV-317-004 Clinical Study Report Table 15
Abbreviations: CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP=immunogenicity evaluable population; N=number of participants in the specified subgroup and treatment group; SNA=serum neutralizing antibody
[a]GMT estimates, together with their 95% CIs, are derived from an ANOVA model that includes site and vaccine group as fixed effects, assuming normality of the log titers. GMTs, GMT ratios, and corresponding 95% CIs are all derived from the same model.
[b]For GMT analyses, the updated ULOQ (10794.8) was used.

Regarding the secondary endpoints, female participants and the 12 to <18 years of age subgroups had higher rates of seroresponse at both early and late timepoints compared with males and older participants, respectively. A similar trend was observed for CHIKV SNA GMTs.

Clinical Reviewer Comment*: No multiplicity adjustments were made for subgroup analyses and some subgroups were too small to yield precise estimates or to provide adequate power for hypothesis testing, which was not pre-specified. Therefore, results of these subgroup analyses should be interpreted with caution. Overall, the subgroup analyses suggest the differences in seroresponse rate between PXVX0317 and placebo were consistent across subgroups.*

6.1.11.4 Dropouts and/or Discontinuations

The overall dropout rate for this study was 11% (356/3258), with 322 (12%) PXVX0317 recipients and 34 (7%) placebo recipients not completing the study. The primary reasons for not completing the study included: lost to follow-up (216 [7%]), withdrawn by participant (109 [3%]), other reasons (25 [0.8%]), physician decision (4 [0.1%]), Sponsor decision (1 [<0.1%]), and death (1 [<0.1%]) (Table 8). A total of 96% of participants in both the PXVX0317 and placebo groups completed the Day 29 study visit, and 98.5% of PXVX0317 and 99.8% of placebo recipients had blood collections performed on Day 22.

Clinical Reviewer Comment*: The PXVX0317 group had a higher dropout rate (12%) than the placebo group (7%), which appears to have been driven primarily by dropouts after the Day 29 study visit and due to lost to follow-up and withdrawal by the participant. Based on this reviewer's review of the safety data, none of the dropouts appeared to be temporally associated with or related to treatment-emergent adverse events. Based on the timing of the dropouts and discontinuations (following Day 29) and adequacy of the immunogenicity population to meet the statistical success criterion, it is unlikely that dropouts and discontinuations had an impact on the safety or immunogenicity study conclusions. In a sensitivity analysis performed by the statistical reviewer, assuming all dropouts showed no seroresponse, the seroresponse rate difference would be 88.5% [95% CI: 86.7, 89.8%], with a LB of the 95% CI ≥70%. See section 6.1.12.6 for a discussion of the impact of dropouts on safety analyses.*

6.1.11.5 Exploratory and Post Hoc Analyses

Baseline Seropositive Participants

A total of 69 baseline seropositive participants were enrolled (defined as Day 1 predose CHIKV SNA titer ≥15 [≥LLOQ]). Of these, 63 participants were in the PXVX0317 group and 6 were in the placebo group. An ad hoc analysis found that baseline seropositive participants had higher GMT values following PXVX0317 than seronegative participants: seropositive participants had a Day 1 (baseline) GMT of 317, a Day 8 GMT of 1148, a Day 15 GMT of 3799, a Day 22 GMT of 3969, and a Day 183 GMT of 1140. Comparatively, baseline seronegative participants in the PXVX0317 group (the IEP) had a Day 1 GMT below the LLOQ, a Day 8 GMT of 93, a Day 15 GMT of 1096, a Day 22 GMT of 1618, and a Day 183 GMT of 338.

Among the 6 baseline seropositive placebo recipients, three had titers ≥100 at Day 1 that remained ≥100 at Day 22; two had titers ≥100 on Day 1 but decreased to <15 on Day 22; and one had a titer between 15 and 100 on both Day 1 and Day 22.

Clinical Reviewer Comment*: The results of this post hoc analysis suggest that (1) PXVX0317 increased the CHIKV-specific immune response among participants who were potentially infected with CHIKV previously, and (2) pre-existing anti-CHIKV antibodies do not adversely impact the immune response induced by PXVX0317.*

The two placebo recipients with titers ≥100 on Day 1 but <15 on Day 22 are potentially suggestive of false-positive Day 1 results, adding to the small number of participants with likely false-positive SNA results.

6.1.12 Safety Analyses

6.1.12.1 Methods

Descriptive safety analyses were conducted on the Safety Population. Please see sections 6.1.7 and 6.1.9.5 for a description of active and passive safety monitoring.

6.1.12.2 Overview of Adverse Events

An overview of all AEs reported during the clinical trial in the safety population is presented in Table 14.

The occurrence of at least one AE (solicited and/or unsolicited) was reported by a numerically higher percentage of participants in the PXVX0317 group (1257/2790 [45%]) than in the placebo group (161/464 [35%]). Most AEs were mild or moderate, with 73 (2.6%) PXVX0317 recipients and 3 (0.6%) placebo recipients experiencing a severe (grade 3) AE.

SAEs were reported by 23 (0.8%) participants in the PXVX0317 group and 1 (0.2%) participant in the placebo group. The percentage of participants with an AESI was similar in the PXVX0317 (6 [0.2%]) and placebo (1 [0.2%]) groups.

The percentage of participants reporting AEs was similar across lots (42% in Lot (b) (4) 46% in Lot (b) (4) 48% in Lot (b) (4).

Clinical Reviewer Comment*: A higher percentage of PXVX0317 recipients reported AEs than placebo recipients; the difference was primarily driven by a higher percentage reporting solicited ARs. Please see the following section on solicited ARs for further details.*

Table 14. Solicited Adverse Reactions and Unsolicited Adverse Events, Safety Population, Study 004

Event	PXVX0317 (b) (4) (N=918) n (%)	PXVX0317 (b) (4) (N=945) n (%)	PXVX0317 (b) (4) (N=927) n (%)	Pooled PXVX0317 (N=2790) n (%)	Placebo (N=464) n (%)
Any AR or AE[a]	382 (41.6)	433 (45.8)	442 (47.7)	1257 (45.1)	161 (34.7)
Grade 3 or higher	20 (2.2)	24 (2.5)	29 (3.1)	73 (2.6)	3 (0.6)
Any solicited AR[b]	319 (35.2)	373 (39.7)	367 (39.9)	1059 (38.3)	124 (27.1)
Grade 3 or higher	10 (1.1)	15 (1.6)	19 (2.1)	43 (1.6)	2 (0.4)
Any systemic solicited AR[b]	272 (30.0)	307 (32.7)	312 (33.9)	891 (32.2)	114 (24.9)
Grade 3 or higher	10 (1.1)	15 (1.6)	17 (1.8)	41 (1.5)	2 (0.4)
Any local solicited AR[b]	200 (22.1)	236 (25.1)	226 (24.6)	662 (23.9)	49 (10.7)
Grade 3 or higher	1 (0.1)	1 (0.1)	3 (0.3)	5 (0.2)	0
Any unsolicited AE	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)
Any SAEs	10 (1.1)	7 (0.7)	6 (0.6)	23 (0.8)	1 (0.2)
Discontinued study due to AE[a]	0	1 (0.1)	1 (0.1)	2 (0.1)	0
Any Fatal AE	0	0	1 (0.1)	1 (0.0)	0
Any AESI[c]	3 (0.3)	2 (0.2)	1 (0.1)	6 (0.2)	1 (0.2)
Any MAAE	81 (8.8)	83 (8.8)	85 (9.2)	249 (8.9)	41 (8.8)
Any treatment-related unsolicited AE[d]	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 (0.0)	0
Any treatment-related SAE	0	0	0	0	0

Source: Adopted from ESBI-CV-317-004 Table 21 and from Response to IR #17 Table 14.3.2.1
Abbreviations: %=n/N*100; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; AR=adverse reaction; MAAE = medically attended adverse event; n=number of participants with events; N=number of safety population participants in the treatment group; SAE = serious adverse event
[a]Inclusive of both solicited adverse reactions and unsolicited adverse events.
[b]Percentages for solicited adverse reactions are based on the number of participants with at least one diary observation (excluding 'Not done/unknown') for a given symptom or a given day.
[c]AESI was defined as new onset or worsening arthralgia that was medically attended.
[d]Relationship for unsolicited AEs was the investigator's assessment.

Solicited Adverse Reactions

Solicited local and systemic reactions are summarized in Table 15. Solicited ARs were reported by a higher percentage of PXVX0317 recipients (1059 [38%]) than placebo recipients (124 [27%]).

Solicited local ARs were reported by a higher percentage of PXVX0317 recipients (662 [24%]) than placebo recipients (49 [11%]), with the majority reported as mild or moderate severity in both arms. Five (0.2%) PXVX0317 recipients experienced severe local solicited ARs including four participants with injection site pain and one participant with injection site redness. No grade 4 local solicited ARs were reported in either group.

Solicited systemic ARs were reported by a higher percentage of PXVX0317 recipients (891 [32%]) than placebo recipients (114 [25%]) with the majority reported as mild or moderate severity in both arms (Table 15). Severe systemic solicited ARs occurred in 41 (1.5%) PXVX0317 recipients and 2 (0.4%) placebo recipients. In the PXVX0317 group, the severe systemic solicited ARs included 19 participants with fatigue, 12 with nausea, 11 with myalgia, 9 with headache, 7 with arthralgia, 6 with fever, and 4 with chills.

The duration of solicited ARs following PXVX0317 was similar to placebo on average, though the maximal duration of symptoms was longer after PXVX0317 than placebo. Specifically, the median duration of symptoms was 1 day following PXVX0317 (range 1-168 days) and 1 day following placebo (range 1-115 days). The solicited AR that persisted for 168 days following PXVX0317 administration was nausea. See section 6.1.12.5. for further details on solicited events of arthralgia.

Table 15. Solicited Local and Systemic Adverse Reactions Within 7 Days Postvaccination, Safety Population, Study 004

System Organ Class Preferred Term	Pooled PXVX0317[a] n/N (%)	Placebo[b] n/N (%)
Any Solicited AR	1059/2765 (38.3)	124/458 (27.1)
Grade 3	43/2765 (1.6)	2/458 (0.4)
Any Local Solicited AR	662/2764 (24.0)	49/458 (10.7)
Grade 3	5/2764 (0.2)	0/458 (0.0)
Injection site pain	656/2764 (23.7)	49/458 (10.7)
Grade 3	4/2764 (0.1)	0/458 (0.0)
Redness	13/2764 (0.5)	0/458 (0.0)
Grade 3	1/2764 (0.0)	0/458 (0.0)
Swelling	10/2764 (0.4)	0/458 (0.0)
Grade 3	0/2764 (0.0)	0/458 (0.0)
Any Systemic Solicited AR	891/2765 (32.2)	114/458 (24.9)
Grade 3	41/2765 (1.5)	2/458 (0.4)
Arthralgia	214/2764 (7.7)	33/458 (7.2)
Grade 3	7/2764 (0.3)	1/458 (0.2)
Chills	238/2764 (8.6)	15/458 (3.3)
Grade 3	4/2764 (0.1)	0/458 (0.0)
Fatigue	551/2764 (19.9)	78/458 (17.0)
Grade 3	19/2764 (0.7)	1/458 (0.2)
Fever	25/2760 (0.9)	1/457 (0.2)
Grade 3	6/2760 (0.2)	0/457 (0.0)
Headache	498/2765 (18.0)	76/458 (16.6)
Grade 3	9/2765 (0.3)	2/458 (0.4)
Myalgia	486/2764 (17.6)	44/458 (9.6)
Grade 3	11/2764 (0.4)	2/458 (0.4)
Nausea	208/2764 (7.5)	30/458 (6.6)
Grade 3	12/2764 (0.4)	0/458 (0.0)

Source: Adapted from ESBI-CV-317-004 Clinical Study Report Table 23 and from Response to IR #17 Table 14.3.2.2.1
Abbreviations: %=n/N*100; AR=adverse reaction; N=number of participants with at least one diary observation (excluding 'Not done/unknown') for a given symptom for a given day; n=number of participants with events
[a]The total safety population for the pooled PXVX0317 group included 2790 participants. For solicited ARs, the denominator (N) for each row was based on the number of participants with at least one diary observation for a given symptom for a given day.
[b]The total safety population for the placebo group included 464 participants. For solicited ARs, the denominator (N) for each row was based on the number of participants with at least one diary observation for a given symptom for a given day.

***Clinical Reviewer Comment**: One participant who received PXVX0317 reported a grade 4 fever, but this was deemed an entry error, so is not included in Table 15.*

Subgroups (Table 16): In the PXVX0317 group, solicited ARs were more commonly reported by female participants (46%) than male participants (30%), by White participants (41%) than Non-White participants (31%), and by Not Hispanic or Latino participants (40%) than Hispanic or

Latino participants (32%). Grade 3 solicited ARs were more commonly reported by female (2.1%) than male (1.0%) participants, by White (1.7%) than Non-White (1.1%) participants, by Hispanic or Latino (1.8%) than Not Hispanic or Latino (1.5%) participants, and by younger participants (44% of 12 to <18 years) than older participants (31% of 46 to <65 years).

More solicited ARs were reported in the PXVX0317 group than in the placebo group across sex, race, ethnicity, and age subgroups (Table 16). The difference in rates of solicited ARs between PXVX0317 and placebo was most pronounced for the youngest age group (22% difference in the 12 to <18 years of age as compared with an 11% difference in 18 to <46 and a 9% difference in 46 to <65 years of age groups).

***Clinical Reviewer Comment**: Overall and across demographic subgroups (by sex, race, ethnicity, and age), PXVX0317 was associated with more solicited ARs than placebo, including a higher incidence of grade 3 solicited ARs. This observation is expected since the active vaccine is more reactogenic than placebo. Many of the subpopulations with higher frequencies of solicited ARs in the PXVX0317 group also had higher GMT values in the immunogenicity evaluations (female participants, White participants, and younger participants), suggesting that the observed reactogenicity was related to the immune response to PXVX0317. For information on solicited ARs in participants who were seropositive at baseline, please refer to the subgroup analyses following Unsolicited Adverse Events.*

Table 16. Solicited Local and Systemic Adverse Reactions Within 7 Days Postvaccination by Subgroup, Safety Population, Study 004

Subgroup	Parameter	PXVX0317 (N=2790) n (%)	Placebo (N=464) n (%)
All	Participants Assessed[a]	2765	458
	Any Solicited AR	1059 (38.3)	124 (27.1)
	Any Systemic Solicited AR	891 (32.2)	114 (24.9)
	Any Local Solicited AR	662 (24.0)	49 (10.7)
Sex	-	-	-
Male	Participants Assessed[a]	1336	230
	Any Solicited AR	404 (30.2)	54 (23.5)
	Any Systemic Solicited AR	335 (25.1)	47 (20.4)
	Any Local Solicited AR	240 (18.0)	18 (7.8)
Female	Participants Assessed[a]	1429	228
	Any Solicited AR	654 (45.8)	70 (30.7)
	Any Systemic Solicited AR	556 (38.9)	67 (29.4)
	Any Local Solicited AR	421 (29.5)	31 (13.6)
Race	-	-	-
White	Participants Assessed[a]	2031	339
	Any Solicited AR	831 (40.9)	102 (30.1)
	Any Systemic Solicited AR	688 (33.9)	94 (27.7)
	Any Local Solicited AR	530 (26.1)	40 (11.8)
Non-White	Participants Assessed[a]	710	115
	Any Solicited AR	220 (31.0)	19 (16.5)
	Any Systemic Solicited AR	197 (27.7)	17 (14.8)
	Any Local Solicited AR	127 (17.9)	8 (7.0)

Subgroup	Parameter	PXVX0317 (N=2790) n (%)	Placebo (N=464) n (%)
Age	-	-	-
12 to <18 years	Participants Assessed[a]	213	37
	Any Solicited AR	94 (44.1)	8 (21.6)
	Any Systemic Solicited AR	86 (40.4)	8 (21.6)
	Any Local Solicited AR	60 (28.2)	5 (13.5)
18 to <46 years	Participants Assessed[a]	1619	268
	Any Solicited AR	676 (41.8)	83 (31.0)
	Any Systemic Solicited AR	556 (34.3)	76 (28.4)
	Any Local Solicited AR	455 (28.1)	31 (11.6)
46 to <65 years	Participants Assessed[a]	933	153
	Any Solicited AR	289 (31.0)	33 (21.6)
	Any Systemic Solicited AR	249 (26.7)	30 (19.6)
	Any Local Solicited AR	147 (15.8)	13 (8.5)
Ethnicity	-	-	-
Hispanic or Latino	Participants Assessed[a]	502	70
	Any Solicited AR	160 (31.9)	22 (31.4)
	Any Systemic Solicited AR	138 (27.5)	20 (28.6)
	Any Local Solicited AR	94 (18.7)	8 (11.4)
Not Hispanic or Latino	Participants Assessed[a]	2201	375
	Any Solicited AR	882 (40.1)	100 (26.7)
	Any Systemic Solicited AR	741 (33.7)	92 (24.5)
	Any Local Solicited AR	557 (25.3)	40 (10.7)

Source: Adapted from ESBI-CV-317-004 Table 25, Response to IR #17 Tables 14.3.2.2.1 – 14.3.2.2.4
Abbreviations: AR = adverse reaction; n=number of participants with events; N=number of safety population participants
[a]The number of participants assessed is the number of participants who completed a diary following vaccination in the specified subgroup.

Unsolicited Adverse Events

Table 17 summarizes unsolicited AEs that occurred in at least 0.5% of participants in the PXVX0317 group during the 28-day postvaccination period.

Unsolicited AEs were reported by a similar percentage of participants in the PXVX0317 (433 [16%]) and placebo (59 [13%]) groups. Most unsolicited AEs were mild or moderate, though a numerically higher percentage of participants in the PXVX0317 group reported grade 3 or higher unsolicited AEs (31 [1.1%]) than in the placebo group (1 [0.2%]).

Among all unsolicited AEs, the percentage of participants with events in most MedDRA SOCs were balanced between the PXVX0317 and placebo groups.

Table 17. Unsolicited Adverse Events Reported by at Least 0.5% of Participants in the PXVX0317 Treatment Group, During the 28 Days Postvaccination, Safety Population, Study 004

System Organ Class Preferred Term	Pooled PXVX0317 (N=2790) n (%)	Placebo (N=464) n (%)
Any unsolicited AE	433 (15.5)	59 (12.7)
Infections and infestations	168 (6.0)	26 (5.6)
COVID-19	61 (2.2)	6 (1.3)
Sinusitis	13 (0.5)	3 (0.6)
Upper respiratory tract infection	14 (0.5)	4 (0.9)

System Organ Class Preferred Term	Pooled PXVX0317 (N=2790) n (%)	Placebo (N=464) n (%)
Musculoskeletal and connective tissue disorders	50 (1.8)	6 (1.3)
Arthralgia	13 (0.5)	1 (0.2)
Nervous system disorders	48 (1.7)	4 (0.9)
Headache	19 (0.7)	2 (0.4)
Skin and subcutaneous tissue disorders	29 (1.0)	2 (0.4)
Rash	13 (0.5)	0

Source: Adapted from ESBI-CV-317-004 Clinical Study Report Table 14.3.5.2, Response to IR #17 Table 14.3.5.2
Abbreviations: AE=adverse event; n=number of participants with events; N=number of safety population participants in the treatment group; n=number of participants with events
Note: Only those PTs that occurred in at least 0.5% of participants in the PXVX0317 group are listed in this table. Participants are counted once within each System Organ Class and Preferred Term.

A total of 31 (1.1%) PXVX0317 and 1 (0.2%) placebo recipients reported grade 3 or higher unsolicited AEs. Grade 3 or higher unsolicited AEs in the PXVX0317 group were reported in the following SOCs: Injury, poisoning and procedural complications (n=7); Infectious and Infestations (n=5); Metabolism and nutrition disorders (n=4); Nervous system disorders (n=4); Hepatobiliary disorders (n=3); Renal and urinary disorders (n=2); Gastrointestinal disorders (n=2); Immune system disorders (n=1); Neoplasms benign, malignant and unspecified (n=1); Respiratory, thoracic and mediastinal disorders (n=1). The grade 3 unsolicited AE in the placebo group was an Injury, poisoning and procedural complication (n=1).

Per the Applicant's assessment, one treatment-related grade 3 unsolicited AE occurred in the PXVX0317 group (dehydration which resolved without medical intervention), and no treatment-related grade 3 unsolicited AEs occurred in the placebo group.

Clinical Reviewer Comment*: This reviewer evaluated the case narrative for the grade 3 unsolicited AE of dehydration (USUBJID* (b) (6) *provided in the response to IR #25): a 57-year-old man with a history of type 2 diabetes mellitus developed chills, headache, nausea, fatigue, joint pain, and myalgia postvaccination. On Day 5 following PXVX0317 administration, the participant was evaluated in an emergency room for dehydration in the context of these other symptoms. The participant was discharged the same day without inpatient admission. The investigator assessed the AE as probably related to the IP. This reviewer concurs that the AE is at least possibly related to the IP in that the other solicited ARs experienced by the participant (e.g., nausea) likely contributed to the dehydration.*

Adverse Events in Baseline Seropositive Participants

As compared with the baseline seronegative participants who received PXVX0317, the 63 PXVX0317 recipients who were seropositive at baseline reported a higher incidence of systemic solicited ARs (33% among seropositive versus 27% among seronegative participants) but a similar incidence of local solicited ARs (20% in both groups) and unsolicited AEs (10% among seropositive versus 13% among seronegative). Baseline seropositive participants also experienced more grade 3 local solicited ARs (1.4% among seropositive versus 0.1% among seronegative) and grade 3 systemic solicited ARs (4.3% among seropositive versus 1.2% among seronegative), but fewer grade 3 unsolicited AEs (0% among seropositive vs 0.9% among seronegative) than seronegative participants following PXVX0317.

Clinical Reviewer Comment*: Baseline seropositive participants experienced a greater frequency and severity of solicited ARs, and the finding was not restricted to a limited number of study sites. Since baseline seropositive participants also had higher GMT values following*

PXVX0317, the increased reactogenicity may have been related to the immune response to PXVX0317. However, the sample size is small (n=63 participants), so definitive conclusions cannot be drawn. In the PMR confirmatory study planned by the Applicant (EBSI-CV-317-007, see section 11.6.1), a "safety subset" of 500 participants will be enrolled in an endemic area and will include both baseline seropositive and seronegative participants. This safety subset will have solicited ARs assessed through seven days postvaccination, which will allow for further assessment of reactogenicity among baseline seropositive participants.

Medically Attended Adverse Events

A similar percentage of participants experienced MAAEs in the PXVX0317 (249 [9%]) and placebo (41 [9%]) groups. The most common MAAEs in the PXVX0317 were reported in the following SOCs: Infections and infestations (3.8% PXVX0317, 3.9% placebo); Injury, poisoning and procedural complications (1.3% PXVX0317, 1.9% placebo); and Musculoskeletal and connective tissue disorders (1.1% PXVX0317, 0.9% placebo). A total of 29 (1.0%) PXVX0317 and 1 (0.2%) placebo recipients reported grade 3 or 4 MAAEs. The grade 3 MAAEs that occurred in two or more PXVX0317 recipients included cholecystitis (n=2) and facial bone fracture (n=2). Per the Applicant's assessment, no grade 3 or 4 treatment-related MAAEs occurred in either group.

***Clinical Reviewer Comment**: Although a higher percentage of PXVX0317 (1.0%) recipients reported grade 3 or 4 MAAEs than placebo (0.2%) recipients, each PT was reported by only one or two participants, and there was no specific event or pattern of events that suggested a safety concern.*

6.1.12.3 Deaths

One death occurred in a PXVX0317 recipient (USUBJID (b) (6), and no deaths occurred among placebo recipients. Participant (b) (6) was a 32-year-old man who died due to a "hit and run accident" (PT road traffic accident) on Day (b) (6) The participant was found dead at the site of the accident. The Investigator and Applicant assessed this death as not related to PXVX0317.

***Clinical Reviewer Comment**: This reviewer concurs that this death is not related to PXVX0317 given the clear alternative etiology.*

6.1.12.4 Nonfatal Serious Adverse Events

Nonfatal SAEs were reported by 23 (0.8%) PXVX0317 and 1 (0.2%) placebo recipients. The most frequent SAEs by SOC in the PXV0317 group were Injury, poisoning and procedural complications (4 [0.1%] PXVX0317, 0 [0%] placebo); Metabolism and nutrition disorders (3 [0.1%], 0 [0%] placebo); and Nervous system disorders (3 [0.1%], 0 [0%] placebo). Non-fatal SAEs by SOC and PT are provided in Table 18.

***Clinical Reviewer Comment**: Based on the case narratives, all the SAEs have plausible alternative causes, were not temporally closely related to vaccination, and/or lacked biologic plausibility for causality; therefore, this reviewer concurs with the Applicant that they are unlikely to be related to the IP. See below for further discussion of the stroke SAEs.*

Table 18. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study 004

System Organ Class Preferred Term[a]	Pooled PXVX0317 (N=2790) n (%)	Placebo (N=464) n (%)
Any SAE	23 (0.8)	1 (0.2)
Congenital, familial and genetic disorders	1 (<0.1)	0
Encephalocele	1 (<0.1)	0
Eye disorders	1 (<0.1)	0
Retinal detachment	1 (<0.1)	0
Gastrointestinal disorders	1 (<0.1)	0
Vomiting	1 (<0.1)	0
Hepatobiliary disorders	1 (<0.1)	0
Cholecystitis	1 (<0.1)	0
Immune system disorders	1 (<0.1)	0
Anaphylactic reaction	1 (<0.1)	0
Infections and infestations	3 (0.1)	1 (0.2)
Appendicitis	0	1 (0.2)
Influenza	1 (<0.1)	0
Pyelonephritis	1 (<0.1)	0
Tubo-ovarian abscess	1 (<0.1)	0
Injury, poisoning and procedural complications	4 (0.1)	0
Craniocerebral injury	1 (<0.1)	0
Femoral neck fracture	1 (<0.1)	0
Gun shot wound	1 (<0.1)	0
Road traffic accident	1 (<0.1)	0
Skin laceration	1 (<0.1)	0
Metabolism and nutrition disorders	3 (0.1)	0
Dehydration	1 (<0.1)	0
Diabetic ketoacidosis	2 (<0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	0
Malignant melanoma	1 (<0.1)	0
Nervous system disorders	3 (0.1)	0
Basal ganglia infarction	1 (<0.1)	0
Cerebrovascular accident	1 (<0.1)	0
Neuropathy peripheral	1 (<0.1)	0
Transient ischemic attack	1 (<0.1)	0
Psychiatric disorders	1 (<0.1)	0
Bipolar disorder	1 (<0.1)	0
Depression	1 (<0.1)	0
Renal and urinary disorders	2 (<0.1)	0
Nephrolithiasis	1 (<0.1)	0
Urinary retention	1 (<0.1)	0
Respiratory, thoracic and mediastinal disorders	1 (<0.1)	0
Chronic obstructive pulmonary disease	1 (<0.1)	0

Source: Adapted from EBSI-CV-317-004 Clinical Study Report Table 28, Response to IR #17 Table 14.3.5.7
Abbreviations: %=n/N*100; N=number of participants per treatment group; n=number of participants with events; N=number of safety population participants in the treatment group; n=number of participants with parameter; PT=preferred term; SAE=serious adverse event; SOC=system organ class
[a]Participants are counted once within each SOC and PT. If one participant experienced two SAE PTs, within the same SOC, the participant would be counted once for each PT and only once for the SOC. For example, under Nervous system disorders, the transient ischemic attack and cerebrovascular accident occurred in the same participant; this participant is counted once per PT (once for transient ischemic attack and once for cerebrovascular accident) and once in the SOC of Nervous systemic disorders.

***Clinical Reviewer Comment**: One participant was diagnosed with Arnold-Chiari malformation during the clinical trial, which was originally counted as an SAE. Since this diagnosis was present since birth, the Applicant and this reviewer moved this AE to medical history. As such, this SAE is no longer included in Table 18.*

Two SAEs were reported in PXVX0317 recipients for which a causal relationship was more difficult to exclude, but the events were ultimately judged to be more likely related to underlying comorbidities and concurrent illness than to PXVX0317. The Applicant assessed both SAEs to be not related to PXVX0317, and neither participant was withdrawn from the study.

1. USUBJID (b) (6) A 64-year-old man with a history of hyperlipidemia, obesity, and bilateral iritis on prednisolone developed right-sided weakness on Day 10 after PXVX0317 administration. He presented to the emergency department where head imaging showed an acute infarct of the left caudate tail. In the emergency department, his COVID-19 test was also positive, and the participant reported symptoms of COVID-19 starting 10 days prior to the test. The participant had not recovered as of Day 183.

***Clinical Reviewer Comment**: Although a close temporal association was observed between PXVX0317 and the SAE, this participant's basal ganglia infarction had other plausible etiologies, including hyperlipidemia and recent COVID-19 infection, and as such, is less likely related to the IP.*

2. USUBJID (b) (6) A 58-year-old man with a history of hypertension who developed left-sided weakness that was worse with standing on Day 49 after PXVX0317 administration. The participant was seen by his primary care physician, who ordered a brain MRI that was unremarkable. Subsequently, on Day 134, the participant developed nausea, vomiting, dizziness, and gait instability. Head imaging was performed but the results are unknown. The participant was treated with clopidogrel and atorvastatin. He was ultimately diagnosed as having a transient ischemic attack on Day 49 and cerebrovascular accident (CVA) on Day 134. The SAE of CVA resolved with sequelae of gait disturbance on Day 138.

