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Statistical Analysis Plan: Protocol 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

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SAP Version	Date
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Summary of Changes

Version	Summary of Major Change(s) and Impact	Revision Date
Version 1.0	First approved version of SAP.	22-MAR-2022
Version 2.0	Updated to correspond to Protocol Amendment 6.0: changed threshold to [redacted], removed references to FDA and EMA, removed hierarchy on coprimary endpoints, designated hierarchical secondary endpoints as key, added success criterion at Day 15, simplified the "other titers" secondary endpoint to ≥15 and 4-fold rise only, added EMA definition of seroresponse rate as the presumptive seroprotection rate, and updated "CHIKV-luc assay anti-CHIKV SNA NT_{80}" to "anti-CHIKV human SNA assay." Made minor edits for consistency. Removed statement that randomization number is hidden. Updated coding dictionary versions. Added clarification that participants missing Day 1 SNA are excluded from IEP. Added analysis visit windows for SNA to mitigate the risk of data entered in an incorrect visit in the database. Added specification for listing of participants not meeting randomization criteria to be programmed from protocol deviations and not (original) entry criteria CRF. Added new AESI table including solicited events, added age strata to selected AE tables, and added new listing of AEs during acute observation period. Removed Appendix III and text referring to MedDRA SMQ. Excluded from tables solicited events starting after Day 8 and those AEs starting past Day 29 that are not SAEs, AESI, or MAAEs. Excluded postdose vital signs fever from solicited AEs.	31-MAR-2023

	Added discussion of screen failure participants and empty participant identifiers.	

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List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
CHIKV	Chikungunya Virus
CI	Confidence Interval
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
e-diary	Electronic Diary
EDC	Electronic Data Capture
EOS	End of Study Visit
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GMFI	Geometric Mean Fold Increase
GMT	Geometric Mean Titer
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEP	Immunogenicity Evaluable Population
IM	Intramuscular
IP	Investigational Product
LLOQ	Lower Limit of Quantification
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified Intent-to-Treat
mL	milliliter(s)
mm	millimeter(s)
NT_{80}	80% Neutralizing Titer
PT	Preferred Term
PXVX0317	Vaccine Investigational Product
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

SDTM	Standard Data Tabulation Model
SMC	Safety Monitoring Committee
SNA	Serum Neutralizing Antibody
SOC	System Organ Class
TFL	Tables, Figures, and Listings
US	United States
VLP	Virus-like Particle
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol 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" (Version 6.0 date 31-MAR-2023). This document specifies details of the definitions of the derived variables, analysis methods, assumptions, and data handling conventions. The document is accompanied by mock-up tables, figures, and listings (TFL shells). Some further details on the calculation of derived variables are provided as programmer's notes in the TFL shells. The TFL shells serve only as a guide for programming the final TFL. They are working documents and can be updated as needed.

2 PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Coprimary Objectives

- To compare the anti-chikungunya virus (CHIKV) serum neutralizing antibody (SNA) response to PXVX0317 and placebo at Day 22, as measured by geometric mean titer (GMT) and clinically relevant difference in seroresponse rate (PXVX0317 minus placebo) in adults ≥65 years of age.

Note: Seroresponse rate (considered the presumptive seroprotection rate) is defined as the percentage of participants who achieve an anti-CHIKV SNA titer [redacted].

- To evaluate the safety of PXVX0317 in adults ≥65 years of age.

2.1.2 Secondary Objectives

- To compare the anti-CHIKV SNA response to PXVX0317 and placebo at Day 15 and Day 183, as measured by GMT and seroresponse rate.
- To compare the anti-CHIKV SNA response to PXVX0317 and placebo in participants ≥65 to <75 and ≥75 years of age as measured by GMT and seroresponse rate.

2.1.3 Exploratory Objective

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

2.2 Study Design and Conduct

This is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study with two treatment groups. This multicenter study is conducted in the US with up to 10 sites. At least 400 enrolled healthy US participants ≥65 years of age and older are enrolled, stratified in two age subgroups (≥65 to <75 and ≥75 years of age) with a target of 25% enrollment of participants ≥75 years of age. Participants are randomized in a 1:1 ratio to receive either a

single intramuscular (IM) dose of PXVX0317 or placebo at Day 1. With 400 participants enrolled, the treatment group totals are estimated as follows:

- Group 1- PXVX0317: n=200
- Group 2- Placebo: n=200

The per participant estimated total study duration is 212 days (including screening). The screening window is no greater than 30 days prior to Day 1 (randomization and administration of investigational product [IP]). Screening assessments include informed consent, review of eligibility criteria, medical history, prior and concomitant medications, demography, physical examination including height and weight for body mass index calculation, vital signs, urine toxicology screening per investigator's discretion, and viral markers for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) and human immune deficiency virus 1 and 2 (HIV-1/HIV-2).

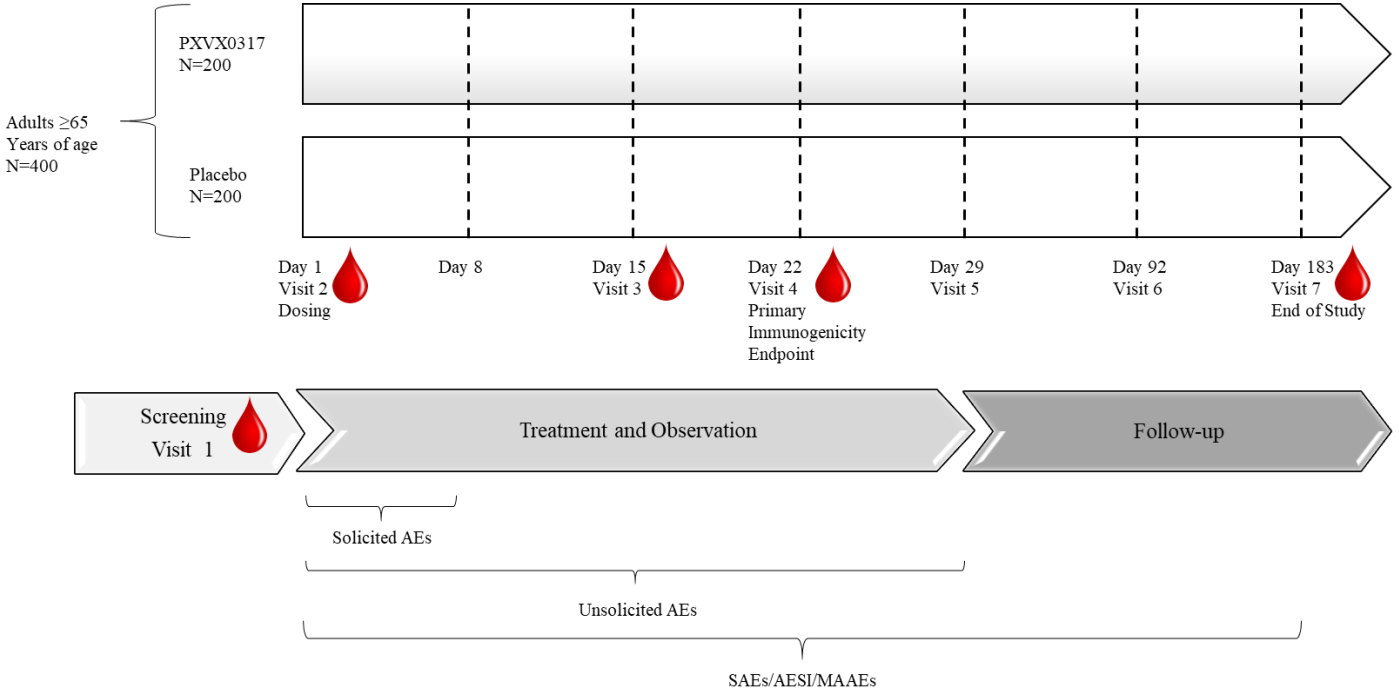
Prior to IP administration on Day 1 (baseline), eligibility, medical history and concomitant medications are reviewed, and a baseline anti-CHIKV SNA sample is drawn. Vital signs including blood pressure, heart rate, respiratory rate and temperature are taken on Day 1 before and after IP administration. Directed physical examinations are performed if indicated at Days 1, 15, 22 and Day 183 End of Study Visit (EOS). The immune response to PXVX0317 is measured by anti-CHIKV SNA at Day 15, Day 22 (coprimary endpoints are at Day 22) and Day 183 EOS (or at Early Discontinuation/ Withdrawal). No safety laboratory samples are collected as part of the study.

There is a safety and immunogenicity preliminary analysis on data for all participants through the Day 29 Visit to facilitate health authority pre-submission preparation. The analyses are performed by an unblinded third-party vendor and results are reported to the Sponsor only at the treatment group summary level, preserving the double-blind status on the participant level. No p-value penalty is assessed because the Day 22 primary immunogenicity endpoint data are final at the time of preliminary analysis and no action regarding the study is made based on these findings. The Sponsor, participants, and site personnel are not unblinded until all follow-up visits are completed for the study through Day 183 EOS and the database is locked.