***Clinical Reviewer Comment**: Since the participant's symptoms did not start until Day 49 following IP administration, and the participant had a known risk factor for stroke (hypertension), this participant's transient ischemic attack and CVA had other plausible etiologies and is thus less likely related to the IP.*

Overall, a slightly higher percentage of PXVX0317 recipients reported serious neurologic disorders than placebo recipients, including basal ganglia infarction, CVA, and transient ischemic attack (collectively referred to as stroke by this reviewer). Additional analyses were conducted to further explore this potential association (see section 8.4.2.3 "Standard Medical Dictionary for Regulatory Activities Query (SMQ) Analysis of Central Nervous System Vascular Disorders").

Finally, with regard to all SAEs, a higher percentage of PXVX0317 recipients reported an SAE (0.8%) than placebo recipients (0.2%), but this higher percentage was driven by several distinct AEs that largely occurred in only a single participant and occurred in the context of 6:1 randomization ratio. As such, the SAE data do not appear to identify any significant safety concerns.

6.1.12.5 Adverse Events of Special Interest

Solicited Arthralgia

Arthralgia was evaluated as a solicited AR during the first seven days post-vaccination. A similar percentage of participants in the PXVX0317 group (7.7%) and the placebo group (7.2%) reported arthralgia, with only a small percentage experiencing grade 3 events (0.3% among PXVX0317 recipients and 0.2% among placebo recipients) and none with Grade 4 events. In subgroup analyses, several subpopulations reported arthralgia more commonly in the PXVX0317 group than placebo, including the 12 to <18 years of age participants (8.0% PXVX0317, 5.4% placebo). For all participants, the median time to onset of arthralgia was 2 days in the PXVX0317 group and 3 days in the placebo group (range 1-8 days for both groups), and the median duration of symptoms was 1 day for both groups (range 1-95 days for the PXVX0317 group, 1-6 days for the placebo group).

Clinical Reviewer Comment*: One participant in the PXVX0317 group had solicited arthralgia symptoms that persisted for more than 30 days: a 68-year-old woman who developed left upper extremity paresthesia and arthralgia (ipsilateral to the injection site) on Day 3 postvaccination that persisted for 95 days. On review of the case narrative, the participant was thought to have developed a cervical radiculopathy, and she was lost to follow-up after Day 29, so the final duration was imputed. As such, the actual duration of symptoms is unclear.*

Unsolicited Arthralgia

Unsolicited arthralgia AEs were experienced by a similar percentage of participants in the PXVX0317 (13 [0.5%]) and placebo (1 [0.2%]) groups and at a similar severity (all grade 1 or 2).

Adverse Event of Special Interest

A total of 6 participants in the PXVX0317 group (0.2%) and 1 in the placebo group (0.2%) experienced an AESI (new onset or worsening arthralgia that was medically attended) (Table 19). All AESIs were nonserious and grade 1 or 2 in severity. The median time to onset was 41 days (range 2-168) in the PXVX0317 recipients; the time to onset in the one placebo recipient was 1 day. The median duration of arthralgia symptoms reported among the PXVX0317 recipients was 43.5 days (range 1-101). The duration of arthralgia symptoms for the one placebo recipient was 2 days.

Table 19. Adverse Events of Special Interest by System Organ Class, Preferred Term, and Highest Reported Severity, Safety Population, Study 004

System Organ Class Preferred Term	Pooled PXVX0317[a] (N=2790) Total n (%)	Pooled PXVX0317 (N=2790) Grade 1 n (%)	Pooled PXVX0317 (N=2790) Grade 2 n (%)	Placebo[a] (N=464) Total n (%)	Placebo (N=464) Grade 1 n (%)	Placebo (N=464) Grade 2 n (%)
Any AESI	6 (0.2)	2 (0.1)	4 (0.1)	1 (0.2)	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	6 (0.2)	2 (0.1)	4 (0.1)	1 (0.2)	0 (0.0)	1 (0.2)
Arthralgia	5 (0.2)	2 (0.1)	3 (0.1)	1 (0.2)	0 (0.0)	1 (0.2)
Spinal osteoarthritis	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from EBSI-CV-317-004 Clinical Study Report Table 30, Response to IR #44 Table 14.3.2.1
Abbreviations: %=n/N*100; AESI=adverse event of special interest (new onset or worsening arthralgia that was medically attended); n=number of participants with events; N=number of safety population participants in the treatment group
Note: Participants are counted once within each System Organ Class and Preferred Term.
[a]There were no grade 3 or 4 AESIs.

Clinical Reviewer Comment: *Though not a pre-specified outcome in the protocol, this reviewer also assessed the frequency of chikungunya-like adverse reactions (CHIK-like ARs) in this trial. A CHIK-like AR was 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. This analysis was performed because of a theoretical concern about immune-mediated symptoms of CHIK following VLP vaccination. In this analysis (Table 20), a total of 12 (0.4%) PXVX0317 recipients and 1 (0.2%) placebo recipient were assessed to have CHIK-like ARs. Given the low percentage in both groups and the similar percentage with a CHIK-like AR between PXVX0317 and placebo recipients, PXVX0317 does not appear to cause a clinically significant number of CHIK-like ARs. A higher percentage of PXVX0317 recipients (11 [0.4%]) reported fever and myalgia than placebo recipients (1 [0.2%]); the majority of these occurred within the first seven days post-vaccination, consistent with a typical, nonspecific inflammatory response post-vaccination (see section 6.1.12.2 for Solicited ARs) and not concerning for a unique CHIK-like AR. Since no concerning safety signal was identified with this analysis, CHIK-like ARs were not included in the USPI. See section 8.4.8 for further details.*

Table 20. CHIK-Like ARs by Preferred Term, Safety Population, Study 004

Preferred Term	Pooled PXVX0317 (N=2790) n (%)	Placebo (N=464) n (%)
Any CHIK-like AR	12 (0.4)	1 (0.2)
Grade 1	7 (0.2)	0 (0.0)
Grade 2	6 (0.2)	1 (0.0)
Grade 3	1 (0.0)	1 (0.2)
Arthralgia	6 (0.2)	1 (0.2)
Grade 1	2 (0.1)	0 (0.0)
Grade 2	4 (0.1)	1 (0.2)
Grade 3	0 (0.0)	0 (0.0)
Fatigue	1 (0.0)	0 (0.0)
Grade 1	1 (0.0)	0 (0.0)
Grade 2	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)

Preferred Term	Pooled PXVX0317 (N=2790) n (%)	Placebo (N=464) n (%)
Headache	1 (0.0)	0 (0.0)
Grade 1	1 (0.0)	0 (0.0)
Grade 2	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)
Myalgia	11 (0.4)	1 (0.2)
Grade 1	7 (0.3)	0 (0.0)
Grade 2	3 (0.1)	0 (0.0)
Grade 3	1 (0.0)	1 (0.2)

Source: Reviewer generated table
Abbreviations: %=n/N*100; AR=adverse reaction; CHIK=chikungunya; n=number of participants with events; N=number of safety population participants in the treatment group.

6.1.12.6 Dropouts and/or Discontinuations

Overall, two participants (0.1%) experienced an AE leading to withdrawal during the study, both of whom were in the PXVX0317 group: one AE was a road traffic accident resulting in death (described in section 6.1.12.3); the other participant gave birth to an infant with a fetal anomaly (fronto-ethmoid encephalocele, described further in section 9.1.1).

Clinical Reviewer Comment*: As discussed in section 6.1.11.4, the percentage of participants not completing the study was higher in the PXVX0317 group (12%) than the placebo group (7%). The difference was driven by lost to follow-up and participant withdrawal. Among participants who discontinued the study early, 26 (8%) in the PXVX0317 group and 2 (6%) in the placebo group also reported AEs. Among the AEs reported, each PT was only reported by a single participant each, save for headache which was reported by two participants. Outside of the single participant in the PXVX0317 group who died during the study (due to a road traffic accident), no temporal association was observed between AE onset and discontinuation from the study (the median duration between AE onset and study discontinuation among those who did not complete the study and reported an AE was 89 days [range 22-192 days]). Thus, the imbalance in early study discontinuations between groups does not appear to be related to treatment-emergent AEs.*

6.1.13 Study Summary and Conclusions

6.1.13.1 Immunogenicity

- Seroresponse rate, defined as the percentage of participants with a CHIKV SNA titer ≥100, was 98% on Day 22 following PXVX0317 vaccination. The seroresponse rate (%) difference was 97% (95% CI: 95, 98). The results met the pre-specified success criterion of LB of 95% CI ≥70%. The seroresponse rate (%) at Day 183 post-vaccination was 86%.
- CHIKV SNA titers peaked at Day 22 days postvaccination with a GMT of 1597 in the PXVX0317 group and subsequently decreased to 338 at Day 183 postvaccination.
- Similar seroresponse rates were observed on Day 22 among age, sex, race, and ethnicity subgroups.

6.1.13.2 Safety

- Overall, the frequency of any AEs, including solicited ARs, was higher in the PXVX0317 group (45%) than placebo group (35%).
- Solicited ARs were reported by a higher percentage of PXVX0317 recipients (38%) than placebo recipients (27%).
    - Solicited local ARs:
        - Solicited local ARs were reported by a higher percentage of PXVX0317 recipients (24%) than placebo recipients (11%).
        - Most solicited local ARs were mild or moderate. Five (0.2%) severe events (four with pain, one with redness) were reported in the PXVX0317 group, and no (0%) severe events were reported in the placebo group.
        - The most common solicited local AR was injection site pain (24% of PXVX0317 recipients, 11% of placebo recipients).
    - Solicited systemic ARs:
        - Solicited systemic ARs were reported by a higher percentage of PXVX0317 recipients (32%) than placebo recipients (25%).
        - 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 (20% of PXVX0317 recipients, 17% of placebo recipients), headache (18% of PXVX0317 recipients, 17% of placebo recipients), and myalgia (18% of PXVX0317 recipients, 10% of placebo recipients).
- Unsolicited AEs in the 28 days following vaccination were reported by a similar percentage of PXVX0317 (16%) and placebo recipients (13%).
- One death occurred following PXVX0317 (<0.1%), which was assessed as not related to the IP.
- Nonfatal SAEs were reported by a similar percentage of PXVX0317 (0.8%) and placebo recipients (0.2%).
    - 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 (0.2%) and placebo (0.2%) recipients.
    - All arthralgia events were mild or moderate in severity.

6.1.13.3 Conclusion

Immunogenicity Conclusion

The immunogenicity results from pivotal Study 004 met the pre-specified success criteria for the primary endpoint, and as such, the available data support the labeled indication.

Safety Conclusion

In general, the safety profile of PXVX0317 is favorable with no serious safety concerns identified and a low incidence of arthralgia post-vaccination.

6.2 Trial #2

NCT05349617
Study EBSI-CV-317-005: A Phase 3 Safety and Immunogenicity Trial of the VLP-Based Chikungunya Virus Vaccine PXVX0317 in Adults ≥65 Years of Age

6.2.1 Objectives

Primary Objectives

1. To compare the anti-CHIKV SNA response to PXVX0317 and placebo at Day 22 in adults ≥65 years of age.
2. To evaluate the safety of PXVX0317 in adults ≥65 years of age.

Key Secondary Objective

1. To compare the anti-CHIKV SNA response in PXVX0317 and placebo at Day 15 and Day 183, as measured by GMT and seroresponse rate.

Key Exploratory Objective

1. To evaluate the ability of PXVX0317-induced CHIKV antibodies to neutralize various CHIKV genotypes.

Clinical Reviewer Comment*: Additional secondary and exploratory objectives were defined but are not discussed in this memo since they did not contribute significantly to the benefit-risk assessment.*

6.2.2 Design Overview

Study 005 was a phase 3, randomized, placebo-controlled, double-blind, parallel-group study with two treatment groups. 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 Applicant aimed to enroll 400 total participants. The planned study duration was 12 months.

6.2.3 Population

Individuals who were ≥65 years of age and in stable health were eligible for enrollment. Individuals were not eligible to participate if they had previously received an investigational CHIKV vaccine/product, had a history of a congenital or acquired immunodeficiency, received or anticipated use of systemic immunomodulatory or immunosuppressive medications during the six months prior to screening, had a bleeding disorder or received anticoagulants in the 21 days prior to screening, received blood or blood-derived products from 90 days prior to screening through Day 22, or received immunoglobulin from 180 days prior to screening through Day 22.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Single dose of PXVX0317 or placebo:
1. *PXVX0317:* 0.8 mL IM injection supplied in a prefilled syringe containing CHIKV VLP (40µg), aluminum hydroxide (b) (4) adjuvant (300µg), and formulation buffer. One lot was used (Batch (b) (4)
2. *Placebo:* 0.8 mL IM injection of formulation buffer in a pre-filled syringe.

6.2.5 Directions for Use

PXVX0317 or placebo was administered IM into the deltoid muscle as a single injection on Day 1 (Visit 2).

6.2.6 Sites and Centers

The study was conducted at 10 investigational sites in the U.S.

6.2.7 Surveillance/Monitoring

Safety monitoring was similar to that described for Trial #1 (in section 6.1.7) save for the following: the independent Safety Monitoring Committee reviewed aggregated, blinded safety data after the first 50 participants completed seven days of safety follow-up.

6.2.8 Endpoints and Criteria for Study Success

6.2.8.1 Primary Endpoints

Safety Endpoints

1. Incidence of solicited ARs through Day 8 for PXVX0317 and placebo.
2. Incidence of unsolicited AEs through Day 29 for PXVX0317 and placebo.
3. Incidence of SAEs, MAAEs, and AESIs through Day 183 for PXVX0317 and placebo.

Coprimary Immunogenicity Endpoints and Success Criterion

1. Difference in anti-CHIKV SNA seroresponse rate (PXVX0317 minus placebo) and associated 95% CI at Day 22.
    a. Success criteria: Statistical superiority to placebo and LB of the two-sided 95% CI ≥70%.
2. Anti-CHIKV SNA GMT and associated 95% CIs at Day 22 for PXVX0317 and placebo.
    a. Success criterion: Significant difference between PXVX0317 and placebo.

6.2.8.2 Key Secondary Endpoints

1. Difference in anti-CHIKV SNA seroresponse rate (PXVX0317 minus placebo) with associated 95% CIs at Day 15 and Day 183, in that order.
    a. No success criteria specified.
2. Anti-CHIKV SNA GMTs and associated 95% CIs at Day 15 and Day 183 for PXVX0317 and placebo.
    a. No success criteria specified.

6.2.8.3 Exploratory Immunogenicity Endpoint

1. GMTs and associated 95% CIs for neutralizing antibodies against various CHIKV genotypes at Day 22.
    a. Note: Cross-reactive neutralizing antibodies to various CHIKV genotypes were measured for a subset of participants in the PXVX0317 group using 50% focus reduction neutralizing test (FRNT50). With FRNT50, the anti-CHIKV neutralization antibody titer is the reciprocal of the antibody dilution that protects a percentage of cells from infection compared to a virus-only control.

6.2.9 Statistical Considerations & Statistical Analysis Plan

6.2.9.1 Study Hypotheses and Analyses of Primary Endpoints

The study hypotheses and analyses of primary endpoints were the same as in Trial #1, save for the lack of a lot equivalency evaluation in this study (see section 6.1.9.1).

6.2.9.2 Sample Size Calculation

The sample size was calculated similarly to Trial #1 (see section 6.1.9.2). Using the same assumptions as stated for Trial #1, the power to show superiority over placebo with 180 PXVX0317 and 180 placebo evaluable participants would be >99.9% for the combined age groups, and the width of the 95% CI would be ±5.4%. The difference in seroresponse rate would need to be above 77% for the LB of the 95% CI to be ≥70%.

6.2.9.3 Methods of Handling Missing Data

The methods of handling missing data are the same as describe for Trial #1 (see section 6.1.9.3).

6.2.9.4 Interim Analysis

A preliminary analysis of safety and immunogenicity data was performed after all participants completed the Day 29 study visit. A third-party vendor performed the analyses. Results were reported only at the treatment group summary level. No p-value penalty was assessed because the Day 22 primary immunogenicity endpoint data were final at the time of preliminary analysis and no action regarding the study was planned based on these findings.

6.2.9.5 Safety Analyses

The same approach was used as is described for Trial #1 (see section 6.1.9.5).

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The analysis populations are defined as in Trial #1 (see section 6.1.10.1). Participants enrolled and analyzed are presented in Table 21.

Table 21. Analysis Sets, Randomized Participants, Study 005

Population	PXVX0317 (N=206) n (%)	Placebo (N=207) n (%)	Total (N=413) n (%)
Randomized	206 (100.0)	207 (100.0)	413 (100.0)
Exposed[a]	206 (100.0)	207 (100.0)	413 (100.0)
Safety[b]	206 (100.0)	207 (100.0)	413 (100.0)
mITT[c]	205 (99.5)	205 (99.0)	410 (99.3)
Immunogenicity Evaluable[d]	189 (91.7)	183 (88.4)	372 (90.1)

Source: Adapted from EBSI-CV-317-005 Clinical Study Report Table 10
Abbreviations: %=n/N*100; mITT = modified intent to treat; N = number of participants per treatment group; n=number of participants with parameter
[a]Exposed population=randomized participants who received study vaccination.
[b]Safety population=exposed participants who provided safety assessment data.
[c]mITT population=exposed participants who had at least one post-injection CHIKV SNA result.
[d]Immunogenicity evaluable population=mITT population participants who had no measurable CHIKV SNA at Day 1, had an evaluable Day 22 serum sample result within window (Day 19 through Day 27, inclusive), and had no important exclusionary protocol deviation or other reason for exclusion as defined prior to unblinding.

***Clinical Reviewer Comment**: The percentage of randomized participants included in the IEP and Safety Population were comparable between treatment groups. See the clinical reviewer comment in section 6.1.10.1 for a discussion of the IEP inclusion criteria.*

6.2.10.1.1 Demographics

As shown in Table 22, baseline demographics were generally balanced between the PXVX0317 and placebo groups (differences in categorical variables were <5%). Overall, the median age was 70 years (range 65-95 years), and 242 (59%) participants were female. The majority of participants were White (83%) and Not Hispanic or Latino (55%). At baseline, 3.6% of participants were seropositive for CHIKV SNA.

***Clinical Reviewer Comment**: In addition to studying an older population than in Study 004, this study has a notably higher percentage of Hispanic or Latino participants (44% versus 18% in Study 004). This is unlikely to have any impact on the generalizability of safety results, and is potentially a strength of the trial, given the higher rates of CHIK infections in areas of the U.S. with larger Hispanic or Latino populations (e.g., local transmission has been detected in Florida and Texas, where approximately 27% and 40% of the population is Hispanic or Latino, respectively, as well as Puerto Rico, where >90% of the population is Hispanic or Latino) (CDC, 2025, US Census, 2024). See section 8.3 for further discussion of differences between Studies 004 and 005 and the impact of those differences on pooled analyses.*

Of note, among the participants who were seropositive at baseline (n=15), 10 (67%) were Hispanic or Latino, suggesting that Hispanic or Latino participants are overrepresented in the baseline seropositive subgroup.

Table 22. Demographic and Baseline Characteristics, Randomized Participants, Study 005

Characteristic	PXVX0317 (N=206)	Placebo (N=207)	All Participants (N=413)
Sex, n (%)	-	-	-
Female	125 (60.7)	117 (56.5)	242 (58.6)
Male	81 (39.3)	90 (43.5)	171 (41.4)
Age (years)	-	-	-
Mean (SD)	71.5 (5.3)	70.8 (4.5)	71.1 (4.9)
Median	70	70	70
(Min, Max)	(65, 95)	(65, 84)	(65, 95)
Age group, n (%)	-	-	-
65 to <75 years of age	159 (77.2)	159 (76.8)	318 (77.0)
≥75 years of age	47 (22.8)	48 (23.2)	95 (23.0)
Race, n (%)	-	-	-
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)
Multiple	4 (1.9)	5 (2.4)	9 (2.2)
Not reported	1 (0.5)	3 (1.4)	4 (1.0)
White	176 (85.4)	168 (81.2)	344 (83.3)
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)
Baseline height (cm)	-	-	-
Mean (SD)	166.36 (9.42)	167.15 (9.84)	166.75 (9.63)
Median	165.1	167.6	166.6
(Min, Max)	(144.8, 195.6)	(142.2, 190.5)	(142.2, 195.6)

Characteristic	PXVX0317 (N=206)	Placebo (N=207)	All Participants (N=413)
Baseline weight[a] (kg)	-	-	-
Mean (SD)	75.83 (13.61)	77.20 (13.29)	76.52 (13.45)
Median	76.2	75.4	76.2
(Min, Max)	(47.2, 110.2)	(44.9, 111.6)	(44.9, 111.6)
Baseline body mass index[a] (kg/m^2)	-	-	-
Mean (SD)	27.34 (3.98)	27.60 (3.90)	27.47 (3.94)
Median	27.5	27.5	27.5
(Min, Max)	(17.5, 34.8)	(19.3, 34.9)	(17.5, 34.9)
Baseline CHIKV SNA serostatus, n (%)	-	-	-
Missing	0	1 (0.5)	1 (0.2)
Negative (<LLOQ)	201 (97.6)	196 (94.7)	397 (96.1)
Positive (≥LLOQ)	5 (2.4)	10 (4.8)	15 (3.6)

Source: Adapted from ESBI-CV-317-005 Clinical Study Report Table 11
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; LLOQ = lower limit of quantitation; Max = maximum; max=maximum; Min = minimum; min=minimum; N = number of participants per Group; n = number of participants per with parameter; N=number of participants per treatment group; SD = standard deviation; SNA = serum neutralizing antibody
[a]Weight and body mass index from screening visit.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The percentage of participants with any medical history was similar between the two groups (94% PXVX0317, 96% placebo), including medical history of arthralgia (4.4% PXVX0317, 6.3% placebo), arthritis (2.4% PXVX0317, 1.4% placebo), and fibromyalgia (1.0% PXVX0317, 1.0% placebo). The most frequently reported categories overall were Vascular disorders (53% of participants), Surgical and medical procedures (50% of participants), Metabolism and nutrition disorders (48% of participants), and Musculoskeletal and connective tissue disorders (38% of participants).

Most participants (83% PXVX0317, 81% placebo) received prior and/or concomitant medications. The most common concomitant medications included atorvastatin (18% PXVX0317, 19% placebo), acetylsalicylic acid (17% PXVX0317, 10% placebo), and lisinopril (14% PXVX0317, 17% placebo). Corticosteroids were used by 3 (1.5%) participants in the PXVX0317 group and 2 (1.0%) in the placebo group.

***Clinical Reviewer Comment**: A higher percentage of participants in this study have a medical history (95%) than those in Study 004 (84%), likely owing to the older age group enrolled in this study as well as the different inclusion/exclusion criteria used in this study which allowed for participants with stable chronic medical conditions. Enrolling such older participants with medical comorbidities will improve the study's generalizability to the general U.S. population that is 65 years of age and older, since medical comorbidities affect at least 83% of this age group in the U.S. (Anderson, 2005).*

Similar to Study 004, the placebo group in this study had a slightly higher baseline rate of arthralgia than the PXVX0317 group. Given the small difference (<2%), this is unlikely to have a significant impact on the interpretation of AEs. Also similar to Study 004, details of prior corticosteroid use among participants are not provided by the Applicant, but prior corticosteroid use is unlikely to have a significant impact on the safety or immunogenicity results since the percentage of participants with prior corticosteroid exposure is small (<2%).

6.2.10.1.3 Subject Disposition

The disposition of participants is provided in Table 23. A higher percentage of PXVX0317 recipients completed the study (97%) than placebo recipients (91%).

Table 23. Disposition of Randomized Participants, Study 005

Disposition	PVXVX0317 (N=206) n (%)	Placebo (N=207) n (%)	Total (N=413) n (%)
Randomized	206 (100.0)	207 (100.0)	413 (100.0)
Treated	206 (100.0)	207 (100.0)	413 (100.0)
Completed study[a]	200 (97.1)	188 (90.8)	388 (93.9)
Reason for discontinuation from 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)
Completed study visit	-	-	-
Day 1	206 (100.0)	207 (100.0)	413 (100.0)
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: Adapted from EBSI-CV-317-005 Clinical Study Report Table 8
Abbreviations: %=n/N*100; N=number of participants per treatment group; n=number of participants with parameter
[a]An individual participant was considered completed based on the Day 183 visit and completion of any required safety follow-up.

Clinical Reviewer Comment*: Fewer participants in the placebo group completed the study than in the PXVX0317 group (91% versus 97%). This difference was driven by a higher percentage of participants in the placebo group who were lost to follow up and who withdrew from the study. The difference in study completion primarily occurred after the Day 29 visit. This difference in completion should not significantly impact the safety findings since the dropouts primarily occurred in the placebo group, after Day 29, and were not driven by AEs. Further, owing to the smaller study size (total N=413), small differences in absolute numbers will result in larger differences in percentages (e.g., the 6% difference in study completion was driven by an absolute difference of 12 participants).*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoints

6.2.11.1.1 Coprimary Endpoint #1: Day 22 Anti-CHIKV Seroresponse Rate

The seroresponse rate in the IEP at Day 22 was 87% (165/189 participants) in the PXVX0317 group and 1% (2/183 participants) in the placebo group (Table 24). The difference in seroresponse rates was thus 86% (95% CI: 80, 90). The LB of the 95% CI is ≥70% and the seroresponse rate was significantly higher in PXVX0317 than placebo recipients, so the success criteria were met. Similar results were observed in the mITT population where the seroresponse rate difference was 86% (95% CI: 80, 90).

Clinical Reviewer Comment*: Two placebo recipients developed a seroresponse at Day 22 despite the lack of circulating CHIKV in the U.S. at the time of trial completion (CDC, 2023) and the requirement for a baseline Day 1 SNA <LLOQ. In response to IR #13, the Applicant reported that Day 22 was the only timepoint where these placebo recipients had a CHIKV SNA titer ≥100.*

In Response to IR #52, the Applicant reported that one of the placebo recipients who originally was reported to have a CHIKV SNA titer ≥100 at Day 22 actually had a CHIKV SNA titer <15 but it was erroneously reported due to a "data transfer error." The other placebo recipient's repeat Day 22 CHIKV SNA titer remained ≥100 on repeat testing. Similar to findings discussed in section 6.1.11.1.1, these two placebo recipients appear to have had false-positive CHIKV SNA titers on Day 22 given that SNA titers were <100 at time points prior to and after Day 22, and this small number of anomalous CHIKV SNA titers (1%) do not change the overall conclusions of the immunogenicity results.

6.2.11.1.2 Coprimary Endpoint #2: Day 22 Anti-CHIKV SNA GMT

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) (Table 24).

***Clinical Reviewer Comment**: The provided GMT and GMT ratio values were computed using the updated ULOQ that was provided by the Applicant in response to IR #12.*

The success criteria for both primary immunogenicity endpoints were met, suggesting PXVX0317 is effective at neutralizing CHIKV at a significantly higher rate than placebo.

Table 24. Day 22 CHIKV SNA GMT, GMT Ratios, Seroresponse Rates, and Seroresponse Rate Differences, IEP, Study 005

Parameter	PXVX0317 (N=189)	Placebo (N=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)	-
Seroresponse Rate, n/N % (95% CI)[b]	165/189 87.3 (81.8, 91.3)	2/183 1.1 (0.3, 3.9)
Seroresponse Rate Difference, % (95% CI)[c]	86.2 (80.0, 90.3)	-

Source: Adapted from EBSI-CV-317-005 Clinical Study Report Tables 14 and 15, Response to IR #12 Table 14.2.2.1.1
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI = confidence interval, GMT = geometric mean titer; IEP=immunogenicity evaluable population; N=number of participants per treatment group; n=number of participants with parameter; SNA=serum neutralizing antibody
[a]GMT estimates, together with their 95% CIs, are derived from an ANOVA model that includes site and vaccine group as fixed effects, assuming normality of the log titers. GMTs ratios and 95% CIs are derived from the same model.
[b]95% CIs are based on the Wilson method.
[c]95% CIs are based on the Newcombe hybrid score method.

6.2.11.2 Analyses of Secondary Endpoints: Day 15 and 183 Difference in Anti-CHIKV SNA seroresponse rate and anti-CHIKV SNA GMT

Seroresponse rates and GMT in the IEP at Days 15 and 183 are displayed in Table 25. At each time point, PXVX0317 recipients had a higher seroresponse rate and GMT compared with placebo.