Solicited adverse events (AEs) are collected from IP administration until Day 8 using an electronic diary (e-diary) or paper diary. Severity and relationship of solicited AEs are assessed by the investigator in the same manner as unsolicited AEs. Unsolicited AEs (AEs not listed in the diary) are collected from Day 1 through 28 days post-vaccination. Serious adverse events (SAEs), adverse events of special interest (AESI; see Section 6.3 for definition), and medically attended AEs (MAAEs) are collected for all participants from Day 1 through Day 183 EOS. Telephonic visits occur at Days 29 and 92 to evaluate unsolicited AEs (Day 29 only), MAAEs, SAEs, and AESI and to review concomitant medications.

Refer to Figure 1, Schematic Diagram of Study Design, and Figure 2, Schedule of Events.

Figure 1 EBSI-CV-317-005 Schematic Diagram of Study Design



Note: Days 29 and 92 are phone call follow-ups.

Figure 2 Schedule of Events

	Screening Visit 1	Day 1 Visit 2	Day 15 Visit 3	Day 22 Visit 4	Day 29 Visit 5 (phone)	Day 92 Visit 6 (phone)	Day 183/Early Discontinuation[k] Visit 7
Window (days)	**Within 30 days of Day 1**	**0**	**-1/+3**	**-1/+3**	**±1**	**±3**	**-14/+7**
Written informed consent	X						
Eligibility criteria	X	X[a]					
Demographics	X						
Medical history[b]	X	X[a,c]					
Vital signs[d]	X	X[e]					
Physical examination	X[f]	X[a,f]	X[f]	X[f]			X[f]
Viral marker testing (HIV-1/2, anti-HCV[g], HBsAg)	X						
Randomization		X[a]					
Administration of IP		X					
Diary or memory aid (electronic or paper) training and device distribution[h]		X[a]					
Acute observation[i]		X					
Diary or memory aid (electronic or paper) collection and review			X				
Investigator assessment of reactogenicity			X				
Unsolicited AEs		X	X	X	X		
SAEs		X	X	X	X	X	X
AESI and MAAEs		X	X	X	X	X	X
Concomitant medications	X	X[a]	X	X	X	X[j]	X[j]
Blood for CHIKV SNA		X[a]	X	X			X
Blood for testing against CHIKV genotypes		X[a]		X			X

	Screening Visit 1	Day 1 Visit 2	Day 15 Visit 3	Day 22 Visit 4	Day 29 Visit 5 (phone)	Day 92 Visit 6 (phone)	Day 183/Early Discontinuation[k] Visit 7

[a] To be done prior to IP administration.
[b] To include any history or current presence of joint pain.
[c] To be updated if necessary.
[d] Vital signs include temperature, heart rate, blood pressure, respiratory rate. Height and weight will be obtained at the screening visit only for BMI calculation. Vitals signs should be measured after at least five minutes of rest. Oral temperature should be measured.
[e] To be taken before and after IP administration. Vital signs will be performed prevaccination and 30 minutes to one-hour postvaccination on Day 1.
[f] Complete physical exam at screening and then targeted exams or per PI discretion at other visits.
[g] If HCV antibody is positive HCV ribonucleic acid (RNA) testing can be performed.
[h] Smart phone (e-Diary), paper diary (memory aid), digital thermometer, and ruler will be provided.
[i] Participants will be monitored by study staff for signs of an acute adverse reaction for at least 30 minutes after injection.
[j] Concomitant medications associated with SAEs/AESI/MAAEs only.
[k] For EDV occurring within seven days postvaccination, from 7 to 21 days postvaccination, or ≥22 days postvaccination, the Visit 3, Visit 4, or Visit 7 schedule will be followed, respectively.

2.3 Randomization and Blinding

2.3.1 Method of Randomization

Participants are randomized on Day 1 following confirmation of eligibility and immediately prior to IP administration. Study personnel randomize the participant within the electronic data capture (EDC) system, and a randomization number is generated from the EDC randomization module. The EDC randomization module matches the randomization number to an IP kit available at the site and informs the study personnel of the assigned kit. Study personnel use the appropriate kit for administration to the participant.

Participants are considered enrolled once a randomization number has been assigned within the EDC system. The study is conducted as a double-blind study through Day 183 EOS. The participants, site personnel (including the investigator) and the Sponsor do not know participants' individual treatment assignments until all participants have completed their participation in the study through the Day 183 EOS and the database has been cleaned and locked.

2.3.2 Randomization Errors

A *misrandomization* is defined as a participant receiving a study treatment other than the one assigned by randomization.

A *stratification error* occurs when a participant is randomized based on incorrect stratification information at Day 1 (baseline) or if a participant is mistakenly put into a wrong block.