Table 25. Days 15 and 183 CHIKV GMT, GMT Ratios, Seroresponse Rates, and Seroresponse Rate Difference, IEP, Study 005

Day	PXVX0317 (N=189)	Placebo (N=183)
Day 15 N	181	176
Day 15 GMT (95% CI)[a]	377.77 (300.71, 474.57)	8.97 (7.10, 11.32)
Day 15 GMT ratio (95% CI)[a]	42.13 (32.08, 55.33)	-
Day 15 Seroresponse Rate, n/N, % (95% CI)[b]	149/181 82.3 (76.1, 87.2)	5/176 2.8 (1.2, 6.5)

Day	PXVX0317 (N=189)	Placebo (N=183)
Day 15 Seroresponse Rate Difference, % (95% CI)[c]	79.5 (72.3, 84.6)	-
Day 183 N	184	173
Day 183 GMT (95% CI)[a]	233.02 (194.05, 279.82)	8.29 (6.87, 10.02)
Day 183 GMT ratio (95% CI)[a]	28.09 (22.31, 35.38)	-
Day 183 Seroresponse Rate, n/N, % (95% CI)[b]	139/184 75.5 (68.9, 81.2)	2/173 1.2 (0.3, 4.1)
Day 183 Seroresponse Rate Difference, % (95% CI)[c]	74.4 (67.1, 80.1)	-

Source: Adapted from EBSI-CV-317-005 Clinical Study Report Tables 16 and 17
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP=immunogenicity evaluable population; N=number of participants per treatment group; n=number of participants with parameter; SNA=serum neutralizing antibody
[a]GMT estimates, together with their 95% CIs, are derived from an ANOVA model that includes site and vaccine group as fixed effects, assuming normality of the log titers. GMTs, GMT ratios, and corresponding 95% CIs are all derived from the same model.
[b]95% CIs are based on the Wilson method.
[c]95% CIs are based on the Newcombe hybrid score method.

Clinical Reviewer Comment: *Secondary analyses suggest a notable increase in CHIKV-specific SNA titers (≥100) as early as Day 15 after PXVX0317 administration in 82% of participants. The immune response persists through Day 183 in the majority of participants (76%) though there is some waning of the antibody response.*

6.2.11.3 Subpopulation Analyses

Day 22 CHIKV seroresponse rates following PXVX0317 (Table 26) were numerically higher in female participants (91%) than male participants (82%). Seroresponse rates did not vary notably across race, ethnicity, and age subgroups.

Table 26. Day 22 CHIKV SNA Seroresponse Rates and Seroresponse Rate Differences by Subgroup, IEP, Study 005

Subgroup	PXVX0317 Seroresponse Rate[a], n/N % (95% CI)	Placebo Seroresponse Rate[a], n/N % (95% CI)	Seroresponse Rate Difference[b], % (95% CI)
All IEP	165/189 87.3 (81.8, 91.3)	2/183 1.1 (0.3, 3.9)	86.2 (80.0, 90.3)
Sex	-	-	-
Male	58/71 81.7 (71.2, 89.0)	1/77 1.3 (0.2, 7.0)	80.4 (68.4, 87.8)
Female	107/118 90.7 (84.1, 94.7)	1/106 0.9 (0.2, 5.2)	89.7 (81.9, 93.8)
Race	-	-	-
White	140/159 88.1 (82.1, 92.2)	2/145 1.4 (0.4, 4.9)	86.7 (79.8, 91.0)
Non-White	25/29 86.2 (69.4, 94.5)	0/35 0 (0, 9.9)	86.2 (66.7, 94.5)
Ethnicity	-	-	-
Hispanic or Latino	70/81 86.4 (77.3, 92.2)	2/78 2.6 (0.7, 8.9)	83.9 (72.8, 90.0)
Not Hispanic or Latino	95/107 88.8 (81.4, 93.5)	0/104 0 (0, 3.6)	88.8 (80.6, 93.5)

Subgroup	PXVX0317 Seroresponse Rate[a], n/N % (95% CI)	Placebo Seroresponse Rate[a], n/N % (95% CI)	Seroresponse Rate Difference[b], % (95% CI)
Age group	-	-	-
≥65 to <75 years	131/149 87.9 (81.7, 92.2)	1/143 0.7 (0.1, 3.9)	87.2 (80.3, 91.6)
≥75 years	34/40 85.0 (70.9, 92.9)	1/40 2.5 (0.4, 12.9)	82.5 (65.0, 90.7)

Source: Adapted from EBSI-CV-317-005 Clinical Study Report Table 14
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; IEP=immunogenicity evaluable population; N=number of participants per treatment group; n=number of participants with parameter; SNA=serum neutralizing antibody
[a]95% CIs are based on the Wilson method.
[b]95% CIs are based on the Newcombe hybrid score method.

Clinical Reviewer Comment*: Overall, the subgroup analyses suggest the differences in seroresponse rate between PXVX0317 and placebo were consistent across subgroups. Although not a primary endpoint with a defined success criterion, it is notable that the LB of the 95% CI is below 70% for the ≥75 years of age subgroup (Table 26) as well as for the male and Non-White subgroups. However, this is likely due in part to the small sample sizes for these subpopulations and the resultant wide confidence intervals. Taking together the small sample sizes along with the lack of adjustment for multiplicity, results of these subgroup analyses should be interpreted with caution.*

Day 22 anti-CHIKV GMT (Table 27) were numerically higher in female participants (967) than male participants (424). GMT values did not vary notably across race, ethnicity, and age subgroups.

Table 27. Day 22 Anti-CHIKV GMT and GMT Ratios by Subgroup, IEP, Study 005

Subgroup	PXVX0317 N GMT (95% CI)[a]	Placebo N GMT (95% CI)[a]	GMT Ratio (95% CI)[a]
All IEP	189 720.98 (582.33, 892.65)	183 8.08 (6.51, 10.04)	89.18 (68.35, 116.36)
Sex	-	-	-
Male	71 423.61 (292.82, 612.82)	77 8.09 (5.76, 11.35)	52.38 (34.09, 80.47)
Female	118 966.94 (744.23, 1256.29)	106 7.81 (5.92, 10.29)	123.87 (88.58, 173.23)
Race	-	-	-
White	159 715.66 (564.14 907.88)	145 8.17 (6.37, 10.47)	87.60 (65.40, 117.34)
Non-White	29 795.11 (428.70 1474.69)	35 9.15 (4.77, 17.59)	86.85 (42.98, 175.49)
Ethnicity	-	-	-
Hispanic or Latino	81 939.93 (494.96, 1784.93)	78 11.82 (6.15, 22.69)	79.55 (51.03, 124.00)
Not Hispanic	107 758.63 (524.44, 1097.40)	104 7.95 (5.53, 11.43)	95.42 (68.29 133.32)

Subgroup	PXVX0317 N GMT (95% CI)[a]	Placebo N GMT (95% CI)[a]	GMT Ratio (95% CI)[a]
Age Group	-	-	-
≥65 to <75 years	149 723.67 (572.48, 914.81)	143 7.90 (6.23, 10.01)	91.62 (68.48, 122.58)
≥75 years	40 712.21 (392.48, 1292.40)	40 8.59 (4.76, 15.50)	82.91 (41.28, 166.54)

Source: Adapted from Table 15 from EBSI-CV-317-005 CSR (page 67)
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP=immunogenicity evaluable population; N=number of participants in the specified subgroup and treatment group; SNA=serum neutralizing antibody
[a]GMT estimates, together with their 95% CIs, are derived from an ANOVA model that includes site and vaccine group as fixed effects, assuming normality of the log titers. GMTs, GMT ratios, and corresponding 95% CIs are all derived from the same model. GMT and GMT ratios are based on the updated ULOQ (= 10794.8) as per IR 12.

Clinical Reviewer Comment*: Although some differences in subgroups were noted when evaluating GMT data, the GMT data are not entirely consistent with the seroresponse data (e.g., Hispanic or Latino participants had a higher GMT but a lower seroresponse rate), the sample sizes are small, and the clinical significance of the differences in GMT values is unknown. As such, results of these GMT subgroup analyses should be interpreted with caution.*

6.2.11.4 Dropouts and/or Discontinuations

The overall dropout rate for this study was 6% (25/413), with 6 (3%) PXVX0317 recipients and 19 (9%) placebo recipients not completing the study. The primary reasons for not completing the study included: 12 (2.9%) withdrawn by participant, 11 (2.7%) lost to follow up, and 2 (0.5%) deaths. A total of 99% of PXVX0317 and 98% of placebo recipients completed the Day 29 study visit, and 98% of PXVX0317 and 95% of placebo recipients had blood collections performed on Day 22.

Clinical Reviewer Comment*: The placebo group had a 6% higher dropout rate than the PXVX0317 group, which appears to have been driven primarily by dropouts after the Day 29 study visit and due to lost to follow-up and withdrawal by the participant, with no evidence that these events were related to treatment-emergent AEs. Based on the timing of the dropouts and discontinuations (following Day 29) and adequacy of the immunogenicity population to meet the statistical success criterion, it is unlikely that dropouts and discontinuations had an impact on the safety or immunogenicity study conclusions. In a sensitivity analysis performed by the statistical reviewer, assuming all dropouts showed no seroresponse, the seroresponse rate difference would be 79.1% [95% CI: 72.7, 84.1], with a LB of the 95% CI ≥70%. See section 6.2.12.6 for a discussion of the impact of dropouts on safety analyses.*

6.2.11.5 Exploratory and Post Hoc Analyses

Baseline Seropositive Participants

A total of 15 baseline seropositive participants were enrolled: 5 in the PXVX0317 group and 10 in the placebo group. An ad hoc analysis found that baseline seropositive participants had higher GMT values following PXVX0317 than baseline seronegative participants: seropositive participants had a Day 1 (baseline) GMT of 209, a Day 15 GMT of 4082, a Day 22 GMT of 5072, and a Day 183 GMT of 1257. Comparatively, baseline seronegative participants in the PXVX0317 group (the IEP) had a Day 1 GMT below the LLOQ, a Day 15 GMT of 378, a Day 22 GMT of 724, and a Day 183 GMT of 233.

Among the 10 baseline seropositive placebo recipients, three had titers ≥100 at Day 1 that remained ≥100 at Day 22; one had a titer ≥100 on Day 1 but decreased to <15 on Day 22; two

had titers between 15 and 100 on both Day 1 and Day 22; two had titers between 15 and 100 on Day 1 that decreased to <15 on Day 22; and two had missing Day 22 titers.

***Clinical Reviewer Comment**: Similar to Study 004, the results of this post hoc analysis suggest that (1) PXVX0317 increased the CHIKV-specific immune response among participants who had evidence of a pre-existing immune response (direct or cross-reactive) to CHIKV antigens, and (2) pre-existing anti-CHIKV antibodies do not adversely impact the immune response induced by PXVX0317.*

The one placebo recipient with a titer ≥100 on Day 1 but <15 on Day 22 is potentially suggestive of a false-positive Day 1 result, adding to the small number of participants with likely false-positive SNA results.

Cross-Neutralization of CHIKV Strains

In a subset of 50 randomly selected Day 22 sera samples from 50 baseline seronegative participants vaccinated with PXVX0317 in Study 005, neutralizing antibodies against West African (IbH35, PM2951), Asian (181/25, 99659, H20235), and ECSA (TO-UFT-7124 [American], LR-2006 OPY-1 [Indian Ocean]) CHIKV genotypes were assessed using a research-level FRNT assay. In total, 43 (86%) participants showed detectable SNA responses (GMT of FRNT50 ≥50) against all strains, with GMTs ranging from 349.0 (95% CI: 222.5, 547.2) for PM2951 to 870.1 (95% CI: 531.4, 1424.7) for LR-2006. When evaluated using the validated CHIKV-luc assay, the NT80 results for the 7 non-responders ranged from 22.5 to 107.9 (with the LLOQ being 15). Of note, the extent to which neutralization of the different study strains differed could not be determined due to the high degree of assay variability and lack of internal control to standardize the results.

***Clinical Reviewer Comment**: This exploratory analysis suggests that in most participants ≥65 years of age, PXVX0317 induced neutralizing antibodies that cross-neutralized WA, Asian, and ECSA genotypes though high inter-assay variability precluded between-strain comparisons.*

6.2.12 Safety Analyses

6.2.12.1 Methods

The methods are the same as described for Trial #1 (see sections 6.1.7 and 6.1.9.5).

6.2.12.2 Overview of Adverse Events

An overview of all AEs during the clinical trial in the safety population is presented in Table 28.

The occurrence of at least one AE (solicited and/or unsolicited) was reported in a similar percentage of participants in the PXVX0317 (47/206 [23%]) and placebo (52/207 [25%]) groups. Most AEs were mild or moderate, with 4 (1.9%) PXVX0317 recipients and 3 (1.4%) placebo recipients experiencing a grade 3 or higher AE.

SAEs were reported by 4 (1.9%) PXVX0317 and 3 (1.4%) placebo recipients. One participant (0.5%) in the placebo group experienced an AESI; no participants in the PXVX0317 group experienced an AESI. Fatal AEs occurred in one participant (0.5%) in the PXVX0317 group and one participant (0.5%) in the placebo group.

***Clinical Reviewer Comment**: In contrast to Study 004, a similar percentage of participants reported any AE in the PXVX0317 (23%) and placebo (25%) groups. Overall, these data indicate a lower rate of AEs in the 65 years of age and older population (23%) compared with 12 to <65 years of age participants (45%) following PXVX0317. See the following sections for additional details about specific AEs.*

Table 28. Overview of Adverse Events, Safety Population, Study 005

Event	PXVX0317 (N=206) n (%)	Placebo (N=207) n (%)
Any AR or AE[a]	47 (22.8)	52 (25.1)
Grade 3 or higher	4 (1.9)	3 (1.4)
Any solicited AR[b]	25 (12.2)	28 (14.0)
Grade 3 or higher	1 (0.5)	0
Any systemic solicited AR[b]	22 (10.7)	27 (13.5)
Grade 3 or higher	1 (0.5)	0
Any local solicited AR[b]	11 (5.4)	4 (2.0)
Grade 3 or higher	0	0
Any unsolicited AE	26 (12.6)	32 (15.5)
Grade 3 or higher	3 (1.5)	3 (1.4)
Any SAEs	4 (1.9)	3 (1.4)
Discontinued study due to AE	1 (0.5)	1 (0.5)
Any Fatal AE	1 (0.5)	1 (0.5)
Any AESI[c]	0	1 (0.5)
Any MAAE	19 (9.2)	23 (11.1)
Any treatment-related unsolicited AE[d]	3 (1.5)	3 (1.4)
Grade 3 or higher	0	0

Source: Adopted from EBSI-CV-317-005 Clinical Study Report Table 19, Response to IR #17 Table 14.3.2.1
Abbreviations: %=n/N*100; AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; AR=adverse reaction; MAAE=medically attended adverse event; n=number of participants with events; N=number of safety population participants in the treatment group; SAE=serious adverse event
[a]Inclusive of both solicited adverse reactions and unsolicited adverse events.
[b]Percentages for solicited adverse reactions are based on the number of participants with at least one diary observation (excluding 'Not done/unknown') for a given symptom or a given day. [c]AESI is defined as new onset or worsening arthralgia that is medically attended.
[d]Relationship for unsolicited AEs is the investigator's assessment.

Solicited Adverse Reactions

Solicited local and systemic reactions are summarized in Table 29. Solicited ARs were reported by a similar percentage of PXVX0317 (25 [12%]) and placebo (28 [14%]) recipients.

Solicited local reactions were reported by 11 (5%) participants in the PXVX0317 group and 4 (2%) in the placebo group. All local reactions in both groups were mild or moderate. The most common local reaction was injection site pain (11 [5%] in PXVX0317 and 3 [1.5%] in placebo).

Solicited systemic ARs were reported by 22 (11%) participants in the PXVX0317 group and 27 (14%) participants in the placebo group. Most systemic ARs were mild or moderate. One participant in the PXVX0317 group (0.5%) experienced grade 3 headache and fatigue. No placebo recipients experienced grade 3 systemic ARs. The most common systemic ARs were fatigue (13 [6.3%] in PXVX0317, 12 [6.0%] in placebo), myalgia (13 [6.3%] in PXVX0317, 13 [6.5%] in placebo), and headache (9 [4.4%] in PXVX0317, 15 [7.5%] in placebo).

The median duration of solicited ARs was 2 days (range 1-6 days) following PXVX0317 and 2 days (range 1-10 days) following placebo.

Table 29. Solicited Local and Systemic Adverse Reactions Within 7 Days Postvaccination, Safety Population, Study 005

System Organ Class Preferred Term	PXVX0317[d] (N=205) n (%)	Placebo[e] (N=200) n (%)
Any Solicited AR[a]	25 (12.2)	28 (14.0)
Grade 3	1 (0.5)	0 (0.0)
Any Solicited Systemic AR[b]	22 (10.7)	27 (13.5)
Grade 3	1 (0.5)	0 (0.0)
Pyrexia	0 (0.0)	2 (1.0)
Chills	6 (2.9)	6 (3.0)
Fatigue	13 (6.3)	12 (6.0)
Grade 3	1 (0.5)	0 (0.0)
Headache	9 (4.4)	15 (7.5)
Grade 3	1 (0.5)	0 (0.0)
Myalgia	13 (6.3)	13 (6.5)
Arthralgia	6 (2.9)	8 (4.0)
Nausea	6 (2.9)	3 (1.5)
Any Solicited Local AR[c]	11 (5.4)	4 (2.0)
Injection site erythema	0 (0.0)	1 (0.5)
Injection site pain	11 (5.4)	3 (1.5)

Source: Adapted from ESBI-CV-317-005 Clinical Study Report Table 21, Response to IR #17 Table 14.3.2.2.1
Abbreviations: %=n/N*100; AE=adverse event; AR=adverse reaction; AR=adverse reaction; N=number of participants with at least one diary observation (excluding 'Not done/unknown') for a given symptom or a given day; n=number of participants with events
[a]The PXVX0317 group had no grade 4 events. The placebo group had no grade 3 or 4 events.
[b]Neither treatment group had any participants with grade 3 or 4 nausea, arthralgia, myalgia, chills, or pyrexia.
[c]Neither treatment group had any participants with injection site swelling. Neither treatment group had any participants with grade 3 or 4 local solicited ARs.
[d]The total safety population for the pooled PXVX0317 group included 206 participants. For solicited ARs, the denominator (N) for each column was based on the number of participants with at least one diary observation for a given symptom for a given day.
[e]The total safety population for the placebo group included 207 participants. For solicited ARs, the denominator (N) for each column was based on the number of participants with at least one diary observation for a given symptom for a given day.

Subgroups (Table 30): In the PXVX0317 group, solicited ARs were more commonly reported by female participants (15%) than male participants (8%), by Non-White participants (21%) than White participants (11%), by Not Hispanic or Latino (15%) than Hispanic or Latino (9%) participants, and by participants ≥75 years of age (15%) than participants 65 to <75 years of age (11%).

Clinical Reviewer Comment*: The higher incidence of solicited ARs following PXVX0317 among female participants may be related to the higher GMT values observed in that subgroup. It is unclear why the Not Hispanic or Latino and Non-White participants reported a higher incidence of solicited ARs in the absence of notably higher GMT values, though the overall low numbers of events and small numbers of participants in these subgroups make these differences difficult to interpret.*

Table 30. Solicited Local and Systemic Adverse Reactions Within 7 Days Postvaccination, by Demographic Subgroup, Safety Population, Study 005

Subgroup	Parameter	PXVX0317 (N=206) n (%)	Placebo (N=207) n (%)
All	Participants Assessed[a]	205	200
-	Any Solicited AR	25 (12.2)	28 (14.0)
-	Any Systemic Solicited AR	22 (10.7)	27 (13.5)
-	Any Local Solicited AR	11 (5.4)	4 (2.0)
Sex	-	-	-
Male	Participants Assessed[a]	80	84
-	Any Solicited AR	6 (7.5)	13 (15.5)
-	Any Systemic Solicited AR	6 (7.5)	12 (14.3)
-	Any Local Solicited AR	3 (3.8)	3 (3.6)
Female	Participants Assessed[a]	125	116
-	Any Solicited AR	19 (15.2)	15 (12.9)
-	Any Systemic Solicited AR	16 (12.8)	15 (12.9)
-	Any Local Solicited AR	8 (6.4)	1 (0.9)
Race	-	-	-
White	Participants Assessed[a]	175	161
-	Any Solicited AR	19 (10.9)	21 (13.0)
-	Any Systemic Solicited AR	17 (9.7)	20 (12.4)
-	Any Local Solicited AR	8 (4.6)	4 (2.5)
Non-White	Participants Assessed[a]	29	36
-	Any Solicited AR	6 (20.7)	5 (13.9)
-	Any Systemic Solicited AR	5 (17.2)	5 (13.9)
-	Any Local Solicited AR	3 (10.3)	0
Ethnicity	-	-	-
Hispanic or Latino	Participants Assessed[a]	93	88
-	Any Solicited AR	8 (8.6)	11 (12.5)
-	Any Systemic Solicited AR	6 (6.5)	11 (12.5)
-	Any Local Solicited AR	3 (3.2)	2 (2.3)
Not Hispanic or Latino	Participants Assessed[a]	111	111
-	Any Solicited AR	17 (15.3)	16 (14.4)
-	Any Systemic Solicited AR	16 (14.4)	15 (13.5)
-	Any Local Solicited AR	8 (7.2)	2 (1.8)
Age	-	-	-
65 to <75 years	Participants Assessed[a]	159	154
-	Any Solicited AR	18 (11.3)	22 (14.3)
-	Any Systemic Solicited AR	16 (10.1)	22 (14.3)
-	Any Local Solicited AR	8 (5.0)	1 (0.6)
≥75 years	Participants Assessed[a]	46	46
-	Any Solicited AR	7 (15.2)	6 (13.0)
-	Any Systemic Solicited AR	6 (13.0)	5 (10.9)
-	Any Local Solicited AR	3 (6.5)	3 (6.5)

Source: Adapted from ESBI-CV-317-005 Clinical Study Report Table 23, Response to IR #17 Tables 14.3.2.2.1 – 14.3.2.2.4
Abbreviations: %=n/participants assessed*100; AR=adverse reaction; n=number of participants with events; N=number of safety population participants in the treatment group
[a]The number of participants assessed is the number of participants who completed a diary following the vaccination in the specified subgroup and treatment group.

Unsolicited Adverse Events

Table 31 summarizes unsolicited AEs that occurred in at least 0.5% of participants (i.e., at least one participant) in the PXVX0317 group during the 28-day postvaccination period.

Unsolicited AEs were reported by a similar percentage of participants in the PXVX0317 (26 [13%]) and placebo (32 [16%]) groups. Most unsolicited AEs were mild or moderate, with 3 (1.5%) PXVX0317 and 3 (1.4%) placebo recipients reporting grade 3 or higher unsolicited AEs.

Grade 3 unsolicited AEs in the PXVX0317 group included respiratory failure, breast cancer and device-related infection (same participant), and cellulitis. None were assessed by the Applicant to be possibly related to the IP.

Among all unsolicited AEs, the percentage of participants with events in most SOCs were balanced between the PXVX0317 and placebo groups.

Clinical Reviewer Comment*: Among the unsolicited AEs, each PT was reported by three or fewer participants, and there was no specific event or pattern of events that suggested a safety concern.*

Table 31. Unsolicited Adverse Events Reported by at Least One (0.5%) Participant in the PXVX0317 Treatment Group, During the 28 Days Postvaccination, Safety Population, Study 005

System Organ Class Preferred Term	PXVX0317 (N=206) n (%)	Placebo (N=207) n (%)
Any unsolicited AE	26 (12.6)	32 (15.5)
Cardiac disorders	2 (1.0)	2 (1.0)
Bradycardia	1 (0.5)	0
Coronary artery disease	1 (0.5)	0
Ear and labyrinth disorders	2 (1.0)	0
Ear pain	1 (0.5)	0
Vertigo	1 (0.5)	0
Gastrointestinal disorders	1 (0.5)	1 (0.5)
Diarrhea	1 (0.5)	1 (0.5)
General disorders and administration site conditions	2 (1.0)	1 (0.5)
Chest pain	1 (0.5)	1 (0.5)
Feeling abnormal	1 (0.5)	0
Infections and infestations	10 (4.9)	13 (6.3)
Abscess limb	1 (0.5)	0
Abscess of eyelid	1 (0.5)	0
Bronchitis	1 (0.5)	2 (1.0)
Cellulitis	1 (0.5)	0
Cellulitis streptococcal	1 (0.5)	0
COVID-19	2 (1.0)	5 (2.4)
Device related infection	1 (0.5)	0
Localized infection	1 (0.5)	0
Sinusitis	1 (0.5)	1 (0.5)
Tooth abscess	1 (0.5)	0
Injury, poisoning and procedural complications	2 (1.0)	4 (1.9)
Muscle strain	1 (0.5)	0
Wrist fracture	1 (0.5)	0
Investigations	1 (0.5)	0
Blood pressure increased	1 (0.5)	0

System Organ Class Preferred Term	PXVX0317 (N=206) n (%)	Placebo (N=207) n (%)
Metabolism and nutrition disorders	1 (0.5)	0
Type 2 diabetes mellitus	1 (0.5)	0
Musculoskeletal and connective tissue disorders	1 (0.5)	7 (3.4)
Arthritis	1 (0.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1 (0.5)
Breast cancer	1 (0.5)	0
Nervous system disorders	1 (0.5)	2 (1.0)
Syncope	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders	3 (1.5)	3 (1.4)
Respiratory failure	1 (0.5)	0
Rhinorrhea	1 (0.5)	2 (1.0)
Throat irritation	1 (0.5)	0
Skin and subcutaneous tissue disorders	2 (1.0)	2 (1.0)
Dermatitis atopic	1 (0.5)	0
Skin tightness	1 (0.5)	0
Vascular disorders	3 (1.5)	0
Hypertension	3 (1.5)	0

Source: Adapted from EBSI-CV-317-005 Clinical Study Report Table 14.3.5.2, Response to IR #17 Table 14.3.5.2
Abbreviations: %=n/N*100; AE=adverse event; n=number of participants with events; N=number of safety population participants in the treatment group
Note: Only those PTs that occurred in at least 0.5% of participants in the PXVX0317 treatment group are listed in this table. Participants are counted once within each system organ class and preferred term.

Adverse Events in Baseline Seropositive Participants

Among the 5 participants who were seropositive at baseline and received PXVX0317, two reported local solicited ARs, and two reported systemic solicited ARs. No baseline seropositive PXVX0317 recipients reported unsolicited AEs or grade 3 or higher solicited ARs.

Clinical Reviewer Comment*: The number of baseline seropositive PXVX0317 recipients is too small (total of 5 participants) to draw any definitive conclusions.*

Medically Attended Adverse Events

A similar percentage of participants experienced MAAEs in the PXVX0317 (19 [9%]) and placebo (23 [11%]) groups. The most common MAAE SOCs in the PXVX0317 group were Infections and infestations (4.4% PXVX0317, 5.3% placebo); Cardiac disorders (1.0% PXVX0317, 1.0% placebo); and Vascular disorders (1.0% PXVX0317, 0% placebo).

One (0.5%) PXVX0317 recipient experienced a treatment-related MAAE (assessed by the Applicant) of worsening hypertension. None (0%) of the placebo recipients reported treatment-related MAAEs.

Clinical Reviewer Comment*: The PXVX0317 recipient with a treatment-related MAAE of hypertension occurred in USUBJID* (b) (6) *A 67-year-old man who developed worsening hypertension on Day 128 postvaccination. The hypertension was toxicity grade 1, required treatment with new medication, and persistent. Although the Applicant assessed this as possibly related to the IP, the prolonged duration between vaccination and onset of worsening hypertension makes it less likely related to the IP.*

Among the MAAEs overall, each PT was reported by only one or two participants, and there was no specific event or pattern of events that suggested a safety concern.

6.2.12.3 Deaths

Two deaths occurred during the study:

1. USUBJID (b) (6) Placebo group. A 71-year-old woman with history of emphysema, hypertension, and smoking, as well as a possible history of lung cancer that was not disclosed to clinical trial personnel at enrollment, was noted to have weight loss and "appeared ill during her study visits." On Day (b) (6) the participant was hospitalized for lung cancer and subsequently died. The Applicant assessed the death as not related to the IP.

***Clinical Reviewer Comment**: This reviewer concurs that this death is not related to the IP given the participant received placebo.*

2. USIBJID (b) (6) PXVX0317 group. A 77-year-old woman with history of hyperlipidemia, hypertension, prior myocardial infarction, and bronchial congestion (on montelukast) was admitted to the hospital on Day 78 postvaccination for shortness of breath. The participant was treated for pneumonia, but due to chronic underlying illnesses, she was discharged to hospice. The participant died due to respiratory failure on Day (b) (6) The Applicant assessed the death as not related to the IP.

***Clinical Reviewer Comment**: This reviewer concurs that this death is unlikely to be related to the IP given the history of bronchial congestion and heart disease which may have contributed to the diagnosis of pneumonia and respiratory failure, as well as the prolonged duration between IP administration and development of pneumonia.*

6.2.12.4 Nonfatal Serious Adverse Events

Nonfatal SAEs were reported by a similar percentage of PXVX0317 (4 [1.9%]) and placebo (3 [1.4%]) recipients. SAEs by SOC and PT are provided in Table 32.

The five SAEs among four PXVX0317 recipients were assessed as not related to the IP by the Applicant. The SAE PTs included: breast cancer and device-related infection (in the same participant), vertigo (grade 1 but resulted in hospitalization for over 24 hours), cellulitis, and respiratory failure (fatal, see section 6.2.12.3 for details).

***Clinical Reviewer Comment**: Based on the case narratives, this reviewer concurs with the Applicant that the nonfatal SAEs are unlikely to be related to the IP based on lack of temporal relationship, lack of plausible biologic mechanism, and/or alternative etiologies for the SAEs. There was no specific event or pattern of events in the SAE data that suggest a safety concern.*

Table 32. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study 005

System Organ Class Preferred Term	PXVX0317 (N=206) n (%)	Placebo (N=207) n (%)
Any SAE	4 (1.9)	3 (1.4)
Ear and labyrinth disorders	1 (0.5)	0 (0.0)
Vertigo	1 (0.5)	0 (0.0)

System Organ Class Preferred Term	PXVX0317 (N=206) n (%)	Placebo (N=207) n (%)
Any SAE	4 (1.9)	3 (1.4)
Eye disorders	0 (0.0)	1 (0.5)
Glaucoma	0 (0.0)	1 (0.5)
Infections and infestations	2 (1.0)	1 (0.5)
Cellulitis	1 (0.5)	0 (0.0)
Clostridium difficile infection	0 (0.0)	1 (0.5)
COVID-19	0 (0.0)	1 (0.5)
Device related infection	1 (0.5)	0 (0.0)
Staphylococcal infection	0 (0.0)	1 (0.5)
Urosepsis	0 (0.0)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1 (0.5)
Breast cancer	1 (0.5)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	1 (0.5)	0 (0.0)
Respiratory failure	1 (0.5)	0 (0.0)

Source: Adapted from EBSI-CV-317-005 Clinical Study Report Table 26, Response to IR #17 Table 14.3.5.7
Abbreviations: %=n/N*100; n=number of participants with events; N=number of safety population participants in the treatment group; SAE=serious adverse event
Note: Participants are counted once within each system organ class and preferred term.

6.2.12.5 Adverse Events of Special Interest

Solicited Arthralgia

A similar percentage of participants in the PXVX0317 group (2.9%) and the placebo group (4.0%) reported arthralgia during the first seven days postvaccination, and all cases were mild or moderate. For participants with solicited arthralgia, the median time to onset of arthralgia was 3 days (range 1-7 days) in the PXVX0317 group and 2.5 days (range 1-8 days) in the placebo group. The median duration of symptoms was 2 days (range 1-4 days) for the PXVX0317 group and 2 days (range 1-5 days) for the placebo group.

Unsolicited Arthralgia

Unsolicited arthralgia AEs were experienced by a similar percentage of PXVX0317 (0 [0%]) and placebo (1 [0.5%]) recipients.

Adverse Event of Special Interest

A single participant in the placebo group (0.5%) experienced an AESI. The AESI was caused by joint dislocation, which the Applicant assessed as not related to the IP. No AESIs were reported in the PXVX0317 group.

***Clinical Reviewer Comment**: Though not a pre-specified outcome in the protocol, the frequency of CHIK-like ARs following PXVX0317 administration was evaluated (see section 6.1.12.5 for the definition of CHIK-like ARs). No (0%) PXVX0317 and one (0.5%) placebo recipient met criteria for a CHIK-like AR. See section 8.4.8 for further details of this analysis.*

6.2.12.6 Dropouts and/or Discontinuations

Two participants experienced an AE leading to withdrawal (one in the PXVX0317 group and one in the placebo group), both due to death unrelated to the IP; see section 6.2.12.3 for details.

Clinical Reviewer Comment*: As discussed in section 6.2.11.4, the percentage of participants not completing the study was slightly higher in the placebo group (9%) than the PXVX0317 group (3%). The difference was driven by loss to follow-up and participant withdrawal. None of the PXVX0317 recipients who discontinued the study early also reported an AE, suggesting the early dropouts were not related to treatment-emergent AEs.*

6.2.13 Study Summary and Conclusions

6.2.13.1 Immunogenicity

- Seroresponse rate was 87% on Day 22 following PXVX0317 vaccination. The seroresponse rate difference was 86% (95% CI: 80, 90). The results met the pre-specified success criterion of LB of 95% CI ≥70%. The seroresponse rate at Day 183 post-vaccination was 76%.
- CHIKV SNA titers peaked at Day 22 postvaccination with a GMT of 721 and subsequently decreased to 233 at Day 183 postvaccination.
- Similar seroresponse rates were observed among subgroups by age, race, and ethnicity. Female participants had a higher seroresponse rate than male participants (91% versus 82%).

6.2.13.2 Safety

- Overall, the frequency of AEs, including solicited ARs, was similar in the PXVX0317 (23%) and placebo (25%) groups.
- Solicited ARs were reported by a similar percentage of PXVX0317 (12%) and placebo (14%) recipients.
    - Solicited local ARs:
        - Solicited local ARs were reported by a slightly higher percentage of PXVX0317 (5%) than placebo (2%) recipients.
        - All solicited local ARs were mild or moderate.
        - The most common solicited local AR was injection site pain (5.4% PXVX0317, 1.5% placebo).
    - Solicited systemic ARs:
        - Solicited systemic ARs were reported by a similar percentage of PXVX0317 (11%) and placebo (14%) recipients.
        - Most solicited systemic ARs were mild or moderate; one participant (0.5%) in the PXVX0317 group reported severe systemic ARs (fatigue and headache) and none (0%) in the placebo group reported severe systemic ARs.
        - The most common solicited systemic ARs were fatigue (6.3% in PXVX0317 and 6.0% in placebo), myalgia (6.3% in PXVX0317 and 6.5% in placebo), and headache (4.4% in PXVX0317 and 7.5% in placebo).
- Unsolicited AEs in the 28 days following vaccination were reported in a similar percentage of PXVX0317 (13%) and placebo (16%) recipients.
- Two deaths occurred (one following PXVX0317, one following placebo), both of which were assessed as unlikely to be related to the IP.
- Nonfatal SAEs were reported by a similar percentage of PXVX0317 (1.9%) and placebo (1.4%) 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.

6.2.13.3 Conclusion

Immunogenicity Conclusion

The immunogenicity results from pivotal Study 005 met the pre-specified success criteria for the primary endpoint, and as such, the available data support the labeled indication.

Safety Conclusion

In general, the safety profile of PXVX0317 is favorable with no serious safety concerns identified and a low incidence of arthralgia post-vaccination.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

For the prevention of disease caused by CHIKV in individuals 12 years of age and older.

7.1.1 Methods of Integration

The ISE evaluated data from participants in the IEPs of four clinical studies: EBSI-CV-317-002, EBSI-CV-317-010, EBSI-CV-317-004, and EBSI-CV-317-005. Participants were counted in the treatment group to which they were randomized.

For study EBSI-CV-317-002, immunogenicity data for both alphavirus-naïve and prior alphavirus-vaccinated participants were included, as no statistically significant differences in immunogenicity were observed between the groups. There was no placebo group in the phase 2 studies (-010 and -002). For EBSI-CV-317-004 and EBSI-CV-317-005, immunogenicity data from individual product lots were pooled and the placebo groups from each study were combined.

ISE analyses included only those participants who received the to-be-licensed PXVX0317 dose regimen and the pooled placebo group.

For all studies included in the ISE, Day 1 was baseline and the day of IP administration, and Day 22 was the primary immunogenicity endpoint. Days 8, 15, and 183 were secondary immunogenicity endpoints. Study EBSI-CV-317-005 did not have a Day 8 immunogenicity time point, Study EBSI-CV-317-002 did not have a Day 15 immunogenicity time point, and EBSI-CV-317-010 did not have a Day 183 immunogenicity timepoint, so these studies were omitted from immunogenicity analyses at those timepoints. The study follow-up duration was 181 days (EBSI-CV-317-002) or 182 days (EBSI-CV-317-010, EBSI-CV-317-004, and EBSI-CV-317-005).

7.1.2 Demographics and Baseline Characteristics

The ISE included 3,436 participants, of whom 2,829 received PXVX0317 and 607 received placebo. A total of 81 (2.9%) participants were included from the open-label phase 2 studies (EBSI-CV-317-002, n=57 [2.0%] and EBSI-CV-317-010, n=24 [0.8%]) and 2,748 (97.1%) participants were included from the pivotal phase 3 studies (EBSI-CV-317-004, n=2559 [90.5%] and EBSI-CV-317-005, n=189 [6.7%]) who received PXVX0317.

Table 33 summarizes the demographic and baseline characteristics of participants in the ISE.

Table 33. Demographic and Baseline Characteristics, IEP, ISE

Characteristic	Study 002 PXVX0317 (N=57)	Study 010 PXVX0317 (N=24)	Study 004 PXVX0317 (N=2559)	Study 004 Placebo (N=424)	Study 005 PXVX0317 (N=189)	Study 005 Placebo (N=183)	Pooled Studies PXVX0317 (N=2829)	Pooled Studies Placebo (N=607)
Age (years)	-	-	-	-	-	-	-	-
Mean (SD)	47 (8.6)	34 (5.8)	39 (14.3)	39 (14.5)	71 (5.3)	71 (4.4)	41 (16.0)	49 (19.1)
Median (range)	47 (27, 64)	34 (25, 44)	38 (12, 64)	38 (12, 64)	70 (65, 95)	70 (65, 84)	40 (12, 95)	50 (12, 84)
Age stratum (years), n (%)	-	-	-	-	-	-	-	-
12 to <18	0	0	201 (7.9)	33 (7.87)	0	0	201 (7.1)	33 (5.4)
18 to <46	24 (42.1)	24 (100)	1480 (57.8)	245 (57.8)	0	0	1528 (54.0)	245 (40.4)
46 to <65	33 (57.9)	0	878 (34.3)	146 (34.4)	0	0	911 (32.2)	146 (24.1)
65 to <75	0	0	0	0	149 (78.8)	143 (78.1)	149 (5.3)	143 (23.6)
≥75	0	0	0	0	40 (21.2)	40 (21.9)	40 (1.4)	40 (6.6)
Sex, n (%)	-	-	-	-	-	-	-	-
Male	39 (68.4)	11 (45.8)	1241 (48.5)	210 (49.5)	71 (37.6)	77 (42.1)	1362 (48.1)	287 (47.3)
Female	18 (31.6)	13 (54.2)	1318 (51.5)	214 (50.5)	118 (62.4)	106 (57.9)	1467 (51.9)	320 (52.7)
Race, n (%)	-	-	-	-	-	-	-	-
American Indian/ Alaska Native	0	0	27 (1.1)	2 (0.5)	1 (0.5)	1 (0.5)	28 (1.0)	3 (0.5)
Asian	4 (7.0)	1 (4.2)	70 (2.7)	14 (3.3)	4 (2.1)	1 (0.5)	79 (2.8)	15 (2.5)
Black/African American	14 (24.6)	8 (33.3)	473 (18.5)	79 (18.6)	20 (10.6)	28 (15.3)	515 (18.2)	107 (17.6)
Native Hawaiian	0	0	6 (0.2)	2 (0.5)	0	0	6 (0.2)	2 (0.3)
Multiracial	2 (3.5)	1 (4.2)	76 (3.0)	8 (1.9)	4 (2.1)	5 (2.7)	83 (2.9)	13 (2.1)
Unknown/Not Reported	0	0	20 (0.8)	4 (0.9)	1 (0.5)	3 (1.6)	21 (0.7)	7 (1.2)

Characteristic	Study 002 PXVX0317 (N=57)	Study 010 PXVX0317 (N=24)	Study 004 PXVX0317 (N=2559)	Study 004 Placebo (N=424)	Study 005 PXVX0317 (N=189)	Study 005 Placebo (N=183)	Pooled Studies PXVX0317 (N=2829)	Pooled Studies Placebo (N=607)
White	37 (64.9)	14 (58.3)	1887 (73.7)	315 (74.3)	159 (84.1)	145 (79.2)	2097 (74.1)	460 (75.8)
Ethnicity, n (%)	-	-	-	-	-	-	-	-
Not Hispanic or Latino	54 (94.7)	23 (95.8)	2049 (80.1)	347 (81.8)	107 (56.6)	104 (56.8)	2233 (78.9)	451 (74.3)
Hispanic or Latino	3 (5.3)	1 (4.2)	457 (17.9)	65 (15.3)	81 (42.9)	78 (42.6)	542 (19.2)	143 (23.6)
Unknown/Not Reported	0	0	53 (2.1)	12 (2.8)	1 (0.5)	1 (0.5)	54 (1.9)	13 (2.1)
Body mass index (kg/m^2)	-	-	-	-	-	-	-	-
Mean (SD)	31.3 (5.27)	28.7 (3.29)	26.8 (4.53)	26.5 (4.61)	27.3 (4.03)	27.7 (3.88)	26.9 (4.55)	26.8 (4.43)
Median (range)	31.0 (20.4, 47.3)	28.5 (22.6, 34.6)	26.8 (13.1, 35.4)	26.3 (15.7, 34.9)	27.5 (17.5, 34.8)	27.6 (19.3, 34.9)	27.0 (13.1, 47.3)	26.8 (15.7, 34.9)

Source: Adapted from Integrated Summary of Effectiveness Table 16
Abbreviations: %=n/N*100; IEP=immunogenicity evaluable population; ISE=integrated summary of effectiveness; kg=kilogram; m=meter; N = number of participants in the treatment group; n=number of participants with parameter; SD = standard deviation
Note: IEP=Exposed participants who have no measurable CHIKV SNA at Day 1, have an evaluable Day 22 serum sample result within analysis window (Day 19 through Day 27, inclusive), and have no exclusionary protocol deviation as defined prior to unblinding. Body mass index is at screening visit.

***Clinical Reviewer Comment**: The median age of the IEP population that received PXVX0317 was younger (40 years [range 12 to 95]) than in the placebo group (50 [range 12 to 84]). This difference in the age distribution between the pooled PXVX0317 and placebo populations is due to the difference in randomization ratios used in Studies 004 (6:1) and 005 (1:1), which led to a greater contribution to the PXVX0317 group from Study 004 (which enrolled those 12 to <65 years of age). Outside of the age distributions, the baseline demographics were generally balanced between the pooled PXVX0317 and placebo groups.*

7.1.3 Subject Disposition

Table 34 summarizes participant disposition for the pooled PXVX0317 and placebo groups. Overall, 91% of PXVX0317 and 95% of placebo recipients completed the studies, and the most common reason for early discontinuation was loss to follow-up (5% PXVX0317, 3% placebo).

***Clinical Reviewer Comment**: A slightly higher percentage of PXVX0317 recipients (9%) did not complete the study compared to placebo (5%). This difference was driven primarily by lost to follow-up and participant withdrawal, with no evidence that these events were related to treatment-emergent AEs (see sections 6.1.11.4 and 6.2.11.4 for details).*

Table 34. Disposition of Participants, IEP, ISE

Disposition	Study 002 PXVX0317 n (%)	Study 010 PXVX0317 n (%)	Study 004 PXVX0317 n (%)	Study 004 Placebo n (%)	Study 005 PXVX0317 n (%)	Study 005 Placebo n (%)	Pooled Studies PXVX0317 n (%)	Pooled Studies Placebo n (%)
N	57	24	2559	424	189	183	2829	607
Completed study	57 (100)	22 (91.7)	2317 (90.5)	403 (95.0)	184 (97.4)	172 (94.0)	2580 (91.2)	575 (94.7)
Early termination	0	2 (8.3)	242 (9.5)	21 (5.0)	5 (2.6)	11 (6.0)	249 (8.8)	32 (5.3)
Reason for not completing study	-	-	-	-	-	-	-	-
Death	0	0	1 (0.0)	0	1 (0.5)	1 (0.5)	2 (0.1)	1 (0.2)
Lost to follow-up	0	2 (8.3)	147 (5.7)	14 (3.3)	2 (1.1)	4 (2.2)	151 (5.3)	18 (3.0)
Participant withdrawal	0	0	75 (2.9)	5 (1.2)	2 (1.1)	6 (3.3)	77 (2.7)	11 (1.8)
Investigator decision	0	0	1 (0.0)	0	0	0	1 (0.0)	0
Other	0	0	18 (0.7)	2 (0.5)	0	0	18 (0.6)	2 (0.3)

Source: Adapted from Integrated Summary of Effectiveness Table 17
Abbreviations: %=n/N*100; IEP=immunogenicity evaluable population; ISE=integrated summary of effectiveness; N = number of participants in the treatment group; n=number of participants with parameter

7.1.4 Analysis of Primary Endpoint(s)

ISE analysis methods for seroresponse rates and GMTs are the same as for the individual studies (see sections 6.1.8 and 6.1.9 for details).

Coprimary Endpoint #1: Day 22 Anti-CHIKV Seroresponse Rate

The seroresponse rate in the IEP at Day 22 was 97% (2749/2829 participants) in the pooled PXVX0317 group and 1% (7/607 participants) in the pooled placebo group, resulting in a difference in seroresponse rate (%) of 96% (95% CI: 95, 97).

Table 35. Day 22 Anti-CHIKV Seroresponse Rates and Seroresponse Rate Differences, IEP, ISE

Study	PXVX0317 Seroresponse Rate n/N %[a] (95% CI[a])	Placebo Seroresponse Rate n/N %[a] (95% CI[a])	Seroresponse Rate Difference % (95% CI)[b]
EBSI-CV-317-002	57/57 100 (93.7, 100)	N/A	N/E
EBSI-CV-317-010	24/24 100 (86.2, 100)	N/A	N/E
EBSI-CV-317-004	2503/2559 97.8 (97.2, 98.3)	5/424 1.2 (0.5, 2.7)	96.6 (95.0, 97.5)
EBSI-CV-317-005	165/189 87.3 (81.8, 91.3)	2/183 1.1 (0.3, 3.9)	86.2 (80.0, 90.3)
Pooled Studies	2749/2829 97.2 (96.5, 97.7)	7/607 1.2 (0.6, 2.4)	96.0 (94.6, 96.8)

Source: Adapted from Integrated Summary of Effectiveness Table 18
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; IEP=immunogenicity evaluable population; ISE=integrated summary of effectiveness; N/A=not applicable; N/E=not estimable; N=number of participants per treatment group; n=number of participants with a CHIKV SNA titer ≥100; SNA=serum neutralizing antibody
[a]95% CIs are based on the Wilson method.
[b]Seroresponse rate difference is PXVX0317 minus placebo; 95% CIs are based on the Newcombe hybrid score method.

Clinical Reviewer Comment*: Twenty-five individuals from Studies 004 and 005 who had baseline CHIKV SNA titers below the LLOQ, received placebo, and then had an SNA titer ≥100 at a single time point after vaccination. For each participant there was a single SNA titer that was ≥100: at only Day 8 (n=2), only Day 15 (n=8), only Day 22 (n=7), or only Day 183 (n=8) (but no other immunogenicity time points). When evaluating placebo recipients with an SNA titer >LLOQ postvaccination (rather than ≥100), a total of 32 placebo recipients had an SNA titer >LLOQ at any timepoint postvaccination, but only a single participant had an SNA titer >LLOQ on more than one day postvaccination (USUBJID* (b) (6) *with SNA titer of 15.2 on Day 8 and 20.1 on Day 183). In Response to IR #52, where seven of the placebo recipients with an SNA titer ≥100 at Day 22 had their titers repeated, three were found to have SNA titers <15 on repeat testing. As discussed in the clinical reviewer comment in section 6.1.11.1, these data are thought to represent false-positive results in the placebo group, likely due to "sample mishandling" per the Applicant. Since the frequency of anomalous results was low (1%), the overall immunogenicity conclusions are unchanged.*

Coprimary Endpoint #2: Day 22 Anti-CHIKV SNA GMT

The Day 22 CHIKV SNA GMT was 1537 for the pooled PXVX0317 group and 9 for the pooled placebo group, resulting in a GMT ratio of 180 (95% CI: 163, 200) for the IEP.

Clinical Reviewer Comment*: The provided GMT and GMT ratio values were computed using the updated ULOQ that was provided by the Applicant in response to IR #12.*

The results of the coprimary immunogenicity endpoints (seroresponse rate and GMT) in the ISE are similar to those observed in the individual trials.

Table 36. Day 22 CHIKV SNA GMT and GMT Ratios, IEP, ISE

Study	PXVX0317 N GMT (95% CI)[a] Median (Min, Max)[b]	Placebo N GMT (95% CI)[a] Median (Min, Max)[b]	GMT Ratio (95% CI)[c]
EBSI-CV-317-002	57 2241.5 (1745.4, 2878.6) 2795.4 (233.3, 10794.8)	N/A	N/E
EBSI-CV-317-010	24 2400.6 (1623.9, 3548.8) 2966.0 (128.3, 9720.9)	N/A	N/E
EBSI-CV-317-004	2559 1597.0 (1504.1, 1695.6) 1787.3 (7.5, 10794.8)	424 7.9 (7.0, 8.8) 7.5 (7.5, 6007.3)	203.3 (181.1, 228.2)
EBSI-CV-317-005	189 721.0 (582.3, 892.7) 1009.6 (7.5, 10794.8)	183 8.1 (6.5, 10.0) 7.5 (7.5, 1166.5)	89.2 (68.4, 116.4)
Pooled Studies	2829 1536.7 (1448.9, 1629.9) 1734.70 (7.5, 10794.8)	607 8.5 (7.7, 9.4) 7.5 (7.5, 6007.3)	180.4 (162.7, 200.0)

Source: Reviewer generated table
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP=immunogenicity evaluable population; ISE=integrated summary of effectiveness; max=maximum; min=minimum; N/A=not applicable; N/E=not estimable; N= number of participants with a sample result available at the indicated visit; SNA=serum neutralizing antibody
[a]GMT estimates, together with their 95% CIs, are derived from an ANOVA model that includes site and treatment group as fixed effects, assuming normality of the log titers. Ratios of GMTs and 95% CIs are derived from the same model.
[b]Median and range are based on raw values.
[c]Ratio of GMTs is (PXVX0317:placebo).

7.1.5 Analysis of Secondary Endpoints: Day 8, 15, and 183 CHIKV SNA seroresponse rate and GMT

At Day 8, 47% (1217/2591) of PXVX0317 recipients had a seroresponse, as compared with 0.5% (2/419) of participants in the placebo group, resulting in a seroresponse rate (%) difference of 47% (95% CI: 44, 48).

At Day 15, 96% (2526/2637) of PXVX0317 recipients had a seroresponse, compared with 1.4% (8/571) of participants in the placebo group, resulting in a seroresponse rate (%) difference of 94% (95% CI: 93, 95).

At Day 183, 85% (2157/2542) of PXVX0317 recipients had a seroresponse, compared with 1.4% (8/574) of participants in the placebo group, resulting in a seroresponse rate (%) difference of 84% (95% CI: 82, 85).

Clinical Reviewer Comment: *As shown in the individual trials, secondary analyses of the ISE suggest a notable increase in CHIKV-specific serum neutralizing antibodies (≥100) as early as Day 15 after PXVX0317 administration in 96% of participants. The immune response persists through Day 183 in the majority of participants (85%) though there is some waning of the antibody response.*

Secondary endpoints for Day 8, 15, and 183 CHIKV SNA GMT and GMT ratios showed a higher response in the PXVX0317 group than the placebo group at all timepoints.

7.1.7 Subpopulations

Seroresponse rates at Day 22 following PXVX0317 did not vary substantially by sex, race, or ethnicity. PXVX0317 displayed a higher seroresponse rate than placebo at Day 22 in all sex, race, and ethnicity subgroups.

Seroresponse rates at Day 22 following PXVX0317 were lower in the 65 to <75 years of age (88%) and ≥75 years of age (85%) subgroups compared with the younger subgroups (12 to <18 years [97%], 18 to <46 years [98%], and 46 to <65 years [97%]). However, PXVX0317 displayed a higher seroresponse rate than placebo at Day 22 in all age subgroups.

Clinical Reviewer Comment*: Note that the IEP used for the integrated efficacy analyses only involved pooling of participants in the 18 to <65 years of age stratum, since those aged 12 to <18 years were only enrolled in Study 004 and those aged ≥65 years were only enrolled in Study 005. Thus, comparisons across age strata involve making comparisons of pooled study data (for 18 to <65 years of age) to individual study data (for 12 to <18 and ≥65 years of age), which may limit the conclusions that can be drawn from these comparisons.*

A total of 86 baseline seropositive participants were enrolled across studies (71 in the PXVX0317 group and 15 in the placebo group). Baseline seropositive participants had higher GMT values following PXVX0317 than seronegative participants: seropositive participants had a Day 1 (baseline) GMT of 266, a Day 8 GMT of 958, a Day 15 GMT of 3196, a Day 22 GMT of 3657, and a Day 183 GMT of 995. Comparatively, baseline seronegative participants in the PXVX0317 group had a Day 1 GMT below the LLOQ, a Day 8 GMT of 98, a Day 15 GMT of 1018, a Day 22 GMT of 1553, and a Day 183 GMT of 327. At Day 22, 67/68 (99%) of the baseline seropositive participants who received PXVX0317 had an SNA titer ≥100 consistent with a seroresponse, similar to the 2766/2846 (97%) baseline seronegative PXVX0317 recipients with a seroresponse.

7.1.8 Persistence of Efficacy

As described in section 7.1.5, CHIKV SNA persistence was assessed up to 6 months postvaccination. In the pooled IEP, at Day 183, 85% (2157/2542) of participants in the PXVX0317 group had a seroresponse.

7.1.11 Efficacy Conclusions

The results of the pooled ISE analyses were consistent with the findings from the individual studies, with a seroresponse rate (%) difference of 96% (95% CI: 95, 97) at 21 days postvaccination with PXVX0317. As such, the pooled data support the proposed indication.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Pooling of data can provide a larger database to detect lower frequency events and permit explorations of possible drug-demographic or drug-disease interactions in

subgroups of the population. It is acknowledged that there are inherent weaknesses of pooling safety data from trials with heterogeneous study designs.

JMP 17 and Analysis Studio version 1.8.1 were used to conduct the analyses. In addition, RStudio (R 4.2.1) was used to modify datasets as needed. Multiple occurrences of the same event in the same participant were counted only once.

For all studies, solicited ARs were collected via a paper or electronic diary for 7 days post-vaccination, unsolicited AEs were collected for 28 days, and SAEs were collected throughout the study period (at least 6 months post-vaccination). In Studies 004, 005, and 010, AESIs and MAAEs were collected throughout the study period (at least 6 months post-vaccination). AESIs and MAAEs were not collected in Studies 001 and 002 and were not recharacterized post hoc.

All analyses are based on the safety population (those participants who received IP and provided safety assessment data), and participants were analyzed as treated (rather than as randomized). The following approaches were used to address heterogeneity in study designs:

- For Study 002, PXVX0317 vaccine data for both alphavirus vaccine-naïve and prior alphavirus-vaccinated participants are included, since no notable differences in AE incidence were observed between the two groups.
- For Study 010, all PXVX0317 data are included.
- For Studies 002, 010, and 001, there was no placebo-only group, although four participants in Study 001 are counted in the placebo-only group due to nonreceipt of PXVX0317.
- For Study 001, Group 4 received a booster vaccination at Day 547, but safety data following this booster vaccination are excluded from ISS analyses.
- For Studies 004 and 005, all PXVX0317 data are included and data from individual product lots are pooled; the placebo groups from each of these studies are combined.
- For Studies 004, 005, and 010, local solicited ARs included injection site pain, redness, and swelling and systemic ARs included fever, chills, fatigue, headache, myalgia, arthralgia, and nausea. Note that “malaise” was also collected as a systemic solicited AR for Studies 001 and 002, and “joint pain” was collected in these two studies in lieu of “arthralgia.” In the ISS summaries, malaise is reported separately, and joint pain is combined with arthralgia.

Table 37. Treatment Groups in the Integrated Safety Summary

Treatment Group	Planned Dose	Study and Groups Included
Single Dose 40/300 µg	CHIKV VLP 40/300 µg single dose	PXVX-CV-317-001: Groups 8 and 10 only EBSI-CV-317-002: PXVX0317 vaccinated (all participants) EBSI-CV-317-010: PXVX0317 vaccinated (all participants) EBSI-CV-317-004: PXVX0317 vaccinated groups (all lots) EBSI-CV-317-005: PXVX0317 vaccinated group

Treatment Group	Planned Dose	Study and Groups Included
Other CHIKV VLP Dose	CHIKV VLP 6, 10, or 20 µg dose with or without 300 µg adjuvant administered twice separated by 14 or 28 days	PXVX-CV-317-001: Groups 1-7 and 9 (includes participants who received only one of two planned PXVX0317 doses, but excludes 4 participants who received only placebo)
Total CHIKV VLP	Any CHIKV VLP dose	PXVX-CV-317-001: All groups (includes participants who received only one of two planned PXVX0317 doses, but excludes 4 participants who received only placebo) EBSI-CV-317-002: PXVX0317 vaccinated (all participants) EBSI-CV-317-010: PXVX0317 vaccinated (all participants) EBSI-CV-317-004: PXVX0317 vaccinated groups (all lots) EBSI-CV-317-005: PXVX0317 vaccinated group
Pooled Placebo	Placebo	PXVX-CV-317-001: 4 participants who received only placebo EBSI-CV-317-004: Placebo group EBSI-CV-317-005: Placebo group
Total Safety Population All Ages	Any CHIKV VLP dose or Placebo	PXVX-CV-317-001: All Groups (PXVX0317 and placebo) EBSI-CV-317-002: PXVX0317 vaccinated (all participants) EBSI-CV-317-010: PXVX0317 vaccinated (all participants) EBSI-CV-317-004: All Groups (all PXVX0317 lots and placebo) EBSI-CV-317-005: Both Groups (PXVX0317 and placebo)

Source: Adapted from the Summary of Clinical Safety Table 2
Abbreviations: CHIKV=chikungunya virus; VLP=virus- like particle

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The ISS includes safety data from five completed clinical studies in healthy adult participants (Studies 004, 005, 001, 002, and 010). Please refer to Table 37 in section 8.1 for details.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The pooled safety population consists of 4,197 participants from the five clinical studies: 3,522 participants were vaccinated with PXVX0317 (3,141 were given a single dose of 40/300µg; 381 were given a different dose or formulation) and 675 participants received placebo (with all but four placebo recipients originating from Studies 004 and 005) (Table 38). All vaccinated participants were included in the pooled safety population according to the treatment received.