In either case, the participant uses up one position in the assigned block and randomization continues. Both misrandomization and stratification errors are reported as protocol deviations.

2.3.3 Blinding and Unblinding

Study participants, the investigator, and study site personnel remain blinded to all randomization assignments throughout the study. Sponsor’s Medical Monitor and personnel who are in regular contact with the study site and/or involved with documentation associated with the study remain blinded to all participant randomization assignments.

Only the unblinded third-party vendor is unblinded to produce preliminary safety and immunogenicity analyses through the Day 29 Visit for all participants. Results are reported to the Sponsor only at the treatment group summary level, preserving the double-blind status on the participant level for the duration of the study.

The following safeguards are employed to reduce the risk of inadvertent unblinding:

- Use of a standardized pre-filled syringe and injection volume for all injections.
- All PXVX0317 and placebo syringes have a semi-transparent barrel cover to mask any difference in appearance between placebo and PXVX0317.

- No Sponsor personnel has access to the randomization schedule. No site personnel have access to treatment assignments. The Randomization and Trial Supply Management component of the vendor EDC system allows for unblinding of individual participants in an emergency by the investigator. The investigator must attempt to notify the Sponsor's Medical Monitor prior to unblinding and must notify the Medical Monitor within 24 hours after unblinding at the latest. If the investigator is unable to access the vendor EDC system, then the Medical Monitor may assist by calling the vendor EDC helpline for emergency unblinding. Emergency unblinding is documented as a protocol deviation.
- Assays are run in a blinded manner. The assay titer results are not delivered to the Sponsor data management and analysis team until after database lock, as they are potentially unblinding. However, unblinded assay titer results are delivered to the third-party vendor for all participants through the Day 29 Visit for preliminary safety and immunogenicity analyses.
- Should any participant or site personnel become inadvertently unblinded, the investigator promptly (within 24 hours of their awareness of the error) discloses the event to the Sponsor's Medical Monitor in a blinded fashion (disclosing only participant number, not treatment) so that corrective action can be initiated. The unblinding sequence of events is documented and retained as source documents. A protocol deviation is entered in the electronic case report form (eCRF).

Refer to the separate Blind Maintenance Plan for further details.

As noted above, the third-party vendor responsible for preliminary safety and immunogenicity analyses receives both unblinded participant randomization assignments and unblinded assay titer results for all participants through the Day 29 Visit. This vendor is independent from the Sponsor and is instructed to maintain the Sponsor's blind. The Sponsor, participants, and site personnel are not unblinded at the participant level until all follow-up visits are completed for the study through Day 183 EOS.

An individual participant is considered to have completed study participation after completion of the Day 183 EOS and any required safety follow-up. Upon completion of the study for all participants, the study database is cleaned and locked per the Sponsor's standard operating procedures. Unblinding occurs per the Sponsor's standard operating procedures after the SAP is finalized and approved and the database is locked. The Sponsor completes an unblinding request form, approved by the study statistician and medical/scientific reviewer and sends the completed and approved form to the EDC vendor to request release of the randomization assignments to the Sponsor for final analysis.

3 STUDY ENDPOINTS

3.1 Immunogenicity Endpoints

3.1.1 Coprimary Immunogenicity Endpoints

- Difference in anti-CHIKV SNA seroresponse rate (PXVX0317 minus placebo) and associated 95% confidence interval (CI) at Day 22.

Note: Seroresponse rate (considered the presumptive seroprotection rate) is defined as the percentage of participants who achieve an anti-CHIK SNA titer [redacted].

- Anti-CHIKV SNA GMT and associated 95% CIs at Day 22 for PXVX0317 and placebo.

Each endpoint is summarized for both age strata pooled and for individual age strata, as well as by sex and by race group (white and non-white) and ethnicity group (Hispanic or Latino and Not Hispanic or Latino).

3.1.2 Secondary Immunogenicity Endpoints

- **Key Secondary Immunogenicity Endpoints:** Difference in anti-CHIKV SNA seroresponse rate (PXVX0317 minus placebo) with associated 95% CI at Day 15 and Day 183, in that order.
- Anti-CHIKV SNA GMTs by study arm with associated 95% CIs at Day 15 and Day 183.
- Geometric mean fold increase (GMFI) in anti-CHIKV SNA titer from baseline (Day 1) to Days 15, 22 and 183.
- Number and percentage of participants with an anti-CHIKV SNA titer ≥15 and 4-fold rise over baseline at Days 15, 22 and 183.

Each endpoint is summarized for both age strata pooled and for individual age strata.