Clinical Reviewer Comment: *The Applicant reports all results stratified by whether the participant received a (1) single dose of 40/300µg PXVX0317 (to-be-licensed dose), (2) other dose of PXVX0317, or (3) placebo. In this memo, the tables show the safety results for (1) all doses of PXVX0317 pooled together ("Total PXVX0317"), (2) a single dose of 40/300µg PXVX0317 ("PXVX0317 Single Dose"), and (3) the pooled placebo group. In the narrative of section 8, only the results for the single dose of 40/300µg PXVX0317 and placebo are described, since the single dose of 40/300µg PXVX0317 is the final dose and formulation to be licensed, and the contribution of the other doses of PXVX0317 to the safety conclusions is minimal (due to the small sample size).*

Table 38. Pooled Safety Population, ISS

Study Phase Study	PXVX0317 Single Dose[a] (N=3141) n (%)	Total PXVX0317[b] (N=3522) n (%)	Pooled Placebo (N=675) n (%)	Total Safety Population (N=4197) n (%)
Phase 2	145 (4.6)	526 (14.9)	4 (0.6)	530 (12.6)
PXVX-CV-317-001	60 (1.9)	441 (12.5)	4 (0.6)	445 (10.6)
EBSI-CV-317-002	60 (1.9)	60 (1.7)	0	60 (1.4)
EBSI-CV-317-010	25 (0.8)	25 (0.7)	0	25 (0.6)
Phase 3	2996 (95.4)	2996 (85.1)	671 (99.4)	3667 (87.4)
EBSI-CV-317-004	2790 (88.8)	2790 (79.2)	464 (68.7)	3254 (77.5)
EBSI-CV-317-005	206 (6.6)	206 (5.8)	207 (30.7)	413 (9.8)
Both phases	3141 (100.0)	3522 (100.0)	675 (100.0)	4197 (100.0)

Source: Adapted from the Integrated Summary of Safety Table 9, Response to IR #29 Table 1.1.1
Abbreviations: %=n/N*100; ISS=integrated summary of safety; N=number of participants in pooled safety population; n=number of participants per study
Note: Safety Population=Exposed participants who provided safety assessment data; participants in PXVX0317 treatment groups who received only placebo and not PXVX0317 are counted in the placebo group only.
[a]Study PXVX-CV-317-001 Groups 8 and 10; studies EBSI-CV-317-002, EBSI-CV-317-010, EBSI-CV-317-004, and EBSI-CV-317-005.
[b]Studies EBSI-CV-317-002, EBSI-CV-317-010, PXVX-CV-317-001, EBSI-CV-317-004, and EBSI-CV-317-005.

Table 39 summarizes the demographic and baseline characteristics of the pooled safety population. The median age was 39 years (range 12-95 years). Female participants comprised 52% of the population. The distribution by race was as follows: 74% White, 19% Black or African American, 3% Asian, 3% Multiracial, 1% American Indian or Alaska Native, 0.3% Native Hawaiian, and 0.8% unknown or not reported. By ethnicity, 19% were Hispanic or Latino.

Table 39. Demographic and Baseline Characteristics, Safety Population, ISS

Characteristic	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Age (years)	-	-	-
Mean (SD)	40.7 (15.93)	39.7 (15.53)	48.5 (19.29)
Median (min, max)	39.0 (12, 95)	38.0 (12, 95)	50.0 (12, 84)
Age group (years), n (%)	-	-	-
12 to <18	217 (6.9)	217 (6.2)	37 (5.5)
18 to <46	1746 (55.6)	2127 (60.4)	274 (40.6)
46 to <65	972 (30.9)	972 (27.6)	157 (23.3)
65 to <75	159 (5.1)	159 (4.5)	159 (23.6)
≥75	47 (1.5)	47 (1.3)	48 (7.1)

Characteristic	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Sex, n (%)	-	-	-
Female	1621 (51.6)	1850 (52.5)	351 (52.0)
Male	1520 (48.4)	1672 (47.5)	324 (48.0)
Race, n (%)	-	-	-
American Indian/Alaska Native	31 (1.0)	33 (0.9)	3 (0.4)
Asian	90 (2.9)	97 (2.8)	17 (2.5)
Black/African American	588 (18.7)	678 (19.3)	119 (17.6)
Multiracial	86 (2.7)	92 (2.6)	14 (2.1)
Native Hawaiian	6 (0.2)	8 (0.2)	4 (0.6)
Unknown/Not Reported	25 (0.8)	25 (0.7)	7 (1.0)
White	2315 (73.7)	2589 (73.5)	511 (75.7)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	606 (19.3)	635 (18.0)	163 (24.1)
Not Hispanic or Latino	2472 (78.7)	2824 (80.2)	497 (73.6)
Unknown/Not Reported	63 (2.0)	63 (1.8)	15 (2.2)

Source: Adapted from Integrated Summary of Safety Table 11, Response to IR #29 Table 2.1.1
Abbreviations: ISS=integrated summary of safety; max=maximum; min=minimum; N=number of participants in the treatment group; n=number of participants per parameter; SD=standard deviation

Clinical Reviewer Comment*: The pooled PXVX0317 and placebo groups were largely balanced in terms of baseline demographics, though the pooled placebo group had a higher median age (50 years) than the PXVX0317 group (39 years), due to the larger contribution of younger adults from Study 004 to the PXVX0317 group.*

8.2.3 Categorization of Adverse Events

All verbatim terms for reported AEs were coded using MedDRA v26.0, and the resulting SOCs and PTs were used for tabulation of rates.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

PXVX0317 data from five studies were pooled in ISS analyses, but inconsistencies in study design across the pooled studies may impact the conclusions, including the following:

- Among the five studies, only Studies 004 and 005 were placebo-controlled, and the total number of participants in the pooled placebo group is much smaller (N=675) than in the pooled PXVX0317 group (N=3,522).
- The study population in Study 004 differed significantly from Study 005 due to the different inclusion criteria for age. (Study 004 enrolled only those 12 to <65 years of age while Study 005 enrolled those ≥65 years of age.)
- Since randomization ratios differed between Study 004 and 005 (6:1 and 1:1, respectively), the PXVX0317 group has a larger percentage of participants 12 to <65 years of age than the placebo group: 89% of participants in the PXVX0317 group are from Study 004 while 69% of participants in the pooled placebo group are from Study 004. This results in a younger average age in the PXVX0317 group relative to the placebo group in the ISS.
- For Study 002, PXVX0317 data for both alphavirus vaccine-naïve and prior alphavirus-vaccinated participants were included. Pooling these groups with the other safety data was considered appropriate because no significant differences in

AE incidence were observed in the prior alphavirus-vaccinated group compared to the alphavirus vaccine-naïve participants. However, this introduces a small subgroup of participants into the ISS pooled safety population with prior alphavirus immunity.

- For Studies 002, 010, and 001, there was no placebo-only group, although four participants in Study 001 were included in the placebo-only group due to nonreceipt of PXVX0317.
- In Study 001, eight different doses and regimens were administered across ten study groups, and all these participants were pooled in the ISS safety population. Since the different doses and regimens may confer different safety risks, pooling these participants adds considerable heterogeneity to the ISS safety population. To mitigate this issue, throughout the ISS, safety data are presented with participants who received different doses or regimens both pooled together with all other participants ("Total PXVX0317") and separately ("Other PXVX0317 doses"). Additionally, only the safety data following the first vaccination were included in the safety analyses (even if the participant ultimately received multiple doses of the IP).

Despite these differences in study approach across trials, all the ISS safety data were generated from prospective interventional trials, and the approach to safety monitoring was similar across studies (e.g., AE collection, duration of AE collection, definition of AE types, grading of AEs, and assessing causality of AEs). As such, pooling the safety data is considered appropriate despite the limitations described above.

8.4 Safety Results

An overview of safety results is provided in Table 40.

Table 40. Adverse Events, Safety Population, ISS

Event	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Any AR or AE[a]	1388/3141 (44.2)	1584/3522 (45.0)	216/675 (32.0)
Grade 3 or higher	88/3141 (2.8)	105/3522 (3.0)	7/675 (1.0)
Any solicited AR[b]	1157/3115 (37.1)	1319/3494 (37.8)	154/661 (23.3)
Grade 3 or higher	49/3115 (1.6)	57/3494 (1.6)	3/661 (0.5)
Any systemic solicited AR[b]	956/3115 (30.7)	1058/3494 (30.3)	143/661 (21.6)
Grade 3 or higher	47/3115 (1.5)	56/3494 (1.6)	3/661 (0.5)
Any local solicited AR[b]	731/3114 (23.5)	843/3493 (24.1)	53/661 (8.0)
Grade 3 or higher	6/3114 (0.2)	6/3493 (0.2)	0/661 (0.0)
Any unsolicited AE	485/3141 (15.4)	568/3522 (16.1)	92/675 (13.6)
Grade 3 or higher	40/3141 (1.3)	52/3522 (1.5)	4/675 (0.6)
Any SAEs	31/3141 (1.0)	37/3522 (1.1)	4/675 (0.6)
Discontinued study due to AE[c]	0/3141 (0.0)	1/3522 (<0.1)	0/675 (0.0)
Any Fatal AE	2/3141 (0.1)	2/3522 (0.1)	1/675 (0.1)
Any AESI[d]	6/3021 (0.2)	6/3021 (0.2)	2/671 (0.3)
Any MAAE[e]	272/3021 (9.0)	272/3021 (9.0)	64/671 (9.5)

Source: Reviewer generated table. Derived from ISS dataset submitted in Response to IR #29 (sequence 0036).
Abbreviations: %=n/N*100; AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; MAAE = medically attended adverse event; n=number of participants with events; N=number of safety population participants in the treatment group; SAE=serious adverse event

[a]Inclusive of both solicited adverse reactions and unsolicited adverse events.
[b]The denominator for solicited adverse reactions is the number of participants with at least one diary observation (excluding 'Not done/unknown') for a given symptom or a given day.
[c]Does not include those who discontinued the study due to death.
[d]AESI is defined as new onset or worsening arthralgia that is medically attended. The denominator for AESIs includes those safety population participants enrolled in studies that captured AESIs (Studies 004, 005, 010).
[e]The denominator for MAAEs includes those safety population participants enrolled in studies that captured MAAEs (Studies 004, 005, 010).

8.4.1 Deaths

A total of three deaths occurred across studies: two in the pooled PXVX0317 group (road traffic accident, respiratory failure due to pneumonia) and one in the placebo group (lung cancer). Of the three deaths, one was reported in Study 004 and the other two were reported in Study 005. The Applicant and this reviewer assessed all deaths as unlikely to be related to the IP. Please refer to sections 6.1.12.3 and 6.2.12.3 for additional details on these cases.

8.4.2 Nonfatal Serious Adverse Events

8.4.2.1 Summary of Nonfatal Serious Adverse Events

Overall, 37 participants reported nonfatal SAEs: 31 (1%) among single dose 40/300ug PXVX0317 recipients, 6 (1.6%) among other PXVX0317 dose recipients, and 4 (0.6%) among placebo recipients. The Applicant assessed all SAEs as not related to the IP. This reviewer also assessed all SAEs as unlikely to be related to the IP (see sections 6.1.12.4, 6.2.12.4, and A1.1. "Safety Results" for details). A summary of SAEs by SOC and PT in the pooled safety population is presented in Table 41.

Table 41. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, ISS

System Organ Class Preferred Term	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Any SAE	31 (1.0)	37 (1.1)	4 (0.6)
Congenital, familial and genetic disorders	1 (0.0)	1 (0.0)	0 (0.0)
Encephalocele	1 (0.0)	1 (0.0)	0 (0.0)
Ear and labyrinth disorders	1 (0.0)	1 (0.0)	0 (0.0)
Vertigo	1 (0.0)	1 (0.0)	0 (0.0)
Eye disorders	1 (0.0)	1 (0.0)	1 (0.1)
Glaucoma	0 (0.0)	0 (0.0)	1 (0.1)
Retinal detachment	1 (0.0)	1 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (0.0)	1 (0.0)	0 (0.0)
Vomiting	1 (0.0)	1 (0.0)	0 (0.0)
Hepatobiliary disorders	2 (0.1)	2 (0.1)	0 (0.0)
Biliary dyskinesia	1 (0.0)	1 (0.0)	0 (0.0)
Cholecystitis	1 (0.0)	1 (0.0)	0 (0.0)
Immune system disorders	1 (0.0)	2 (0.1)	0 (0.0)
Anaphylactic reaction	1 (0.0)	2 (0.1)	0 (0.0)

System Organ Class Preferred Term	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Infections and infestations	7 (0.2)	8 (0.2)	2 (0.3)
Appendicitis	1 (0.0)	1 (0.0)	1 (0.1)
Cellulitis	1 (0.0)	1 (0.0)	0 (0.0)
Clostridium difficile infection	0 (0.0)	0 (0.0)	1 (0.1)
COVID-19	0 (0.0)	0 (0.0)	1 (0.1)
Device related infection	1 (0.0)	1 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	1 (0.0)	0 (0.0)
Influenza	1 (0.0)	1 (0.0)	0 (0.0)
Pneumonia	1 (0.0)	1 (0.0)	0 (0.0)
Pyelonephritis	1 (0.0)	1 (0.0)	0 (0.0)
Staphylococcal infection	0 (0.0)	0 (0.0)	1 (0.1)
Tubo-ovarian abscess	1 (0.0)	1 (0.0)	0 (0.0)
Urosepsis	0 (0.0)	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications	4 (0.1)	7 (0.2)	0 (0.0)
Craniocerebral injury	1 (0.0)	1 (0.0)	0 (0.0)
Femoral neck fracture	1 (0.0)	1 (0.0)	0 (0.0)
Gun shot wound	1 (0.0)	1 (0.0)	0 (0.0)
Induced abortion hemorrhage	0 (0.0)	1 (0.0)	0 (0.0)
Laryngeal injury	0 (0.0)	1 (0.0)	0 (0.0)
Road traffic accident	1 (0.0)	2 (0.1)	0 (0.0)
Skin laceration	1 (0.0)	1 (0.0)	0 (0.0)
Metabolism and nutrition disorders	3 (0.1)	3 (0.1)	0 (0.0)
Dehydration	1 (0.0)	1 (0.0)	0 (0.0)
Diabetic ketoacidosis	2 (0.1)	2 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.0)	1 (0.0)	0 (0.0)
Pain in extremity	1 (0.0)	1 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.1)	2 (0.1)	1 (0.1)
Breast cancer	1 (0.0)	1 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	1 (0.1)
Malignant melanoma	1 (0.0)	1 (0.0)	0 (0.0)
Nervous system disorders	3 (0.1)	3 (0.1)	0 (0.0)
Basal ganglia infarction	1 (0.0)	1 (0.0)	0 (0.0)
Cerebrovascular accident	1 (0.0)	1 (0.0)	0 (0.0)
Neuropathy peripheral	1 (0.0)	1 (0.0)	0 (0.0)
Transient ischemic attack	1 (0.0)	1 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	2 (0.1)	0 (0.0)
Hyperemesis gravidarum	0 (0.0)	1 (0.0)	0 (0.0)
Premature separation of placenta	0 (0.0)	1 (0.0)	0 (0.0)
Threatened labor	0 (0.0)	1 (0.0)	0 (0.0)

System Organ Class Preferred Term	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Psychiatric disorders	1 (0.0)	1 (0.0)	0 (0.0)
Bipolar disorder	1 (0.0)	1 (0.0)	0 (0.0)
Depression	1 (0.0)	1 (0.0)	0 (0.0)
Renal and urinary disorders	2 (0.1)	2 (0.1)	0 (0.0)
Nephrolithiasis	1 (0.0)	1 (0.0)	0 (0.0)
Urinary retention	1 (0.0)	1 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	1 (0.0)	0 (0.0)
Vaginal hemorrhage	0 (0.0)	1 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (0.1)	2 (0.1)	0 (0.0)
Chronic obstructive pulmonary disease	1 (0.0)	1 (0.0)	0 (0.0)
Respiratory failure	1 (0.0)	1 (0.0)	0 (0.0)

Source: Adapted from Integrated Summary of Safety Table 35, Response to IR #29 Table 10.1.1
Abbreviations: %=n/N*100; ISS=integrated summary of safety; n=number of participants with events; N=number of safety population participants in the treatment group; PT=preferred term; SAE=serious adverse event

Clinical Reviewer Comment*: Although a higher percentage of PXVX0317 recipients (1%) reported SAEs than placebo recipients (0.6%), the difference is difficult to interpret in light of the small number of events and the significantly smaller placebo group. Of note, the ISS evaluation showed nonfatal SAEs under the SOC Neurologic Disorders occurring in the PXVX0317 group, all from Study 004 (see section 6.1.12.4), while there were no events in the placebo group. Additional analyses were conducted to explore a potential association between neurologic AEs and PXVX0317 (see section 8.4.2.3). Ultimately, none of the SAEs in the PXVX0317 group were assessed as likely to be related to the IP due to lack of temporal relationship to IP administration, lack of a plausible biologic mechanism linking the IP to SAE, and/or plausible alternative etiologies for the SAEs.*

8.4.2.2 Subgroup Analyses of Nonfatal Serious Adverse Events

Subgroup analyses of nonfatal SAEs are presented in Table 41. The percentage of PXVX0317 recipients reporting SAEs varied across age strata with the highest percentage observed among those ≥75 years of age (2.1%) and the lowest percentage among those 12 to <18 years of age (0.5%). The percentage of PXVX0317 recipients reporting SAEs was higher among White (1.1%) and Other race (1.6%) than Black or African American (0.5%) participants. The percentage of PXVX0317 recipients reporting SAEs was similar across sex and ethnicity subgroups. All SAEs were reported among baseline seronegative participants.

Clinical Reviewer Comment*: Given the low percentage of participants reporting SAEs in the pooled ISS population, any comparisons of SAE incidence between subgroups should be approached with caution, and no definitive conclusions can be drawn.*

Table 42. Serious Adverse Events by Demographic and Baseline Characteristics, Safety Population, ISS

Characteristic	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Age group (years), n (%)	-	-	-
12 to <18	1/217 (0.5)	1/217 (0.5)	0/37 (0.0)
18 to <46	17/1746 (1.0)	23/2127 (1.1)	1/274 (0.4)
46 to <65	9/972 (0.9)	9/972 (0.9)	0/157 (0.0)
65 to <75	3/159 (1.9)	3/159 (1.9)	1/159 (0.6)
≥75	1/47 (2.1)	1/47 (2.1)	2/48 (4.2)
Sex, n (%)	-	-	-
Female	18/1621 (1.1)	23/1850 (1.2)	4/351 (1.1)
Male	13/1520 (0.9)	14/1672 (0.8)	0/324 (0.0)
Race, n (%)	-	-	-
Black or African American	3/588 (0.5)	5/678 (0.7)	0/199 (0.0)
Other	2/123 (1.6)	2/133 (1.5)	0/21 (0.0)
White	26/2315 (1.1)	30/2589 (1.2)	4/511 (0.8)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	6/606 (1.0)	6/635 (0.9)	2/163 (1.2)
Not Hispanic or Latino	25/2472 (1.0)	31/2824 (1.1)	2/497 (0.4)

Source: Adapted from Response to IR #29 Tables 10.1.2 – 10.2.1
Abbreviations: %=n/N*100Note: Percentages are based on the number of safety population participants in each treatment group; ISS=integrated summary of safety; n=number of participants with events; N=number of safety population participants in the treatment group

8.4.2.3 SMQ Analysis of Central Nervous System Vascular Disorders

Due to the observation of an imbalance in events of stroke in the PXVX0317 group compared with placebo recipients, the broad SMQ of *Central nervous system vascular disorders* was used to query the safety database. The results of the search did not reveal any additional cases of central nervous system vascular disorders (all of which were previously identified as SAEs in Study 004). See section 6.1.12.4 for additional details on these cases.

8.4.3 Study Dropouts/Discontinuations

Study participants who dropped out or discontinued from the studies and the corresponding reasons for withdrawal in the pooled ISS population are summarized in Table 43. The overall discontinuation rates were similar in the PXVX0317 (11%) and placebo (8%) groups. The most common reasons for discontinuation included lost to follow-up and withdrawal by participant. Only one participant did not complete the study due to an AE: a grade 3 unsolicited AE in the other PXVX0317 dose group that was assessed as not related to the IP (PT: nephrocalcinosis; see Appendix A1.1 “Safety results”).

Table 43. Participant Disposition, Safety Population, ISS

Disposition	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Completed Study	2803 (89.2)	3121 (88.6)	619 (91.7)
Early Termination from Study	338 (10.8)	401 (11.4)	56 (8.3)
Primary Reason for Not Completing Study	-	-	-
Adverse Event	0	1 (0.0)	0
Death	2 (0.1)	2 (0.1)	1 (0.1)
Investigator Decision	4 (0.1)	4 (0.1)	0
Lost to Follow-up	209 (6.7)	248 (7.0)	32 (4.7)
Other	20 (0.6)	21 (0.6)	4 (0.6)
Participant Withdrawal	103 (3.3)	125 (3.5)	19 (2.8)

Source: Adapted from Response to IR #29 Table 3.1.1
Abbreviations: %=n/N*100Percentages are based on the number of safety population participants in each column; ISS=integrated summary of safety; n=number of participants with events; N=number of safety population participants in the treatment group

8.4.4 Common Adverse Events

8.4.4.1 Overview of Unsolicited Adverse Events

Unsolicited AEs up to 28 days following vaccination are presented in Table 44. Unsolicited AEs were reported by 485 (15%) PXVX0317 recipients and 92 (14%) placebo recipients. The only PT to occur in >1% of the participants was COVID-19 infection (2% of PXVX0317 and placebo recipients). Unsolicited arthralgia was reported by a similar percentage of PXVX0317 (0.4%) and placebo (0.3%) recipients.

Treatment-related unsolicited AEs (as assessed by the Applicant) occurred in 62 (2.0%) PXVX0317 recipients and 6 (0.9%) placebo recipients. The most common treatment-related unsolicited AEs in order of decreasing frequency for the PXVX0317 group were headache (0.2%), arthralgia (0.2%), dizziness (0.2%), and rash (0.2%).

Table 44. Unsolicited Adverse Events Occurring in at Least 0.5% of Participants in the PXVX0317 Single Dose Treatment Group, Safety Population, ISS

System Organ Class Preferred Term	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Any unsolicited AE	485 (15.4)	568 (16.1)	92 (13.6)
Infections and infestations	181 (5.8)	206 (5.8)	39 (5.8)
COVID-19	64 (2.0)	64 (1.8)	11 (1.6)
Sinusitis	15 (0.5)	15 (0.4)	4 (0.6)
Nervous system disorders	57 (1.8)	61 (1.7)	6 (0.9)
Headache	20 (0.6)	20 (0.6)	3 (0.4)

Source: Adapted from Response to IR #29 Table 5.1.1
Abbreviations: %=n/N*100; AE=adverse event; ISS=integrated summary of safety; n=number of participants with events; N=number of safety population participants in the treatment group
Note: Only those PTs that occurred in at least 0.5% of participants in the PXVX0317 Single Dose treatment group are listed in this table.

Grade 3 or higher unsolicited AEs were reported by 40 (1.3%) PXVX0317 recipients and 4 (0.6%) placebo recipients. Grade 3 or higher unsolicited AEs occurring in two or more

PXVX0317 recipients included: cholecystitis (n=2), anaphylactic reaction (n=2), facial bone fracture (n=2), dehydration (n=2), and diabetic ketoacidosis (n=2).

Treatment-related grade 3 or higher unsolicited AEs included one report of grade 3 dehydration (probably related) in the PXVX0317 group. No treatment-related grade 4 unsolicited AEs were reported.

***Clinical Reviewer Comment**: Although grade 3 or higher unsolicited AEs were reported by a higher percentage of PXVX0317 (1.3%) than placebo (0.6%) recipients, the difference was not driven by any single SOC or PT (the maximal difference between PXVX0317 and placebo groups in the percentage of participants with events in any individual SOC was 0.1%). Further, only one of the grade 3 unsolicited AEs in the PXVX0317 group (dehydration) was considered treatment-related (see section 6.1.12.2 for details of the dehydration case). As such, there was no specific event or pattern of events that suggested a safety concern.*

8.4.4.2 Subgroup Analysis of Unsolicited Adverse Events

Subgroup analyses of unsolicited AEs are presented in Table 45.

Age Subgroups

The percentage of PXVX0317 recipients reporting any unsolicited AE generally decreased with increasing age (19% among 12 to <18 years of age subgroup, 14% among ≥65 years of age subgroup). The percentage of participants with grade 3 or higher unsolicited AEs following PXVX0317 administration did not differ notably between age strata (ranging from 1.2% in the 18 to <65 years of age subgroup to 1.6% in the ≥65 years of age subgroup).

Sex Subgroups

Overall, a higher percentage of female participants reported unsolicited AEs (18% PXVX0317, 16% placebo) than males (13% PXVX0317, 11% placebo). The percentage of participants with grade 3 or higher unsolicited AEs following PXVX0317 administration did not differ notably by sex.

Race Subgroups

White participants reported the highest percentage of unsolicited AEs (17% PXVX0317, 16% placebo), while Black or African American participants reported the lowest percentage of unsolicited AEs (11% PXVX0317, 5% placebo). The percentage of participants with grade 3 or higher unsolicited AEs following PXVX0317 administration did not differ notably by race.

***Clinical Reviewer Comment**: Among Black or African American participants, the difference in the percentage of participants reporting unsolicited AEs between PXVX0317 (11%) and placebo (5%) was driven primarily by events in the Infections and infestations (3% PXVX0317, 1.7% placebo) and Nervous system disorders (2.4% PXVX0317, 0% placebo) SOCs. The percentage of participants reporting events in the Nervous system disorders SOC was <1% each for events of headache, dizziness, paresthesia, hypersomnia, neuropathy peripheral, and sciatica. Overall, no clinically meaningful differences in specific events or patterns of events were identified in the subgroup analysis.*

Ethnicity Subgroups

Not Hispanic or Latino participants reported a higher percentage of unsolicited AEs (16% PXVX0317, 15% placebo) than Hispanic or Latino participants (12% PXVX0317, 11% placebo). The percentage of participants with grade 3 or higher unsolicited AEs following PXVX0317 administration did not differ notably by ethnicity.

Baseline Serostatus Subgroups

Baseline seronegative participants reported a higher percentage of unsolicited AEs (16% PXVX0317, 14% placebo) than seropositive participants (10% PXVX0317, 6% placebo). Grade 3 or higher unsolicited AEs were reported by 1.3% of baseline seronegative participants and 0% of baseline seropositive participants following PXVX0317.

Clinical Reviewer Comment*: The number of baseline seropositive PXVX0317 recipients is too small (n=72) to draw any definitive conclusions.*

The percentage of participants with unsolicited AEs did not vary considerably by subgroup but were reported slightly less commonly by older participants than younger participants following PXVX0317 (14% among ≥65 years of age and 19% among 12 to <18 years of age groups). This difference does not present a significant safety concern but is notable insofar as the PXVX0317 group was younger on average than the placebo group, so the older placebo group may be less likely to report AEs than the younger PXVX0317 group, which would bias the results towards a less favorable safety profile for PXVX0317.

Table 45. Unsolicited Adverse Events and Grade 3 or 4 Unsolicited Adverse Events, by Demographic Subgroup, Safety Population, ISS

Subgroup	PXVX0317 Single Dose (N=3141) Any Unsolicited AE n (%)	Total PXVX0317 (N=3522) Any Unsolicited AE n (%)	Placebo (N=675) Any Unsolicited AE n (%)	PXVX0317 Single Dose (N=3141) Grade 3 or 4 Unsolicited AE n (%)	Total PXVX0317 (N=3522) Grade 3 or 4 Unsolicited AE n (%)	Placebo (N=675) Grade 3 or 4 Unsolicited AE n (%)
Sex	-	-	-	-	-	-
Male	197/1520 (13.0)	232/1672 (13.9)	35/324 (10.8)	19/1520 (1.3)	20/1672 (1.2)	1/324 (0.3)
Female	288/1621 (17.8)	336/1850 (18.2)	57/351 (16.2)	21/1621 (1.3)	32/1850 (1.7)	3/351 (0.9)
Race	-	-	-	-	-	-
Asian	11/90 (12.2)	12/97 (12.4)	2/17 (11.8)	0	0	0
Black/African American	66/588 (11.2)	81/678 (12)	6/119 (5.0)	6/588 (1.0)	10/678 (1.5)	1/119 (0.8)
Other	21/123 (17.1)	22/133 (16.6)	3/21 (14.3)	3/123 (2.4)	3/133 (2.3)	0
White	382/2315 (16.5)	448/2589 (17.3)	79/511 (15.5)	31/2315 (1.3)	39/2589 (1.5)	3/511 (0.6)
Ethnicity	-	-	-	-	-	-
Hispanic or Latino	75/606 (12.4)	84/635 (13.2)	18/163 (11.0)	9/606 (1.5)	9/635 (1.4)	1/163 (0.6)
Not Hispanic/Latino	407/2472 (16.5)	481/2824 (17.0)	73/497 (14.7)	31/2472 (1.3)	43/2824 (1.5)	3/497 (0.6)
Age (years)	-	-	-	-	-	-
12 to <18	41/217 (18.9)	41/217 (18.9)	3/37 (8.1)	3/217 (1.4)	3/217 (1.4)	0
18 to <65	418/2738 (15.3)	501/3119 (16.1)	58/449 (12.9)	34/2738 (1.2)	46/3119 (1.5)	1/449 (0.2)
65 and older	26/186 (14.0)	26/186 (14.0)	31/189 (16.4)	3/186 (1.6)	3/186 (1.6)	3/189 (1.6)

Source: Adapted from Response to IR #29 Tables 5.1.2 - 5.2.1
Abbreviations: %=n/N*100; AE=adverse event; ISS=integrated summary of safety; n=number of participants with events; N=number of safety population participants in the treatment group

8.4.4.3 Summary of Medically Attended Adverse Events

MAAEs were reported in Studies 004, 005, and 010, so the pooled safety population for MAAEs is limited to 3,021 PXVX0317 (only single dose 40/300µg) and 671 placebo recipients.

MAAEs were reported by 272 (9%) PXVX0317 recipients and 64 (10%) placebo recipients. The most common MAAEs in the PXVX0317 group by SOC were *Infections and infestations* (4% PXVX0317, 4% placebo), with the most frequent PTs being COVID-19 (1% PXVX0317, 1% placebo) and sinusitis (0.4% PXVX0317, 0.6% placebo), followed by *Injury, poisoning and procedural complications* (1.3% PXVX0317, 1.9% placebo).

Subgroups

In the PXVX0317 group, MAAEs were more commonly reported by female (11%) than male (7%) participants; White or Asian participants (both 10%) than Black or African American participants (6%); Not Hispanic or Latino participants (10%) than Hispanic or Latino participants (7%); and baseline seronegative participants (9%) than baseline seropositive participants (4%). In age subgroups, MAAEs were reported most frequently among those 12 to <18 years of age (11%) and least frequently among those ≥75 years of age (4%) following PXVX0317 administration.

Of note, among the 12 to <18 years of age male participants, 18 (15%) PXVX0317 recipients reported MAAEs compared to 0 (0%) placebo recipients. This was driven by Infections and infestations (5% PXVX0317, 0% placebo); Injury, poisoning and procedural complications (5% PXVX0317, 0% placebo); and Skin and subcutaneous tissue disorders (3% PXVX0317, 0% placebo), though no single PT within those SOCs accounted for the difference.

Clinical Reviewer Comment*: Overall, the percentage of participants with MAAEs was similar between PXVX0317 and placebo groups, suggesting a lack of concerning safety findings in the MAAE data. Subgroup analyses did show MAAEs reported by a higher percentage of female, White and Asian, and Not Hispanic or Latino subgroups, though differences were small (<5% difference between subgroups). The percentage of participants with MAAEs was similar across the younger age cohorts (ranging between 8 and 11% in those 12 through 75 years of age) and then lower (4%) among those ≥75 years of age; however, the subgroup was that ≥75 years of age was limited to 47 participants, so any differences should be interpreted with caution. Further, the difference in MAAEs between PXVX0317 and placebo groups among 12 to <18 years of age male participants was not driven by a single PT, and the sample size in this age- and sex-stratified subgroup was also small (N=143), limiting the conclusions that can be drawn from this data.*

8.4.5 Clinical Test Results

Clinical tests were not performed for safety monitoring in the phase 3 studies (004 and 005). The only study to perform clinical tests beyond screening was Study 002, where a complete blood count, creatinine, and liver enzymes (AST/ALT) were performed at screening and Days 1 and 8. Of note, test results were collected but the results were not

included in the study database unless they showed an abnormality (see appendix 1, section A1.2.).

8.4.6 Systemic Adverse Reactions

8.4.6.1 Overview of Systemic Adverse Reactions

Solicited systemic ARs are summarized in Table 46.

Solicited systemic ARs were reported by 956 (31%) PXVX0317 recipients and 143 (22%) placebo recipients. The most common solicited systemic ARs for both PXVX0317 and placebo recipients were fatigue (19% PXVX0317, 14% placebo), headache (17% PXVX0317, 14% placebo), and myalgia (17% PXVX0317, 9% placebo). Fever was uncommonly reported (<1% of PXVX0317 and placebo recipients). Grade 3 systemic ARs were reported by 47 (1.5%) PXVX0317 and 3 (0.5%) placebo recipients; no grade 4 systemic ARs were reported in either group. The most common grade 3 systemic AR in the PXVX0317 group was fatigue (0.7%).

The median duration of solicited systemic ARs was 1 day in both the PXVX0317 and placebo groups (range 1-168 days for PXVX0317, 1-115 days for placebo).

Arthralgia or joint pain was reported by 230 (7%) PXVX0317 recipients and 41 (6%) placebo recipients, with 0.2% of both PXVX0317 and placebo recipients reporting grade 3 arthralgia or joint pain. No grade 4 arthralgia or joint pain was reported in either study group.

***Clinical Reviewer Comment**: A sensitivity analysis was performed in which missing solicited AR events were assumed to have occurred (e.g., if data on fever was missing for a participant, the sensitivity analysis assumed the participant did have a fever occur). This analysis did not result in significant changes to the percentage of participants in either group with systemic ARs (31% of PXVX0317 and 23% of placebo recipients).*

Table 46. Solicited Adverse Reactions and Grade 3 or 4 Solicited Adverse Reactions Within 7 Days Postvaccination, Safety Population, ISS

System Organ Class Preferred Term	PXVX0317 Single Dose (N=3141) Any Solicited AR n (%)	PXVX0317 Single Dose (N=3141) Grade 3 Solicited AR n (%)	Total PXVX0317 (N=3522) Any Solicited AR n (%)	Total PXVX0317 (N=3522) Grade 3 Solicited AR n (%)	Pooled Placebo (N=675) Any Solicited AR n (%)	Pooled Placebo (N=675) Grade 3 Solicited AR n (%)
Any Solicited AR	1157 (37.1)	49 (1.6)	1319 (37.8)	57 (1.6)	154 (23.3)	3 (0.5)
Local AR	731 (23.5)	6 (0.2)	843 (24.1)	6 (0.2)	53 (8.0)	0 (0.0)
Injection site pain	725 (23.3)	5 (0.2)	837 (24.0)	5 (0.1)	52 (7.9)	0 (0.0)
Redness	13 (0.4)	1 (0.0)	14 (0.4)	1 (0.0)	1 (0.2)	0 (0.0)
Swelling	10 (0.3)	0 (0.0)	11 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic AR	956 (30.7)	47 (1.5)	1058 (30.3)	55 (1.6)	143 (21.6)	3 (0.5)
Arthralgia/joint pain	230 (7.4)	7 (0.2)	255 (7.3)	10 (0.3)	41 (6.2)	1 (0.2)
Chills	246 (7.9)	5 (0.2)	258 (7.4)	8 (0.2)	21 (3.2)	0 (0.0)
Fatigue	582 (18.7)	23 (0.7)	623 (17.8)	27 (0.8)	90 (13.6)	1 (0.2)
Fever[a]	26 (0.8)	6 (0.2)	27 (0.8)	6 (0.2)	3 (0.5)	0 (0.0)
Headache	530 (17.0)	12 (0.4)	582 (16.7)	14 (0.4)	92 (13.9)	2 (0.3)
Malaise[b]	7 (5.8)	0 (0.0)	35 (7.0)	3 (0.6)	0 (0.0)	0 (0.0)
Myalgia	523 (16.8)	13 (0.4)	575 (16.5)	18 (0.5)	58 (8.8)	3 (0.5)
Nausea	219 (7.0)	12 (0.4)	240 (6.9)	13 (0.4)	34 (5.1)	0 (0.0)

Source: Adapted from the Integrated Summary of Safety Table 16, Response to IR #29 Table 13.1.1
Abbreviations: %=n/N*100; AR=adverse reaction; ISS=integrated summary of safety; N=number of participants with at least one diary observation (excluding 'Not done/unknown') for a given symptom or a given day.; n=number of participants with events
Note: For Study PXVX-CV-317-001, only events occurring after the first PXVX0317 dose (not placebo) are counted. No participants in any treatment group reported Grade 4 ARs.
[a]One participant who received PXVX0317 reported a grade 4 fever, but this was deemed an entry error, so is not included in this table.
[b]Malaise was assessed in Studies PXVX-CV-317-001 and EBSI-CV-317-002 only. As such, the denominator for PXVX0317 Single Dose is 120 and the denominator for Total PXVX0317 is 499 for malaise.

8.4.6.2 Subgroup Analyses of Solicited Systemic Adverse Reaction

Subgroup analyses of solicited systemic ARs are presented in Table 47.

Age Subgroups

The percentage of PXVX0317 recipients reporting systemic ARs decreased with increasing age, with 40% of those 12 to <18 years of age reporting systemic ARs compared to 9% of those ≥65 years of age. Grade 3 solicited ARs following PXVX0317 also decreased with increasing age (1.9% of 12 to <18 years, 1.6% of 18 to <65 years, and 0.5% of ≥65 years of age subgroup).

Clinical Reviewer Comment*: The percentage of PXVX0317 recipients reporting systemic ARs decreased with increasing age, similar to what was observed with unsolicited AEs.*

Sex Subgroups

A higher percentage of female participants receiving PXVX0317 reported systemic ARs (37%) than male (24%) participants. Female participants also reported more grade 3 systemic ARs (2%) than male participants (1%).

Clinical Reviewer Comment*: The higher percentage of female participants reporting systemic ARs (compared to male participants) is consistent with the individual trials and correlates with higher seroresponse and GMT values in female participants, suggesting the increased reactogenicity among female participants may be related to the immune response to PXVX0317.*

Race Subgroups

Among race subgroups receiving PXVX0317, White participants had the highest percentage reporting systemic ARs (32%) while Black or African American participants had the lowest percentage reporting systemic ARs (26%). The percentage of participants reporting grade 3 or higher systemic ARs did not vary notably across race subgroups (1.6% among White, 1.4% among Black or African American, 1.6% among Other race, and 0% among Asian participants).

Clinical Reviewer Comment: *The higher percentage of White than Non-White participants reporting systemic ARs is consistent with Study 004 results (though differs from the results of the smaller Study 005) and was driven primarily by differences in the percentage reporting fatigue, headache, and myalgia. The etiology of this difference is unclear given the seroresponse rates following PXVX0317 did not differ substantially across races. The clinical significance of this difference is difficult to interpret in light of the small sample sizes.*

Ethnicity Subgroups

A higher percentage of Not Hispanic or Latino participants reported systemic ARs (33%) than Hispanic or Latino participants (24%) following PXVX0317. The percentage of participants reporting grade 3 or higher systemic ARs did not vary notably across ethnicity subgroups (1.5% among both Not Hispanic or Latino and Hispanic or Latino participants).

Clinical Reviewer Comment: *The higher percentage of Not Hispanic or Latino participants reporting systemic ARs is consistent with the individual trial results, though the etiology of this difference and clinical significance of this difference are unclear given the seroresponse rates following PXVX0317 did not differ substantially across ethnicities.*

Similar to the individual trial results, the incidence of solicited ARs was higher in PXVX0317 than placebo recipients across all demographic subgroups, save for the 65 years of age and older subgroup.

Table 47. Solicited Systemic Adverse Reactions, Safety Population, ISS

Subgroup	PXVX0317 Single Dose (N=3141) n/N (%)	Total PXVX0317 (N=3522) n/N (%)	Placebo (N=675) n/N (%)
Sex	-	-	-
Male	361/1500 (24.1)	392/1650 (23.8)	59/314 (18.8)
Female	595/1615 (36.8)	666/1844 (36.1)	84/347 (24.2)
Race	-	-	-
Asian	26/89 (29.2)	26/96 (27.1)	2/17 (11.8)
Black or African American	152/574 (26.5)	168/664 (25.3)	16/114 (14.0)
Other	38/122 (31.2)	40/132 (30.3)	4/21 (19.1)
White	734/2305 (31.8)	818/2577 (31.7)	116/502 (23.1)
Ethnicity	-	-	-
Hispanic or Latino	145/603 (24.1)	153/631 (24.3)	32/160 (20.0)
Not Hispanic or Latino	799/2449 (32.6)	893/2800 (31.9)	108/487 (22.2)
Age (years)	-	-	-
12 to <18	86/213 (40.4)	86/213 (40.4)	8/37 (21.6)
18 to <65	853/2717 (31.4)	955/3096 (30.9)	110/441 (24.9)
≥65	17/185 (9.2)	17/185 (9.2)	25/183 (13.7)

Source: Adapted from Response to IR #29 Tables 13.1.2 – 13.2.1
Abbreviations: %=n/N*100; ISS=integrated summary of safety; N= number of participants with at least one diary observation (excluding 'Not done/unknown') for a given symptom or a given day in the specified subgroup; n=number of participants with events
Note: Percentages are based on the number of safety population participants in each treatment group who have completed any diary at any time.

Baseline Serostatus Subgroups

Among the 72 PXVX0317 recipients who were baseline seropositive, 34% reported systemic ARs compared with 31% of PXVX0317 recipients who were seronegative at baseline. Four percent of baseline seropositive participants reported grade 3 systemic ARs compared with 1.5% of baseline seronegative participants.

Clinical Reviewer Comment*: Consistent with Study 004, a higher percentage of the baseline seropositive PXVX0317 recipients reported systemic ARs and grade 3 systemic ARs than seronegative PXVX0317 recipients, though conclusions are limited by the small sample size of the baseline seropositive subgroup.*

8.4.7 Local Reactogenicity

8.4.7.1 Overview of Solicited Local (Injection Site) Adverse Reactions

Solicited local reactions are summarized above in Table 46.

Solicited local ARs were reported by 731 (24%) PXVX0317 recipients and 53 (8%) placebo recipients. The most common solicited local AR was injection site pain (23% PXVX0317, 8% placebo). Grade 3 local ARs were reported by 0.2% of PXVX0317 and 0% of placebo recipients. In the PXVX0317 group, one case (0.03%) of grade 3 injection site redness was reported; all other grade 3 local ARs were injection site pain (n=5 [0.2%]). No grade 4 local ARs were reported in either study group.

The median duration of local AR symptoms was 1 day for both PXVX0317 and placebo groups (range 1-44 days for PXVX0317, 1-5 days for placebo).

Clinical Reviewer Comment*: A sensitivity analysis was performed in which missing solicited AR events were assumed to have occurred (e.g., if data on injection site pain was missing for a participant, the sensitivity analysis assumed the participant did have injection site pain occur). This analysis did not result in significant changes to the incidence of local solicited ARs (25% of PXVX0317 and 10% of placebo recipients).*

8.4.7.2 Subgroup Analyses of Solicited Local Reactions

Subgroup analyses of solicited local reactions are presented in Table 48.

Age Subgroups

Local ARs were reported by a higher percentage of participants following PXVX0317 in the 12 to <18 years of age (28%) and 18 to <65 years of age (24%) subgroups than among the 65 years of age and older subgroup (5%). Grade 3 local ARs did not vary notably by age group (0.5% of 12 to <18 years of age, 0.2% of 18 to <65 years of age, and 0% of ≥65 years of age subgroups).

The median duration of local AR symptoms following PXVX0317 did not vary notably by age group.

Clinical Reviewer Comment*: The percentage of PXVX0317 recipients reporting local ARs was lower in the older age group, similar to what was observed with unsolicited AEs and systemic ARs.*

Sex Subgroups

A higher percentage of female participants receiving PXVX0317 reported local ARs (28%) than male participants (18%). Grade 3 local ARs did not vary notably by sex (0.1% of female participants, 0.3% of male participants).

Clinical Reviewer Comment*: The higher percentage of female participants reporting local ARs (compared to male participants) is consistent with the individual trials and correlates with higher seroresponse and GMT values in female participants, suggesting the increased reactogenicity among female participants may be related to the immune response to PXVX0317.*

Race Subgroups

Among race subgroups receiving PXVX0317, a higher percentage of White (26%) and Asian (28%) participants reported local ARs while a lower percentage of Black or African American participants reported local ARs (17%). The difference was largely due to a difference in reports of injection site pain. Grade 3 or higher local ARs did not vary notably by race (<0.5% for all races).

Clinical Reviewer Comment: *The higher percentage of White and Asian than Black or African American participants reporting local ARs is consistent with Study 004 results (though differs from the results of the smaller Study 005), though the etiology of this difference and clinical significance of this difference are unclear given the seroresponse rates following PXVX0317 did not differ substantially across races.*

Ethnicity Subgroups

A higher percentage of Not Hispanic or Latino participants receiving PXVX0317 reported local ARs (25%) than Hispanic or Latino participants (17%). Grade 3 or higher local ARs did not vary notably by ethnicity (<0.5% for both ethnicities).

Clinical Reviewer Comment: *The higher percentage of Not Hispanic or Latino participants reporting local ARs is consistent with the individual trial results, though the etiology of this difference and clinical significance of this difference are unclear (given the seroresponse rates following PXVX0317 did not differ substantially across ethnicities).*

Table 48. Solicited Local Adverse Reactions by Subgroup, Safety Population, ISS

Subgroup	PXVX0317 Single Dose (N=3141) n/N (%)	Total PXVX0317 (N=3522) n/N (%)	Placebo (N=675) n/N (%)
Sex	-	-	-
Male	274/1500 (18.3)	307/1650 (18.6)	21/314 (6.7)
Female	457/1614 (28.3)	536/1843 (29.1)	32/347 (9.2)
Race	-	-	-
White	578/2305 (25.1)	667/2577 (25.9)	44/502 (8.8)
Black or African American	100/573 (17.5)	118/663 (17.8)	6/114 (5.3)
Asian	25/89 (28.1)	28/96 (29.2)	2/17 (11.8)
Other	24/122 (19.7)	26/132 (19.7)	0
Ethnicity	-	-	-
Not Hispanic or Latino	618/2448 (25.3)	722/2799 (25.8)	42/487 (8.6)
Hispanic or Latino	102/603 (16.9)	110/631 (17.4)	10/160 (6.3)
Age	-	-	-
12 to <18	60/213 (28.2)	60/213 (28.2)	5/37 (13.5)
18 to <65	662/2716 (24.4)	774/3095 (25.0)	44/441 (10.0)
65 and older	9/185 (4.9)	9/185 (4.9)	4/183 (2.2)

Source: Adapted from Response to IR #29 Tables 13.1.2 – 13.2.1
Abbreviations: %=n/N*100; ISS=integrated summary of safety; N=number of participants with at least one diary observation (excluding 'Not done/unknown') for a given symptom or a given day; n=number of participants with events

Baseline Serostatus Subgroups

Among the 72 baseline seropositive PXVX0317 recipients, 20% reported local ARs compared with 24% of baseline seronegative PXVX0317 recipients, and 1.4% reported a grade 3 local AR compared to 0.2% of seronegative participants.

***Clinical Reviewer Comment**: A lower percentage of baseline seropositive participants reported local ARs compared with baseline seronegative participants, in contrast to what was observed for systemic ARs. However, a higher percentage of baseline seropositive participants reported grade 3 or higher local ARs, similar to that observed for systemic ARs. As discussed for systemic ARs, the small number of baseline seropositive participants precludes any definitive conclusions.*

8.4.8 Adverse Events of Special Interest

8.4.8.1 Arthralgia

In Studies 004, 005, and 010, AESIs were defined as the occurrence of new onset or worsening arthralgia that was medically attended. AESIs were not collected in Studies 001 and 002, so the ISS evaluation of AESIs excludes those studies.

Overall, 6 (0.2%) participants in the PXVX0317 group and 2 (0.3%) participants in the placebo group reported an AESI (Table 49). All AESIs were nonserious and grade 1 or 2 in severity. In the PXVX0317 group, the median time to onset of AESI symptoms was 41 days (range 2-168 days) and the median duration of AESI symptoms was 43.5 days (range 1-101 days).

***Clinical Reviewer Comment**: On review of the case narratives of those participants with AESIs in the PXVX0317 group, three of the six were possibly related to the IP: (1) USUBJID* (b) (6) *a 55 year-old female who developed new left hip pain on Day 85; (2) USUBJID* (b) (6) *, a 45 year-old female with a history of left knee pain who developed worsening left knee pain on Day 15; (3) USUBJID* (b) (6) *a 37 year-old woman who developed new left shoulder pain and left upper extremity paresthesia on Day 3 postvaccination and who was discontinued early from the study due to lost to follow-up. However, the percentage of participants reporting new onset or worsening arthralgia that was medically attended was low and was balanced between PXVX0317 and placebo groups, suggesting that PXVX0317 is unlikely to cause significant arthralgia complications in vaccine recipients.*

Table 49. Adverse Events of Special Interest, Safety Population, ISS

System Organ Class Preferred Term	PXVX0317 Single Dose (N=3021) n (%)	Total PXVX0317 (N=3021) n (%)	Pooled Placebo (N=671) n (%)
Any AESI	6 (0.2)	6 (0.2)	2 (0.3)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (0.2)
Joint dislocation	0 (0.0)	0 (0.0)	1 (0.2)

System Organ Class Preferred Term	PXVX0317 Single Dose (N=3021) n (%)	Total PXVX0317 (N=3021) n (%)	Pooled Placebo (N=671) n (%)
Musculoskeletal and connective tissue disorders	6 (0.2)	6 (0.2)	1 (0.2)
Arthralgia	5 (0.2)	5 (0.2)	1 (0.2)
Spinal osteoarthritis	1 (0.0)	1 (0.0)	0 (0.2)

Source: Adapted from Response to IR #29 Table 11.1.1, Response to IR #44 Table 14.3.2.1
Abbreviations: %=n/N*100; AESI=adverse event of special interest (new onset or worsening arthralgia that was medically attended); ISS=integrated summary of safety; n=number of participants with events; N=number of safety population participants in the treatment group

8.4.8.2 Chikungunya-Like Adverse Reactions

An analysis of CHIK-like ARs was performed in the pooled safety population of the ISS. As described in section 6.1.12.5, a CHIK-like AR was 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. Both solicited and unsolicited AE PTs were evaluated. As shown in Table 50, 14 (0.4%) participants in the PXVX0317 group and 2 (0.3%) in the placebo group met criteria for CHIK-like ARs.

Table 50. CHIK-Like ARs, Safety Population, ISS

Preferred Term	PXVX0317 Single Dose (N=3141) n (%)	Total PXVX0317 (N=3522) n (%)	Pooled Placebo (N=675) n (%)
Any CHIK-like AR	13 (0.4)	14 (0.4)	2 (0.3)
Arthralgia	6 (0.2)	7 (0.2)	1 (0.1)
Fatigue	1 (0.0)	1 (0.0)	0 (0.0)
Headache	1 (0.0)	1 (0.0)	0 (0.0)
Myalgia	12 (0.4)	13 (0.4)	2 (0.3)

Source: Reviewer generated table
Abbreviations: %=n/N*100; AR=adverse reaction; CHIK=chikungunya; ISS=integrated summary of safety; n=number of participants with events; N=number of safety population participants in the treatment group

Table 51 lists participants who met criteria for CHIK-like AR: seven participants with fever and myalgia that began within 7 days of PXVX0317 administration; five participants with fever, arthralgia, and myalgia that began within 7 days of PXVX0317 administration; one participant with arthralgia starting on Day 5 and fever starting on Day 26 following PXVX0317; and one participant with fever, arthralgia, myalgia, headache, and fatigue starting on Day 13 following PXVX0317. The two placebo recipients exhibited (1) fever and myalgia within 7 days, and (2) fever, arthralgia, and myalgia within 7 days following placebo administration. The median time to onset of pyrexia was 3.5 days (range 1-26 days) (n=14), to arthralgia was 2 days (range 1-17 days) (n=7), and to myalgia was 2 days (range 1-17 days) (n=13). Five PXVX0317 recipients had grade 3 symptoms including three with grade 3 pyrexia and two with grade 3 myalgia, as well as one placebo recipient with grade 3 myalgia. In the PXVX0317 group, the median duration of fever was 1 day (range 1-44 days), arthralgia was 2 days (range 1-101 days), and myalgia was 2 days (range 1-101 days).

Table 51. Participants With CHIK-Like ARs, Safety Population, ISS

USUBJID	Preferred Term	Severity Grade	Time to Onset (Study Day)	Duration (Days)
Study group: PXVX0317 Single Dose	-	-	-	-
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Pyrexia	3	5	1
-	Myalgia	1	4	2
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Pyrexia	2	26	44
-	Arthralgia	2	5	1
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Arthralgia	1	5	2
-	Pyrexia	1	5	1
-	Myalgia	1	5	1
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Arthralgia	2	2	7
-	Pyrexia	2	1	1
-	Myalgia	1	2	7
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Pyrexia	2	4	5
-	Myalgia	2	4	2
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Arthralgia	2	2	1
-	Pyrexia	1	2	1
-	Myalgia	3	2	1
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Pyrexia	1	1	1
-	Myalgia	1	1	1
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Pyrexia	1	4	1
-	Myalgia	1	3	1
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Arthralgia	1	17	101
-	Fatigue	1	13	105
-	Headache	1	13	2
-	Myalgia	1	17	101
-	Pyrexia	1	13	2
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Pyrexia	3	2	1
-	Myalgia	2	2	1
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Arthralgia	2	2	5
-	Pyrexia	2	3	2
-	Myalgia	2	2	5
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Pyrexia	3	2	1
-	Myalgia	1	2	1
EBSI-CV-317-010-(b) (6)	-	-	-	-
-	Pyrexia	1	7	1
-	Myalgia	3	7	2
Study group: Total PXVX0317	-	-	-	-
CV317(b) (6)	-	-	-	-

USUBJID	Preferred Term	Severity Grade	Time to Onset (Study Day)	Duration (Days)
-	Arthralgia	2	1	2
-	Pyrexia	1	1	2
-	Myalgia	2	1	2
Study Group: Placebo	-	-	-	-
EBSI-CV-317-004-(b) (6)	-	-	-	-
-	Arthralgia	2	3	1
-	Pyrexia	1	4	1
-	Myalgia	3	2	3
EBSI-CV-317-005-(b) (6)	-	-	-	-
-	Pyrexia	1	6	1
-	Myalgia	1	6	1

Source: Reviewer generated table
Abbreviations: AR=adverse reaction; CHIK=chikungunya; ISS=integrated summary of safety
[a]Participant EBSI-CV-317-(b) (6) reported arthralgia, chills, and fatigue as solicited ARs on Day 5 postvaccination. Subsequently, on Day 26 postvaccination, the participant reported fever, cough, and nasal congestion, all of which resolved on Day 69 postvaccination.

Clinical Reviewer Comment*: 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. Specifically, there were no grade 3 events of arthralgia and only one event of prolonged arthralgia, which had a plausible alternative etiology (namely, gonococcal arthritis). Since this analysis did not identify any concerning events or pattern of events, CHIK-like ARs were not included in the USPI.*

8.4.8.3 Standardized MedDRA Query Analyses of Arthritis and Rash

To further evaluate for the possibility of CHIK-like ARs, the broad SMQs of *Arthritis* and *Rash* were used to query the pooled ISS safety database. The results of the search showed (1) low frequency of arthritis in the PXVX0317 (1%) and placebo (1%) groups, all of which were non-severe; (2) low frequency of rash in the PXVX0317 (0.5%) and placebo (0%) groups, all of which were non-severe.

8.4.8.4 Standardized MedDRA Query Analyses of Cardiac Arrythmias and Cardiomyopathy

To further evaluate cardiac AEs, the broad SMQs of *Cardiac arrhythmia* and *Cardiomyopathy* were used to query the pooled ISS safety database. The results of the search showed (1) low frequency of cardiac arrhythmia in the PXVX0317 (0.3%) and placebo (0.1%) groups, all of which were non-severe; (2) low frequency of cardiomyopathy in the PXVX0317 (0.4%) and placebo (0.1%) groups, all of which were non-severe.

Clinical Reviewer Comment: *Analyses of cases retrieved using SMQs for arthritis, rash, cardiac arrhythmia, and cardiomyopathy did not reveal any new safety concerns.*

8.6 Safety Conclusions

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-licensed single dose of 40/300µg PXVX0317) in five studies. Overall, no new safety issues were identified in the integrated safety analyses. In

particular, no treatment-related deaths or treatment-related nonfatal SAEs were observed. Additionally, there was no evidence of an increased incidence of CHIK-like ARs, including in a prospective analysis of new onset or worsening arthralgia that was medically attended, in post hoc analyses of CHIK-like ARs, and in analyses of arthritis and rash using SMQs. Finally, unsolicited AE and solicited AR results were similar in the integrated safety analyses compared with the individual studies. 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 as well as the content of Section 6 of the USPI.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 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.

Four pregnancies were associated with SAEs:

1. Study 004
    a. Birth to a child with a congenital anomaly (fronto-ethmoid encephalocele).
2. Study 001
    a. Hyperemesis gravidarum.
    b. Threatened preterm labor, vaginal bleeding, and placental abruption.
    c. Hemorrhage from incomplete abortion.

Clinical Reviewer Comment*: As discussed in section 4.3, the rabbit DART study demonstrated decreased viability of rabbit kits in the vaccine group, while the rat DART study did not observe a difference in offspring viability between vaccine and control groups. The clinical significance of the discrepant animal DART study findings is unclear but will be included in USPI section 8.1. The 11 pregnancies observed in clinical trials are insufficient to inform the benefit-risk assessment of PXVX0317 in pregnancy, though no concerning pattern of events was observed among this limited sample size. Due to the limited number of pregnant study participants, as well as the rabbit DART study, the safety of PXVX0317 in pregnancy will be further evaluated in a postmarketing commitment pregnancy registry. Please refer to Section 11.6 for details.*

9.1.2 Use During Lactation

No data available.

9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups. The Applicant requested a deferral for the pediatric assessment for children <12 years of age. CBER agreed to grant the deferral request, and the application included an agreed pediatric study plan (PSP).

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. See section 6.1 for details.

Clinical Reviewer Comment*: This licensing application and request for deferral of pediatric assessments in children <12 years of age were presented to the Pediatric Research Committee (PeRC) on 17 December 2024. PeRC agreed with the proposed indication that includes individuals 12 years of age and older, as well as the requested deferral of pediatric studies for ages 0 to <12 years.*

9.1.4 Immunocompromised Patients

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

9.1.5 Geriatric Use

A total of 413 adults ≥65 years of age were enrolled in Study 005 (206 received PXVX0317, 207 received placebo). In the PXVX0317 group, the seroresponse rate (%) was 87% with a seroresponse rate (%) difference of 86% (95% CI: 80, 90). Although numerically lower than in those 12 to <65 years of age (98% seroresponse rate, 97% seroresponse rate difference), the seroresponse rate (%) difference in those ≥65 years of age met the success criterion (LB of the 95% CI ≥70%).

Adults ≥65 years of age reported a lower incidence of solicited ARs (12% PXVX0317, 14% placebo) and a lower incidence of grade 3 or higher solicited ARs (0.5% PXVX0317, 0% placebo) than those 12 to <65 years (any solicited AR: 38% PXVX0317, 27% placebo; grade 3 or higher solicited AR: 1.6% PXVX0317, 0.4% placebo).

Adults ≥65 years of age also reported fewer unsolicited AEs following PXVX0317 (13% PXVX0317, 16% placebo) than those 12 to <65 years (16% PXVX0317, 13% placebo) but more grade 3 or 4 unsolicited AEs (1.5% PXVX0317, 1.4% placebo) than those 12 to <65 years of age (1.1% PXVX0317, 0.2% placebo).

Adults ≥65 years of age reported a similar number of MAAEs (9% PXVX0317, 11% placebo) as those 12 to <65 years of age (9% PXVX0317, 9% placebo).

No adults ≥65 years of age experienced an AESI following PXVX0317 administration.

SAEs were reported by a higher percentage of adults ≥65 years of age (1.9% PXVX0317, 1.4% placebo) than among those 12 to <65 years of age (0.8% PXVX0317, 0.2% placebo). Two deaths occurred among adults ≥65 years of age, both of which were assessed as not related to the IP.

See section 6.2 for details of the study results.

Clinical Reviewer Comment*: Note that the above comparisons between those 65 years of age and older with those 12 through 64 years of age are derived from cross-trial comparisons (since Study 004 enrolled those under 65 years of age and Study 005 enrolled those 65 years of age and older). Due to differences in study design, any*

differences in the results noted above for these two age strata should be interpreted with caution.

10. CONCLUSIONS

10.1 Vaccine Effectiveness

The pivotal immunogenicity Studies 004 and 005 demonstrated that 98% of participants aged 12 to <65 years and 87% of participants aged ≥65 years achieved a CHIKV SNA titer ≥100 at Day 22 following a single dose vaccination with PXVX0317, which is considered reasonably likely to predict clinical benefit. The seroresponse rate remained at 86% and 76%, respectively, at Day 183 postvaccination.

In conclusion, immunogenicity data from Studies 004 and 005 indicate that a single IM injection of PXVX0317 is likely effective in preventing disease caused by CHIKV based on the surrogate endpoint of seroresponse rates; however, a postmarketing confirmatory study will be needed to confirm clinical benefit (see section 11.6 for details).

10.2 Safety

Safety of PXVX0317 was assessed in the U.S. in 3,522 healthy participants ≥12 years of age who received at least one dose of PXVX0317 in five clinical studies. The safety data of PXVX0317 demonstrated:

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

Overall, the safety profile of PXVX0317 is considered favorable with no major concerns that substantively affect the benefit-risk assessment. Section 6 of the USPI reflects the above safety information with regard to serious and nonserious AEs and ARs.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 52. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	CHIKV often causes sudden large outbreaks affecting approximately 33 to 75% of the population in areas where the virus is circulating. CHIK manifests as a highly heterogenous spectrum of symptoms and severity of disease. Up to 97% of infected individuals become symptomatic. Some studies estimate that severe arthralgia or chronic arthralgia develops in 2% to 57% of individuals with CHIK, while other studies do not identify any severe cases following natural CHIKV infection. CHIK affects all age groups and both sexes in areas of ongoing transmission. Uncertainties: In some reports, CHIK did not appear to be a serious condition; it is unknown whether disease severity is associated with specific CHIKV lineages. Additional uncertainties include an incomplete understanding of mechanisms of pathogenesis of chronic arthralgia and risk for severe disease (e.g., virulence of different CHIKV lineages, environmental factors, pre-existing medical conditions).	While the mortality rate due to CHIKV infection is low (<0.1%), the frequency and severity of morbidity is high (30% to 70%). Acute arthralgia caused by CHIKV infection may be incapacitating. Chronic disease usually manifests as disabling polyarthritis or polyarthralgia, significantly affecting day-to-day functioning. CHIK is generally considered a serious medical condition.
Unmet Medical Need	No vaccine with verified clinical benefit is available to prevent CHIKV infection. Prevention is otherwise limited to mosquito control and restricting exposure to vector mosquitos such as wearing long sleeves and pants, and use of insect repellants. Treatment is mainly supportive, such as symptomatic relief by using analgesics and antipyretics. Uncertainties: The clinical benefit of the currently licensed CHIK vaccine has not been confirmed.	An unmet medical need exists for effective prevention of CHIKV infection and disease.
Clinical Benefit	Vaccine efficacy as demonstrated by disease prevention has not yet been assessed due to unpredictable CHIKV outbreaks. A CHIKV SNA titer ≥100, estimated based on prevention of CHIKV viremia in a passive transfer NHP challenge study, was used as a surrogate endpoint that is reasonably likely to predict a clinical benefit. The phase 3 immunogenicity trials demonstrated that 97% of participants achieved a CHIKV SNA titer ≥100 at 21 days after a single dose of PXVX0317. Uncertainties: The surrogate endpoint was estimated based on its prevention of CHIKV viremia but not disease in the NHP model. Other nonclinical challenge studies showed that CHIKV neutralizing antibodies prevented CHIKV viremia but not CHIKV in joints or joint pathology.	PXVX0317 is reasonably likely to prevent CHIKV disease. Uncertainties need to be addressed through an adequate and well-controlled postmarketing confirmatory study

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	The most substantial and common risks of vaccination with PXVX0317 are injection site pain, fatigue, myalgia, and headache. Most of the reactions are mild to moderate and resolve in a few days without sequelae. Uncertainty: It is unknown whether vaccination with PXVX0317 has any adverse effects on pregnancy due to few pregnancies among the study participants.	The potential benefit of vaccination with PXVX0317 outweighs its risk.
Risk Management	The Applicant has proposed a postmarketing pharmacovigilance plan for routine safety monitoring and a pregnancy registry for postmarketing assessment of pregnancy outcomes.	The current pharmacovigilance plan and pregnancy registry would be adequate to monitor and manage the risks.

Source: Reviewer generated table
Abbreviations: CHIK=chikungunya; CHIKV=chikungunya virus; NHP=nonhuman primate; SNA=serum neutralizing antibody

11.2 Risk-Benefit Summary and 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% (Suhrbier, 2012). 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 98% of participants aged 12 to <65 years and 87% of participants aged ≥65 years achieved a CHIKV SNA titer ≥100 at 21 days after a single dose of PXVX0317, and the 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 endpoint of a CHIKV SNA titer ≥100, considered a surrogate marker reasonably likely to predict clinical benefit, was based on a passive transfer NHP challenge study in which NHPs were protected from CHIKV viremia. One nonclinical study in a NHP model (Pal, 2014) reported that a single dose of passively transferred CHIKV neutralizing antibodies completely prevented CHIKV viremia but did not prevent high CHIKV RNA levels (similar to control group) in joints, muscles, and lymph tissues. The required postmarketing confirmatory efficacy study is designed to address uncertainties in clinical benefit.

Risks of vaccination with PXVX0317 include local and systemic reactogenicity, but no treatment-related deaths, SAEs, or serious AESIs were identified.

The currently available data support a benefit-risk profile that is favorable for approving PXVX0317 for use in individuals 12 years of age and older under an accelerated approval pathway. Mitigation of the observed risks and uncertainties will be accomplished through labeling (including statements regarding uncertainties of the clinical benefit), the postmarketing pharmacovigilance plan, and through an adequate and well-controlled postmarketing confirmatory study to confirm clinical benefit. Please refer to section 11.5 for recommended labeling changes and section 11.6 for PMR and commitment studies.

11.3 Discussion of Regulatory Options

The Applicant is seeking accelerated approval of PXVX0317 for the indication of prevention of disease caused by CHIKV. Accelerated approval of PXVX0317 will require the Applicant to carry out a postmarketing confirmatory study to verify and describe the clinical benefit of PXVX0317 with due diligence (see section 11.6.1). Due to the unpredictability of CHIK outbreaks, the timeline for completion of such confirmatory studies could evolve.

11.4 Recommendations on Regulatory Actions

CHIK is generally considered a serious condition, and only one licensed vaccine is currently available to prevent CHIK and its clinical benefit is yet to be confirmed. A single dose of PXVX0317 induced a CHIKV SNA titer that is considered reasonably likely to predict a clinical benefit in 98% of those aged 12 to <65 years and 87% of those aged 65 years and older. The safety profile of PXVX0317 is considered acceptable. The data provided in this application support accelerated approval of PXVX0317.

Please refer to section 11.6 for recommended postmarketing actions to fulfill the regulatory requirement for approval under accelerated approval.

11.5 Labeling Review and Recommendations

Major recommendations for the package insert are summarized in Table 53.

Table 53. Updates to the USPI

Section	Approved Labeling
6	Presentation of comparative safety data from Studies 004 and 005 only, rather than pooled analyses. Descriptions of Studies 004 and 005. Presentation of unsolicited AEs. Presentation of new onset or worsening arthralgia that was medically attended and at least possibly related to the IP.
8.1	Description of additional details of rabbit DART study. Description of pregnancy registry. Description of Clinical Considerations including the impact of perinatal wild type CHIKV infection on neonatal outcomes.
8.5	Summary statement comparing safety and immunogenicity in participants aged 65 years and older to younger adults.

Section	Approved Labeling
14	Presentation of immunogenicity data from Studies 004 and 005 only, rather than pooled analyses. Presentation of seroresponse rate and GMT data at Day 22. Presentation of seroresponse rate data at Day 183.
17	Description of pregnancy registry information. Additional patient information regarding how the vaccine may not protect all vaccine recipients and that personal precautions are recommended to avoid mosquito exposures.

Source: Reviewer generated table
Abbreviations: AE=adverse event; CHIKV=chikungunya virus; DART=developmental and reproductive toxicology; GMT=geometric mean titer; IP=investigational product; USPI=United States prescribing information

11.6 Recommendations on Postmarketing Actions

11.6.1 Postmarketing Requirement Studies

Confirmatory Clinical Studies to Verify Clinical Benefit

In accordance with the accelerated approval regulations, adequate and well-controlled confirmatory studies to verify and describe clinical benefit must be conducted with due diligence to fulfill the regulatory requirements. The Applicant submitted a randomized, double-blind, placebo-controlled study protocol EBSI-CV-317-007 to verify clinical benefit. The evidence from this study will inform our postmarketing assessment of benefit-risk.

Study EBSI-CV-317-007 is a phase 3b randomized, double-blind, placebo-controlled study evaluating safety, efficacy, and immunogenicity of PXVX0317 in healthy adolescents and adults (≥12 years of age) with no history of CHIKV infection or vaccination. The primary objectives are to (1) evaluate vaccine efficacy of PXVX0317 (single dose 40/300µg) compared with placebo in the prevention of laboratory-confirmed acute CHIK (defined as fever; one more of arthralgia, myalgia, or rash; and RT-qPCR confirmation of CHIKV RNA), and (2) to evaluate the safety of PXVX0317. The study will enroll up to 6144 participants (randomized 1:1, stratified by age group [12 to <18, 18 to <46, 46 to <65, 65 to <75, and ≥75 years of age] and site) with 3072 participants per treatment group. Participants will be monitored for at least 6 months and up to 3 years. The study will be event-driven with a goal of 64 cases of laboratory-confirmed acute CHIK. The study will initially focus on multiple locations in arbovirus endemic regions in Thailand and the Philippines; if no or limited transmission is observed at the initial locations, additional locations in other regions will be considered. Of note, the study will include a “safety subset” in which 500 participants will be enrolled in an endemic region, regardless of baseline seropositivity and regardless of whether a CHIK outbreak is currently ongoing in that region; solicited ARs, unsolicited AEs, SAEs, MAAEs, and AESIs will be assessed in this safety subset, and will inform estimates of reactogenicity in baseline seropositive participants in an endemic region.

Clinical Reviewer Comment*: In a communication from CBER to the Applicant (sent 2022 September 19), CBER stated that “The regulations for the accelerated approval state that the PMR confirmatory study would usually be underway at the time of licensure; given the logistical challenges associated with a confirmatory study for a CHIK vaccine, we agree that the current and planned activities being conducted in support of the field efficacy program, and in preparation for the EBSI-CV-317-007 clinical trial, would address the expectation for conducting the confirmatory study with due diligence.”*

Comments regarding protocol EBSI-CV-317-007 were sent to the Applicant under IND 17998, including a review by CMC, Statistics, Digital Health Technology (DHT), and Real-World Evidence (RWE) consultants. The clinical comments addressed reporting of SUSARs, the number of participants to be randomized in each age strata, contraception requirements for participants, timing of safety visits, collection of MAAEs, reporting of arthralgia AEs, plans for interim analyses, analyses of ethnicity subgroups, matching by age in the correlate of protection subset, plans for addressing missing solicited AR data, tabulation of prior and concomitant medications, updates to the informed consent forms, feasibility assessments and milestones for completion, testing of participants with acute CHIK symptoms, exclusion of participants who are seropositive at baseline for chikugunya virus, and validation of the rapid diagnostic test. Responses from the Applicant were received in IND 17998 Amendments 134, 135, 138, and 139. These responses adequately addressed the clinical comments.

Pediatric Studies

According to the PREA (21 CFR 314.55(b) and 601.27(b)), the Applicant requested deferred pediatric studies for the pediatric population <12 years of age. The following proposed deferred pediatric studies are agreed upon by the Agency (presented at PeRC meeting 17 December 2024):

1. EBSI-CV-317-006: Safety and immunogenicity study in children (2 to <12 years of age)
2. EBSI-CV-317-009: Safety and immunogenicity study in neonates/infants (0 to <2 years of age)

11.6.2 Postmarketing Commitment Studies

Pregnancy Registry

Since the DART study conducted in rabbits showed an imbalance in rabbit kit survival through postnatal day 28, the clinical review team recommends a PMC study for pregnancy outcomes to address this potential safety concern. The Applicant proposes to conduct a five-year prospective observational pregnancy registry in the U.S. and European Union to evaluate the safety of the vaccine in at least 50 women exposed to the vaccine up to 28 days before conception or at any time during pregnancy ("VIMKUNYA Pregnancy Registry: An Observational Prospective Study of the Safety of VIMKUNYA Vaccine Exposure in Pregnant Women and their Offspring"). The pregnancy registry will collect pregnancy outcomes as well as outcomes in the offspring through one year of age. Please refer to the Office of Biostatistics and Pharmacovigilance (OBPV) review of the pregnancy registry PMC for details.

APPENDIX 1: SUMMARY OF SUPPORTIVE CLINICAL TRIALS

A1.1. Study PXVX-CV-317-001

Study Title: 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)

Study Period: 2018 Apr 18 – 2020 Sep 21

Study Sites:
- Alliance for Multispecialty Research, LLC (formerly The Center for Pharmaceutical Research LLC) (Site #9)
- Johnson County Clin-Trials (Site #13)
- Advanced Clinical Research, A Velocity Clinical Research Site (Site #33)

Study Objectives
Primary:
- To assess the induction of anti-CHIKV neutralizing antibody responses by different formulations and schedules at 28 days after the last injection (Day 57).
- To study the safety and tolerability of eight different formulations and dosing schedule combinations of PXVX0317 in healthy adults.

Secondary:
- To assess the kinetics of induction of anti-CHIKV neutralizing antibody responses by different formulations and schedules, measured from 7 days after the first injection (Day 8) to 28 days after the last injection (Day 57).
- To assess persistence of neutralizing antibody responses induced by different formulations and schedules, measured up to 731 days after the last injection (Day 760).

Exploratory:
- To assess cross-neutralizing antibodies to two CHIKV genotypes

Clinical Reviewer Comment*: Additional secondary and exploratory objectives were evaluated by the Applicant, but they are not discussed in this memo since they did not contribute to the risk-benefit assessment for the IP.*

Study Design
Study 001 was a phase 2 dose-finding, randomized, double-blind, parallel-group design with ten treatment groups. Individuals who were 18 to 45 years of age, generally healthy, and using contraception were eligible for enrollment. Except for the open-label Groups 9 and 10, eligible participants were randomized in a 1:1:1:1:1:1:1:1 ratio into one of eight treatment groups. Treatment groups are shown in Table 54. The open label groups were added to evaluate cellular immune responses and to provide anti-CHIKV antibodies for use in animal studies. The Applicant aimed to enroll 430 total participants. The maximum study duration for an individual participant was 760 days.

Participants received between one and three doses of PXVX0317 (which ranged from 6 to 40 µg VLP and included adjuvanted and unadjuvanted formulations) and/or placebo as an IM injection on study Days 1, 15, 29, and/or 547 as shown in Table 54.

Table 54. Planned Treatment Groups, Study 001

Treatment Group	N	Day 1 Dose (VLP/(b) (4) or Placebo)	Day 15 Dose (VLP/(b) (4) or Placebo)	Day 29 Dose (VLP/(b) (4) or Placebo)	Day 547 Dose (VLP/(b) (4) or Placebo)
1	50	20/unadjuvanted	Placebo	20/unadjuvanted	N/A
2	50	6/300	Placebo	6/300	N/A
3	50	10/300	Placebo	10/300	N/A
4	50	20/300	Placebo	20/300	40/300
5	50	Placebo	6/300	6/300	N/A
6	50	Placebo	10/300	10/300	N/A
7	50	Placebo	20/300	20/300	N/A
8	50	Placebo	Placebo	40/300	N/A
9[a]	20	20/300	N/A	20/300	N/A
10[a]	10	40/300	N/A	N/A	N/A
Total	430	-	-	-	-

Source: Adapted from PXVX-CV-317-001 Clinical Study Report Table 6
Abbreviations: N/A=not applicable; N=number of participants planned; VLP=viral like particle
Note: VLP and (b) (4) doses given in µg
[a]Open label group

Immunogenicity was measured via CHIKV neutralizing antibodies as determined by a luciferase-based assay (NT80), the same assay as was used in Studies 004 and 005. GMT was assessed between Days 1 through 760 postvaccination. The primary immunogenicity endpoint was CHIKV SNA GMT at Day 57 (28 days after the last injection) for each group. No success criteria were defined.

Safety monitoring was similar to that described for Trial #1 (in section 6.1.7) except for the following:

- Solicited ARs were collected for 7 days after each injection (as opposed to following a single injection) and an additional solicited AR of “malaise” was collected. In this study, “joint pain” was collected as a solicited AR rather than “arthralgia.”
- Unsolicited AEs were collected for 28 days following each injection.
- AESIs were not defined or captured.
- MAAEs were not defined or captured.
- AEs related to apheresis (plasmapheresis and leukapheresis) procedures were collected at the Day 57 and Day 182 visits for Group 9 and at Day 22 for Group 10.
- A medical monitor provided safety oversight for the study, and the medical monitor reviewed blinded study data and assessed causality of SAEs on an ongoing basis throughout the duration of the clinical study.
- MedDRA version 20.1 was initially used for coding AEs, but the AEs were re-coded to MedDRA version 24.1 at the time of BLA submission. Following the change in MedDRA version, safety analyses were repeated and re-presented in the addendum to the CSR.

Clinical Reviewer Comment*: This review will focus on the immunogenicity and safety data from study groups 8 and 10, since these participants received a single dose of 40/300µg PXVX0317, the to-be-licensed dose regimen.*

Study Participants

A total of 445 participants were enrolled across the 10 study groups: the median age was 31 years (range 18-45 years), and 259 (58%) participants were female. By race, 72% were White, 23% Black, 2% Asian, 2% Multiracial, 0.4% American Indian or Alaska

Native, and 0.4% Hawaiian/Pacific Islander. By ethnicity, 92% were Not Hispanic or Latino.

Participants enrolled and analyzed are presented in Table 55.

Clinical Reviewer Comment*: This study primarily enrolled young adults who are White and Not Hispanic or Latino. Slight imbalances in baseline demographics between some groups were likely due to the small sample size in each group.*

Table 55. Analysis Sets, Randomized Population, Study 001

Analysis Set	Group 1 (N=53) n (%)	Group 2 (N=52) n (%)	Group 3 (N=51) n (%)	Group 4 (N=50) n (%)	Group 5 (N=53) n (%)	Group 6 (N=53) n (%)	Group 7 (N=51) n (%)	Group 8 (N=52) n (%)	Group 9 (N=20) n (%)	Group 10 (N=10) n (%)	Total (N=445) n (%)
Randomized[a]	53 (100.0)	52 (100.0)	51 (100.0)	50 (100.0)	53 (100.0)	53 (100.0)	51 (100.0)	52 (100.0)	20 (100.0)	10 (100.0)	445 (100.0)
Exposed[b]	53 (100.0)	52 (100.0)	50 (98.0)	51 (102.0)	53 (100.0)	53 (100.0)	51 (100.0)	52 (100.0)	20 (100.0)	10 (100.0)	445 (100.0)
Safety[c]	53 (100.0)	52 (100.0)	50 (98.0)	51 (102.0)	53 (100.0)	53 (100.0)	51 (100.0)	52 (100.0)	20 (100.0)	10 (100.0)	445 (100.0)
mITT[d]	53 (100.0)	51 (98.1)	51 (100.0)	50 (100.0)	53 (100.0)	53 (100.0)	50 (98.0)	52 (100.0)	20 (100.0)	10 (100.0)	443 (99.6)
Immunogenicity Evaluable[e]	47 (88.7)	44 (84.6)	44 (86.3)	45 (88.2)	48 (90.6)	48 (90.6)	47 (92.2)	50 (96.2)	20 (100.0)	10 (100.0)	403 (90.6)
Immunogenicity Evaluable Boost	0	0	0	39 (78.0)	0	0	0	0	0	0	39 (8.8)
Safety Boost	0	0	0	42 (84.0)	0	0	0	0	0	0	42 (9.4)

Source: Adapted from PXVX-CV-317-001 Clinical Study Report Table 13
Abbreviations: %=n/N*100; mITT=modified intent-to-treat; N=number of participants in the treatment group; n=number of participants with the parameter
[a]Randomized population=All screened participants who provided informed consent and provided demographic and other baseline screening measurements who were randomized to Group 1 through 8 or assigned a study subject identification in open-label Group 9 or 10.
[b]Exposed population=All randomized participants who received at least one study vaccination. One participant was randomized in Group 3 but received the vaccination in Group 4 due to the dispensing error.
[c]Safety population=All participants in the exposed population who provided safety assessment data.
[d]mITT population=All participants in the randomized population who were treated and had evaluable immunogenicity results for baseline (Day 1) and at least one later on-study sample.
[e]Immunogenicity evaluable population=Participants in the exposed population who had no major protocol deviations or other reason to be excluded as defined prior to unblinding or analysis; received all three scheduled vaccinations through Day 29; had not received a prohibited medication; provided evaluable serum sample results for baseline, the relevant postvaccination time points, and within the required time frames (Group 1 through Group 8 only).

Immunogenicity Results

Primary Endpoint: Day 57 CHIKV SNA GMT Across Study Groups

At Day 57 (28 days after the last dose), the SNA GMTs ranged from 920.1 to 2057.0 across Groups 1-8 (Table 56). The GMT increased with increasing vaccine dose. The inclusion of the adjuvant resulted in higher GMTs after the first active vaccination (GMTs higher in Groups 4 and 7 than 1 after the first injection) but did not result in a significant increase in GMTs after the second dose (GMTs in Groups 2-8 were similar or lower than in Group 1 after the second active vaccination).

In Group 8, the GMT 28 days postvaccination was 1712.5 (95% CI 1330.0, 2205.0) which was not significantly different from the GMT in Group 1. In Group 10, the GMT 21 days postvaccination was 2687.3 (no comparison to Group 1 was made).

Table 56. CHIKV SNA GMT at Day 57 for Groups 1-9 and Day 22 for Group 10, IEP, Study 001

Variable	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9[b]	Group 10[b]
N	47	44	44	45	48	48	47	50	20	10
GMT[a]	2057.0	1116.2	1465.3	2023.8	920.1	1206.9	1562.8	1712.5	4197.4	2687.3
95% CI	[1584.8, 2670.0]	[852.5, 1461.4]	[1119.1, 1918.4]	[1550.5, 2641.7]	[710.9, 1190.9]	[932.4, 1562.2]	[1204.1, 2028.3]	[1330.0, 2205.0]	[2515.8, 7003.2]	[815.9, 8851.6]

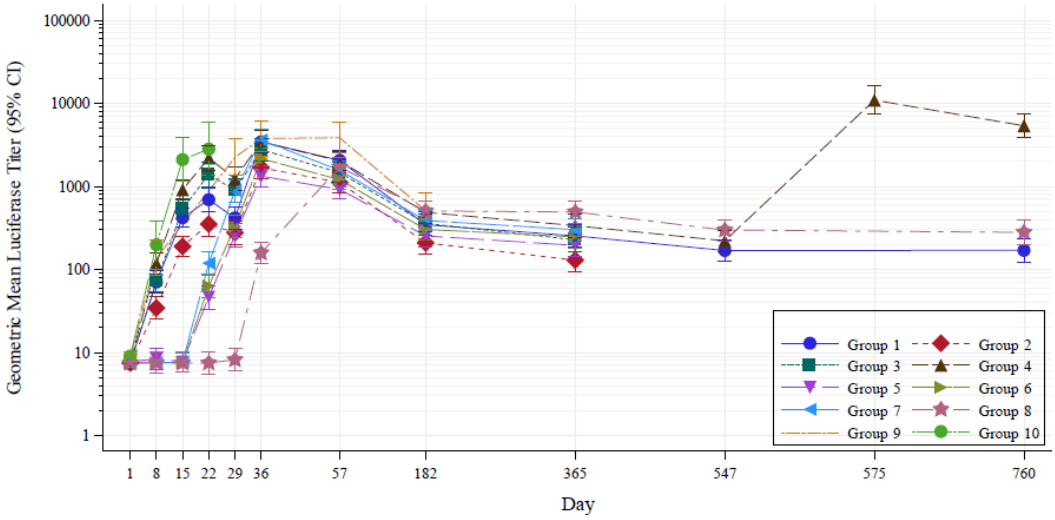
Source: Adapted from PXVX-CV-317-001 Clinical Study Report Table 15
Abbreviations: CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP=immunogenicity evaluable population; N=number of participants in the treatment group; SNA=serum neutralizing antibody
[a]GMT estimates, together with their 95% CIs, are derived from ANOVA model that includes site and treatment group as fixed effects, assuming normality of the log titers.
[b]No adjustment for Groups 9 and 10.

Clinical Reviewer Comment*: Subsequent to this study, an SNA GMT of ≥100 was chosen as the seroresponse threshold based on the results of a passive transfer study in NHPs (see section 4.3 for details); this threshold was considered conservative, since a titer >50 was predicted to result in >99% (95% CI: 81, 100) probability of protecting NHPs against viremia. In Study 001, all dose groups had GMTs ≥100, including Groups 8 and 10 (the to-be-licensed dose which contained the highest evaluated antigen content, 40 µg). Groups 8 and 10 achieved GMTs ≥100 at 28 and 21 days postvaccination, respectively.*

Secondary Endpoint: CHIKV SNA GMT at Days 1 Through 760

All dosage groups demonstrated similar GMT kinetics (see Figure 1) with GMT peaking at 21-28 days postvaccination. In Group 8, the GMT was 8.2 at Day 29 (day of active vaccination), 157.9 at Day 36 (7 days after active vaccination), 1712.5 at Day 57 (28 days after active vaccination), 505.7 at Day 182, 491.7 at Day 365, and 279.7 at Day 760.

Figure 1. CHIKV SNA GMT Between Day 1 and 760, IEP, Study 001



Source: PXVX-CV-317-001 Clinical Study Report Figure 8 (page 75)
Abbreviations: CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; IEP=immunogenicity evaluable population; SNA=serum neutralizing antibody

Clinical Reviewer Comment: *The secondary analyses show an SNA GMT ≥100 at 2 years post-vaccination with the to-be-licensed dose regimen. These data are referenced in the proposed USPI from the Applicant. Of note, however, these data are derived from 38 participants and a secondary endpoint with no placebo group. Accordingly, this reviewer recommends removal of these data from the USPI.*

Exploratory Post-hoc Endpoint: Cross-Neutralizing Antibodies to two CHIKV Genotypes

Per the response to IR #13 (Sequence 0015), the Applicant evaluated serum samples from the 20 participants who received two doses of 20/300µg PXVX0317 for their cross-neutralization activity (via FRNT) against (1) the Asian genotype RSU1 strain, (2) the ECSA genotype LR-2006 strain, and (3) the VLP parent West African genotype 37997 strain (Raju, 2023). On Day 1, neutralization was below detection limits for all but one participant who showed pre-existing CHIKV VLP binding IgG and low-level half maximal inhibition (EC50) values of ~150 - 400 depending on CHIKV strain. Day 29 sera showed a GMT of ~6800 against the VLP parent strain as well as the Asian and ECSA strain. Cross-neutralizing antibodies were detectable against all three strains in the Day 182 samples, with EC50 values for the parent strain of ~1000 and all values against the other strains at ~100 or above.

Safety Results

Overview of Adverse Events

An overview of AEs is provided in Table 57. A total of 292 (66%) participants reported at least one AE (solicited and/or unsolicited), with 60% reporting a solicited AR and 30% reporting an unsolicited AE.

Table 57. Overview of Adverse Events, Safety Population, Study 001

Event	Group 1 (N=53) n (%)	Group 2 (N=52) n (%)	Group 3 (N=50) n (%)	Group 4 (N=51) n (%)	Group 5 (N=53) n (%)	Group 6 (N=53) n (%)	Group 7 (N=51) n (%)	Group 8 (N=52) n (%)	Group 9 (N=20) n (%)	Group 10 (N=10) n (%)	Total (N=445) n (%)
Number of participants assessed	53	51	49	51	53	53	50	52	20	10	442
Any AR or AE[a]	34 (64.2)	38 (73.1)	37 (74.0)	35 (68.6)	31 (58.5)	30 (56.6)	34 (66.7)	37 (71.2)	12 (60.0)	4 (40.0)	292 (65.6)
Grade 3 or 4	0	5 (9.6)	9 (18.0)	6 (11.8)	4 (7.5)	2 (3.8)	3 (5.9)	6 (11.5)	0	0	35 (7.9)
Any solicited AR	25 (47.2)	36 (70.6)	36 (73.5)	34 (66.7)	29 (54.7)	26 (49.1	29 (58.0)	34 (65.4)	12 (60.0)	4 (40.0)	265 (60.0)
Grade 3 or 4	0	4 (7.8)	7 (14.3)	5 (9.8)	4 (7.5)	2 (3.8)	2 (4.0)	3 (5.8)	0	0	27 (6.1)
Any systemic solicited AR	21 (39.6)	24 (47.1)	25 (51.0)	30 (58.8)	20 (37.7)	18 (34.0	22 (44.0)	27 (51.9)	6 (30.0)	2 (20.0)	195 (44.1)
Grade 3 or 4	0	4 (7.8)	7 (14.3)	4 (7.8)	4 (7.5)	2 (3.8)	2 (4.0)	3 (5.8)	0	0	26 (5.9)
Any local solicited AR	19 (35.8)	27 (52.9)	23 (46.9)	29 (56.9)	18 (34.0)	18 (34.0)	18 (36.0)	26 (50.0)	10 (50.0)	2 (20.0)	190 (43.0)
Grade 3 or 4	0	0	0	1 (2.0)	0	0	0	0	0	0	1 (0.2)
Any unsolicited AE	19 (35.8)	19 (36.5)	12 (24.0)	17 (33.3)	14 (26.4)	11 (20.8)	18 (35.3	19 (36.5	3 (15.0)	1 (10.0)	133 (29.9)
Grade 3 or 4	0	3 (5.8)	6 (12.0)	2 (3.9)	0	0	2 (3.9)	4 (7.7)	0	0	17 (3.8)
Any treatment-related unsolicited AE	4 (7.5)	3 (5.8)	2 (4.0)	3 (5.9)	2 (3.8)	1 (1.9)	4 (7.8)	3 (5.8)	0	0	22 (4.9)
Grade 3 or 4	0	0	0	0	0	0	0	0	0	0	0
Any SAE	0	1 (1.9)	2 (4.0)	1 (2.0)	0	0	2 (3.9)	3 (5.8)	0	0	9 (2.0)
Permanently discontinued study due to AE	0	0	1 (2.0)	0	0	0	0	0	0	0	1 (0.2)
Died during study	0	0	0	0	0	0	0	0	0	0	0

Source: Adapted from PXVX-CV-317-001 Clinical Study Report Table 22, Response to IR #17 Table 14.3.1
Abbreviations: %=n/N*100; SAE=serious adverse event; AE=adverse event; AR=adverse reaction; N=number of participants in the treatment group; n=number of participants with events
Note: Percentages for solicited ARs are based on number of participants assessed in each treatment group. Percentages for unsolicited events are based on the total number participants in the safety population in each treatment group.
[a]Inclusive of both solicited adverse reactions and unsolicited adverse events.

Deaths

No deaths occurred during this study.

Nonfatal Serious Adverse Events

Nonfatal serious AEs were reported by a total of 9 (2%) participants across groups including three participants (6%) in Group 8 and no (0%) participants in Group 10. The 12 SAEs among 9 participants were assessed as not likely to be related to the IP by the Applicant and by this reviewer. The SAE PTs included: thyroid cartilage fracture (n=1); anaphylaxis to nuts (n=1); acute gastroenteritis and hyperemesis gravidarum (both in same participant, n=1); threatened preterm labor, vaginal bleeding, placental abruption (all in same participant, n=1); ruptured appendix (n=1); pneumonia (n=1); biliary dyskinesia (n=1); incomplete abortion (n=1); and motor vehicle accident (n=1).

Solicited Adverse Reactions

Solicited ARs following any injection were reported by 40-74% of participants across groups, with 65% of participants in Group 8 and 40% of participants in Group 10 reporting solicited ARs. Across groups, most solicited ARs were mild or moderate, with 3 participants (6%) in Group 8 reporting a grade 3 solicited AR and no participants in Group 10 reporting a grade 3 or higher solicited AR.

In Group 8, the median duration of solicited AR symptoms was 2 days (range 1-8 days). In Group 10, the median duration of solicited AR symptoms was 3 days (range 2-5 days).

Unsolicited Adverse Events

In total, 133/445 (30%) participants reported at least one unsolicited AE through Day 57. The most common PTs were upper respiratory tract infection (5%), injection site bruising (2%), and gastroenteritis (2%). The majority of unsolicited AEs were mild or moderate, with grade 3 or higher unsolicited AEs reported by 17 (4%) participants. Four participants (8%) in Group 8 and no (0%) participants in Group 10 experienced a grade 3 or higher unsolicited AE. The Group 8 severe unsolicited AEs included one participant each with upper abdominal pain, biliary dyskinesia, heat illness, pneumonia, and muscle spasms. The Applicant assessed 22 (5%) participants as having experienced a treatment-related unsolicited AE through Day 57, none of which were grade 3 or higher.

Medically Attended Adverse Events

MAAEs were not captured in this study.

Arthralgia

Prespecified AESIs were not collected during the study, however joint pain and arthralgia were noted among IP-exposed participants:

- Solicited joint pain: Six (12%) participants in Group 8 and 1 (10%) participant in Group 10 reported joint pain; none of these events were severe. Across all groups, after any injection, a total of 5 (1%) participants reported severe joint pain.
- Unsolicited arthralgia: Arthralgia was reported as an unsolicited AE by two participants (0.4%) across all groups through Day 57.

Dropouts and/or Discontinuations

One participant experienced an AE leading to withdrawal (worsening nephrocalcinosis), which the Applicant and this reviewer assessed as unlikely to be related to the IP.

Clinical Reviewer Comment*: Safety analyses stratified by demographic subgroups were not performed by the Applicant and are not included in this memo due to the small sample sizes after stratification.*

Conclusions

Immunogenicity

- At Day 57 (28 days after the last vaccine dose), the SNA GMTs ranged from 920.1 to 2057.0 across Groups 1-8.
- In Group 8 (single dose of 40/300µg), the GMT at Day 57 (28 days postvaccination) was 1712.5 (95% CI: 1330.0, 2205.0). In Group 10 (single dose of 40/300µg), the GMT at Day 22 (21 days postvaccination) was 2687.3. In the reference group (Group 1, where participants received two doses of unadjuvanted 20µg VLP), the Day 57 (28 days following the last vaccine dose) GMT was 2057.0 (95% CI: 1584.8, 2670.0).
- At Day 760 (2 years after the final dose), the GMT in Group 8 was 279.7 (95% CI: 200.1, 391.1) (N=38).

Safety

- Overall, 292/445 (66%) participants experienced any AE, including solicited ARs.
- Solicited ARs following any injection were reported by 40-74% of participants across groups, with 65% of participants in Group 8 and 40% of participants in Group 10 reporting solicited ARs.
- Solicited local ARs:
    - Solicited local ARs were reported by 20%-57% of participants across groups following any injection, with one event (0.2%) being graded as severe.
    - A total of 26 (50%) participants in Group 8 and 2 (20%) participants in Group 10 reported solicited local ARs; all were mild or moderate in severity.
- Solicited systemic ARs:
    - Solicited systemic ARs were reported by 20%-59% of participants across groups following any injection, with 26 (6%) reporting severe systemic ARs.
    - A total of 27 (52%) participants in Group 8 and 2 (20%) participants in Group 10 reported solicited systemic ARs; three (6%) severe systemic solicited ARs were reported in Group 8 and none (0%) in Group 10.

- Unsolicited AEs through Day 57 were reported in 30% of participants.
- No deaths occurred during the study.
- Nonfatal SAEs were reported by 2% of participants (12 SAEs in 9 participants). No treatment-related SAEs were reported.

Clinical Reviewer Comment*: The results from this phase 2 study demonstrated that a single dose of 40/300µg PXVX0317 with adjuvant was immunogenic: The group receiving a single dose of adjuvanted 40µg VLP showed an initial response similar to the 20µg doses (with or without the adjuvant) but had more durable neutralizing antibodies over the two years of follow-up. The GMTs in Groups 8 and 10 (who received the to-be-licensed dose regimen) were ≥100 at 28 and 21 days postvaccination, respectively, (the threshold that was later selected to mark seroresponse). Additionally, in general, the safety profile of PXVX0317 was favorable with no deaths and no treatment-related SAEs. The safety profile of a single dose of 40/300µg PXVX0317 was not meaningfully different than other dosages or regimens evaluated in this study. Given its preferable immunogenicity, a single dose of 40/300µg was selected for late phase trials.*

A1.2. Study EBSI-CV-317-002

Study Title: 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

Study period: 2019 Nov 20 – 2021 Jan 19

Study Sites
- US Army Medical Research Institute of Infectious Diseases (USAMRIID) immunization clinic
- Walter Reed Army Institute of Research (WRAIR) clinical trials center

Study Objectives

Safety objective
- Evaluate the safety of PXVX0317 when administered to prior alphavirus vaccine recipients versus sex and age-matched controls.

Immunogenicity objectives

Primary:
- Evaluate the neutralizing antibody response to CHIKV induced by PXVX0317 when administered to prior alphavirus vaccine recipients versus sex- and age-matched controls.

Secondary:
- Evaluate the overall antibody responses to CHIKV and Venezuelan equine encephalitis virus (VEEV) induced by vaccination with PXVX0317 when administered to prior alphavirus vaccine recipients versus sex and age-matched controls.

Exploratory:

- Evaluate for cross-neutralization to four additional CHIKV strains via PRNT assay: 181/25, 15561, LR, and PM2951.

Clinical Reviewer Comment*: Additional exploratory objectives were included in this study, but they are not described in this memo since they do not contribute meaningfully to the benefit-risk assessment of the IP.*

Study Design

Study 002 was a phase 2, parallel-group, age- and sex-matched, open-label study in healthy adults 18-65 years of age. A total of 60 participants were enrolled, 30 of whom had previously received an investigational heterologous alphavirus vaccine (termed "alphavirus-experienced") and 30 age- and sex-matched participants to serve as alphavirus-naïve controls (termed "alphavirus-naïve"). All alphavirus-experienced recipients were enrolled at the USAMRIID immunization clinic, while all alphavirus-naïve controls were enrolled at the WRAIR clinical trials center. The alphavirus-experienced participants had previously received vaccination against VEEV (either TC83 or TC84), Eastern Equine Encephalitis and/or Western Equine Encephalitis.

Participants were administered PXVX0317 40µg VLP/300µg alum adjuvant as a single 0.8 mL dose IM in the deltoid muscle.

Immunogenicity was measured via CHIKV neutralizing antibodies as determined by a luciferase-based assay (NT80), the same assay as was used in Studies 004 and 005. GMTs, GMT ratios, and seroconversion rates were assessed, where seroconversion was defined by a 4-fold rise over baseline in CHIKV SNA. Immunogenicity to VEEV was measured via PRNT assay.

Safety monitoring included collecting local and systemic solicited ARs through Day 8 (pain, redness, and swelling at the injection site, as well as fever, fatigue, chills, malaise, headache, myalgia, arthralgia, and nausea), unsolicited AEs through Day 29, and SAEs through the end of study (Day 182).

Clinical Reviewer Comment*: The Applicant does not have a record of the specific prior VEEV vaccination provided to the alphavirus-experienced participants, nor does the Applicant have a record of whether other alphavirus vaccines were administered to the alphavirus-experienced participants. As such, there may be heterogeneity in the baseline alphavirus immunity that is not characterized or described, which in turn, creates limitations for the interpretation of the PXVX0317 immune response in the alphavirus-experienced participants.*

Study Participants

A total of 60 participants were enrolled: the median age was 47 years (range 27-64 years), and 67% were male. By race, 67% were White, 23% Black or African American, 7% Asian, and 3% Multiple races. The majority (95%) were Not Hispanic or Latino. The median time since prior alphavirus vaccine was 16 years (range 1-37 years) in the alphavirus-experienced group.

Immunogenicity Results

All participants (100%) in both groups (alphavirus-experienced and alphavirus-naïve) developed a 4-fold or greater rise in SNA titer between baseline (Day 1 vaccination day) and Day 22 (Table 58).

Alphavirus-experienced participants showed a more rapid rise in GMT following PXVX0317 administration than the alphavirus-naïve group, as there was a statistically significant difference in GMTs between the alphavirus-experienced (271.9) and alphavirus-naïve (87.5) group at Day 8. The GMTs of both groups peaked at Day 22 and were similar on Day 22 (2032.5 in alphavirus-experienced, 2299.2 in alphavirus-naïve participants) and all subsequent visits.

PXVX0317 vaccination had no impact on anti-VEEV neutralizing activity in both alphavirus-experienced and alphavirus-naïve participants (Table 58).

Table 58. Neutralizing Antibody Titers Against CHIKV and VEEV at Days 1 and 22, Study 002

Parameter	Alphavirus-Experienced (N=30)	Alphavirus-Naïve (N=30)
Anti-CHIKV seroresponse rate[a], n/N % (95% CI)	-	-
Day 1	ref	ref
Day 22	30/30 100 (88.6, 100.0)	30/30 100 (88.6, 100.0)
Anti-CHIKV GMT NT80 (95% CI)[b]	-	-
Day 1	9.21 (7.80, 10.87)	7.69 (N/E, N/E)
Day 22	2032.45 (1412.95, 2923.56)	2299.18 (1598.09, 3307.84)
Anti-VEEV PRNT neutralizing antibody titer (95% CI)	-	-
Day 1	449.82 (262.84, 769.80)	9.96 (N/E, N/E)
Day 22	467.95 (278.47, 786.34)	9.89 (N/E, N/E)

Source: Adapted from EBSI-CV-317-002 Clinical Study Report Tables 10 and 15
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; N/E=not estimable; N=number of participants per in the group; n=number of participants with parameter; PRNT=plaque reduction neutralization test; ref=reference; VEEV=Venezuelan Equine Encephalitis Virus
[a]Seroresponse rate was defined as a 4-fold or greater rise in neutralizing antibody titers compared to Day 1
[b]GMT point estimates and 95% CIs are based on an ANOVA model with log10-transformed titer as the dependent variable, and study group, age, and sex as predictors.

***Clinical Reviewer Comment**: Results of anti-VEEV PRNT and ELISA analyses show discordant responses in that a significant change in the ELISA total IgG level following PXVX0317 was observed but no significant change in the PRNT SNA titers following PXVX0317 administration was seen. Per the CMC Reviewer and the Applicant (IR #25), it is conceivable that PXVX0317 may only affect total IgG while not impacting SNA titers, but further study would be needed to fully understand the impact of PXVX0317 on the anti-VEEV antibody response.*

Regarding anti-CHIKV immunogenicity, prior alphavirus vaccination does not appear to interfere with, nor potentiate, the generation of CHIKV neutralizing antibodies following PXVX0317 administration.

In CSR Addendum 2 (Table 59), serum samples collected from vaccinated participants were tested for cross-neutralization to four additional CHIKV strains via PRNT assay (since the luciferase neutralization assay is specific to the 181/25 CHIKV genotype). The additional strains included: 181/25 (derivative of Thailand/Asian genotype AF15561), 15561 (Thailand/Asian genotype), LR (French Indian Ocean lineage), and PM2951 (Senegal/West African genotype). At Day 22, GMTs for strains 181/25, 15561, LR, and PM2951 were 584, 551, 905, and 2584, respectively, and a seroresponse (defined by a titer ≥20 for this PRNT analysis) was seen in 100% of participants. At Day 182, PRNT50 GMTs for strains 181/25, 15561, LR, and PM2951 were 204, 184, 148, and 686, respectively, and seroconversion was 100% for strains 181/25 and PM2951, 98% for 15561, and 95% for LR. For all strains, at both Day 22 and Day 182, alphavirus-naïve participants had a higher GMT than the alphavirus-experienced recipients, though in some instances, the difference was small.

Table 59. Day 22 CHIKV Seroresponse Rate and PRNT50 Titers Against Heterologous CHIKV Strains, Study 002

Virus Strain Cohort	Seroresponse Rate[a] n/N % (95% CI)	GMT PRNT50 (95% CI)[b]
CHIKV-PM2951	-	-
Alphavirus-naïve	30/30 100 (88.6, 100.0)	3300.79 (2227.43, 4891.37)
Alphavirus-experienced	30/30 100 (88.6, 100.0)	2022.85 (1195.54, 3422.65)
CHIKV-15561	-	-
Alphavirus-naïve	30/30 100 (88.6, 100.0)	701.97 (430.52, 1144.56)
Alphavirus-experienced	30/30 100 (88.6, 100.0)	432.11 (259.03, 720.85)
CHIKV-181/25	-	-
Alphavirus-naïve	30/30 100 (88.6, 100.0)	654.96 (353.28, 1214.26)
Alphavirus-experienced	30/30 100 (88.6, 100.0)	519.84 (367.21, 735.91)
CHIKV-LR	-	-
Alphavirus-naïve	30/30 100 (88.6, 100.0)	1436.75 (1015.36, 2033.02)
Alphavirus-experienced	30/30 100 (88.6, 100.0)	570.18 (350.77, 926.81)

Source: Adapted from EBSI-CV-317-002 Addendum Tables 14.2.6.1 and 14.2.6.2
Abbreviations: %=n/N*100; CHIKV=chikungunya virus; CI=confidence interval; GMT=geometric mean titer; N=number of participants per group; n=number of participants with parameter; PRNT=plaque reduction neutralization titer
[a]Seroresponse defined by serum neutralizing antibody titers ≥20.
[b]GMT point estimates, together with their 95% CIs, are based on an ANOVA model with log10-transformed titer as the dependent variable, and study group, age, and sex as predictors.

Safety Results

A total of 17 (57%) participants in both groups (alphavirus-experienced and alphavirus-naïve) reported an AE during the study, with 2 (7%) participants in the alphavirus-naïve group reporting a grade 3 or higher AE.

Deaths

No deaths occurred during the study.

Nonfatal SAEs

One participant (3%) in the alphavirus-naïve group reported an SAE (USUBJID (b) (6) a 45-year-old male with a history of chronic right foot pain due to a history of fracture/dislocation injury of the foot who developed worsening of chronic right foot pain at 6 months postvaccination). This event was assessed by the Applicant as not related to the IP.

Clinical Reviewer Comment*: This reviewer concurs that this SAE is unlikely to be related to the IP given the chronic nature of the foot pain and the lack of temporal relationship to symptom worsening (6 months postvaccination).*

Solicited ARs

A total of 28 (47%) participants reported solicited ARs, with a numerically higher percentage of alphavirus-experienced participants (53%) having solicited ARs than alphavirus-naïve participants (40%). Two participants in the alphavirus-naïve group (7%) reported three grade 3 solicited ARs (one each of headache, myalgia, and fatigue).

Systemic solicited ARs were reported by 18 (30%) participants (8 [27%] in alphavirus-experienced and 10 [33%] in alphavirus-naïve), with two (7%) in the alphavirus-naïve group being grade 3 (one each of headache, myalgia, and fatigue). Overall, headache (18%) and myalgia (18%) were the most frequently reported systemic solicited ARs.

Local solicited ARs were reported by 22 (37%) participants (13 [43%] in alphavirus-experienced and 9 [30%] in alphavirus-naïve), with one (3%) of the alphavirus-naïve participants reporting grade 3 injection site pain. The most common local AR was injection site pain, which was reported by 43% of the alphavirus-experienced and 30% of the alphavirus-naïve participants.

The median duration of solicited AR symptoms was 2 days (range 1-2 days).

A total of 6 (10%) participants reported solicited arthralgia (3 [10%] in each group); all events were mild or moderate in severity.

Unsolicited AEs

A total of 10 (17%) participants reported an unsolicited AE (3 [10%] alphavirus-experienced, 7 [23%] alphavirus-naïve), none of which were grade 3 or higher. The most common SOC was Investigations (n=3, 5%). The Applicant assessed that 3 (5%) participants had a total of four unsolicited AEs that were vaccine-related (1 [3%] alphavirus-experienced, 2 [7%] alphavirus-naïve): one each of dizziness, injection site bruising, lethargy, night sweats, and paresthesia.

With regard to Musculoskeletal and connective tissue disorders, one participant in the alphavirus-naïve group (2%) reported mild neck pain.

AESIs and *MAAEs* were not captured or reported in this study.

Clinical Reviewer Comment*: No clinically meaningful difference in the rates of AEs among alphavirus-experienced and alphavirus-naïve participants were observed, though the number of participants is small and definitive conclusions cannot be drawn.*

Conclusions

Safety
- No deaths or vaccine-related SAEs were reported.
- 28/60 (47%) participants reported solicited ARs (18 [30%] with systemic ARs, 22 [37%] with local ARs), including 2 (3%) participants who reported a grade 3 solicited AR.
- 10/60 (17%) participants reported unsolicited AEs, none of which were grade 3 or higher.
- No clinically significant difference in AE incidence was observed between the alphavirus-exposed and alphavirus-naïve groups.

Immunogenicity
- Alphavirus-experienced participants had an earlier rise in GMT following PXVX0317 than alphavirus-naïve participants, with a statistically significant difference in GMTs between the groups at Day 8. The GMTs of both groups peaked at Day 22 and were similar on Day 22 and at all subsequent visits.
- PXVX0317 vaccination had no impact on anti-VEEV neutralizing antibodies in the alphavirus-experienced and alphavirus-naïve groups.
- PXVX0317 vaccination resulted in cross-neutralization of four additional CHIKV strains (181/25, 15561, LR, and PM2951).

A1.3. Study EBSI-CV-317-010

Study title: A Phase 2 Open-Label Study to Assess the Safety and Immunogenicity of PXVX0317 (Chikungunya Virus Virus-Like Particle Vaccine [CHIKV VLP], alum adjuvanted)

Study period: 2021 Oct 11 – 2022 May 05

Study site: Johnson County ClinTrials

Study Objectives

Primary objectives
- To assess the induction of CHIKV SNA responses following a single dose of PXVX0317 (40µg CHIKV VLP adjuvanted with 300µg aluminum hydroxide) as measured 21 days after vaccination (Day 22).
- To assess the induction of CHIKV SNA following a single dose of PXVX0317 as measured 7 days (Day 8), 14 days (Day 15), and 56 days (Day 57) after vaccination.

Secondary objective
- To assess the safety of a single dose of PXVX0317 in healthy adults.

Exploratory objectives

- To obtain plasma and sera at Days 22 and 57 from participants immunized with a single dose of PXVX0317 to support nonclinical studies.

Clinical Reviewer Comment*: Additional exploratory objectives were defined but are not discussed in this memo since they did not contribute significantly to the benefit-risk assessment.*

Study Design

Study 010 was an open-label, single-arm phase 2 study in healthy adults 18 to 45 years of age. A total of 25 participants from a single center were enrolled.

Participants were administered PXVX0317 40/300µg as a single 0.8 mL dose IM in the deltoid muscle.

Immunogenicity was measured via CHIKV SNA as determined by a luciferase-based assay (NT80, the same assay used in Studies 004 and 005) as well as binding IgG and IgM antibodies by ELISA. GMT and seroresponse rates were assessed, where seroresponse was defined by a titer ≥40.

Safety monitoring included collecting local and systemic solicited ARs through Day 8 (pain, redness, and swelling at the injection site, as well as fever, fatigue, chills, headache, myalgia, arthralgia, and nausea), unsolicited AEs through Day 29, and SAEs through the end of study (Day 183). AESIs (defined as new onset or worsening arthralgia that was medically attended) were collected for all participants from Day 1 through the end of study (Day 183). AEs related to plasmapheresis procedures were collected at the Day 22 and Day 57 visits.

Study Participants

A total of 25 participants were enrolled: the median age was 34 years (range 25-44 years), and 56% were female. By race, 60% were White, 32% Black or African American, 4% Asian, and 4% Multiracial. By ethnicity, 96% were Not Hispanic or Latino.

Immunogenicity Results

At baseline (Day 1), none of the participants had detectable CHIKV SNA titers. At Day 22, 25/25 (100%) participants had a seroresponse with a GMT of 2365.2 (95% CI 1625.0, 3442.4). At Day 57, 24/24 (100%) participants continued to have a seroresponse (GMT 1069.7, 95% CI: 720.2, 1588.9). All participants had SNA titers ≥100 by Day 15, which persisted through Day 57.

Safety Results

A total of 17 (68%) participants reported an AE during the study with 3 (12%) reporting a grade 3 or higher AE.

Deaths

No deaths occurred during the study.

Nonfatal SAEs

No nonfatal SAEs occurred during the study.

Solicited ARs

A total of 17 (68%) participants reported solicited ARs, with two participants (8%) reporting grade 3 or higher solicited ARs.

Fourteen participants (56%) reported local solicited ARs, all of which were injection site pain and none of which were severe.

Twelve participants (48%) reported a systemic solicited AR, two of whom (8%) reported a total of three severe systemic ARs. The severe systemic ARs included fatigue (n=2), chills (n=1), and myalgia (n=1). The most commonly reported systemic solicited ARs of any severity were fatigue (n=8, 32%), headache (n=7, 28%) and myalgia (n=5, 20%).

A total of two (8%) participants reported solicited arthralgia, with both cases assessed as mild.

Unsolicited AEs

A total of eight participants (32%) reported unsolicited AEs with one (4%) participant experiencing a grade 3 AE (anaphylaxis to ibuprofen). The most common unsolicited AEs included presyncope (n=3, 12%), vessel puncture site bruise (n=2, 8%), dizziness (n=2, 8%), and rhinorrhea (n=2, 8%). Two presyncope events, one mild and one of moderate intensity, occurred in two participants (8.0%) within 30 minutes of plasmapheresis. The Applicant assessed that three participants (12%) had treatment-related unsolicited AEs (dizziness, hot flushes, and rhinorrhea), none of which were severe.

Regarding Musculoskeletal and connective tissue disorders, one participant (4%) reported mild myalgia.

Clinical Reviewer Comment*: The case narrative for the participant with anaphylaxis was reviewed and consistent with a hypersensitivity reaction to ibuprofen. This reviewer assessed the AE as unlikely to be related to the IP.*

AESIs

No AESIs were reported during the study.

MAAEs

Three participants (12%) reported MAAEs, including one participant who experienced presyncope during a scheduled study visit. The other two cases included sinusitis and anaphylaxis to ibuprofen. All MAAEs were assessed as not treatment-related by the Applicant.

Conclusions

Immunogenicity

- At Day 22, 25 (100%) participants had a seroresponse (defined by SNA titer ≥40) with a GMT of 2365.2.
- At Day 57, 100% of participants had ongoing evidence of a seroresponse (GMT 1069.7).
- All participants had SNA titers ≥100 by Day 15, which persisted through Day 57.

Safety

- No deaths or SAEs were reported.
- 17/25 (68%) participants reported solicited ARs (12 [48%] systemic ARs, 14 [56%] local ARs), including 2 (8%) with grade 3 or higher solicited ARs.
- 8/25 (32%) participants reported unsolicited AEs, with one (4%) being grade 3 or higher.
- No AESIs were reported.
- 3/25 (12%) participants reported MAAEs, none of which were assessed by the Applicant to be related to the vaccine.