3.1.3 Exploratory Immunogenicity Endpoint

- Geometric mean titers and associated two-sided 95% CIs for neutralizing antibodies against various CHIKV genotypes measured at Day 22 (and at baseline if necessary) for a subset of participants in the PXVX0317 group.

3.2 Safety Endpoints

- Incidence of solicited AEs through Day 8 for PXVX0317 and placebo.
- Incidence of unsolicited AEs through Day 29 for PXVX0317 and placebo.
- Incidence of AESI and SAEs and MAAEs through Day 183 for PXVX0317 and placebo.

3.3 Pharmacokinetic Endpoints

Not applicable.

3.4 Pharmacodynamics Endpoints

Not applicable.

3.5 Exploratory Endpoint

See Section 3.1.3.

4 POWER AND SAMPLE SIZE CONSIDERATIONS

4.1 Sample Size and Power for Immunogenicity

Based on the data from the Phase 2 study (protocol PXVX-CV-317-001), the seroresponse rate for PXVX0317 vaccine is expected to be approximately [redacted] versus <5% for the placebo participants. With an assumed 10% rate of non-evaluable participants, the power to show superiority over placebo with 180 PXVX0317 vaccine and 180 placebo evaluable participants is >99.9% for the combined age groups.

The difference in seroresponse rate between PXVX0317 and placebo groups that is considered clinically relevant is [redacted]. With 180 baseline seronegative PXVX0317-treated participants and a target seroresponse rate of [redacted] vs. a rate of 5% for placebo, the width of a two-sided 95% CI would be ±5.4%. If the target PXVX0317 seroresponse is [redacted], the width would be ±6.9%. Therefore, the difference in seroresponse rates must be above [redacted] for the lower bound of the 95% CI for the difference to be [redacted].

5 DATA CONSIDERATIONS

5.1 Participant Screening

5.1.1 Screen Failure Participants

A note to file was generated for this study to document that no data collection conventions were prespecified for screen failure participants. The only data domains considered necessary for screen failure participants are demographics, eligibility criteria, and disposition data.

5.1.2 Rescreening and Empty Participant Identifiers

The study protocol states that rescreened participants should use the original participant identifier. However, in some cases, sites rescreened participants with a new participant identifier number. Once data were consolidated for rescreened participants into the participant identifier used for randomization, an empty participant identifier resulted. In other cases, extra participant identifier numbers were generated inadvertently. These blank identifiers were not deleted from the study database for technical reasons. A note to file was written for this study to specify that participant identifiers empty of data (i.e., blank participant IDs) would not be mapped to SDTM nor included in any clinical study report analyses.

5.2 Protocol Deviations

A deviation occurs when site personnel or a participant does not adhere to the protocol's stipulated requirements, whether inadvertently or planned. All identified protocol deviations are documented (entered by the monitor in EDC) and classified by category and type (important/not important). In addition, nonoverlapping programmatic checks for protocol deviations are run by both the Sponsor and the EDC vendor. Programmatically identified

protocol deviations are also entered/uploaded to the EDC and classified by category and type (important/not important).

5.2.1 Important Deviations

Important protocol deviations are defined by ICH E3 (ICH, 1996) as those "that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being". Examples of important protocol deviations include:

- Participants who were enrolled/randomized but did not meet study eligibility criteria.
- Participants randomized but not treated.
- Participants with misrandomization or stratification errors.
- Participants who received a prohibited prior or concomitant medication or vaccine.
- Participants who previously received an investigational CHIKV vaccine/product, including but not limited to prior vaccination in EBSI-CV-317-004.
- Other deviations from key study procedures such as accidental unblinding or participant noncompliance with assessment of primary outcome measures (e.g., missing serum samples, significantly out of window assessments).

5.2.2 Reporting of Protocol Deviations

All protocol deviations are contained in the Study Data Tabulation Model (SDTM) datasets. Protocol deviations assessed as important are tabulated by treatment group and listed by participant for the randomized population (see Section 7.2).

Deviations excluding participants from any analysis population are finalized prior to unblinding. Reasons for exclusion from analysis populations are summarized by treatment group for all randomized participants and listed by participant.

5.3 Analysis Populations

Analyses are based on the following study populations:

Randomized Population: All screened participants who provide informed consent and provide demographic and other screening measurements and are randomized (i.e., have a randomization number assigned within the EDC system). Most baseline summaries and the IP administration summary use the randomized population.

Exposed Population: All participants in the randomized population who receive IP.

Safety Population: All participants in the exposed population who provide safety assessment data. This generally includes any participant who was not lost to follow-up at Day 1 (baseline), as they are at risk for reporting an SAE. Participants are analyzed as treated (i.e., according to the treatment a participant received, rather than the treatment to which the participant was randomized). All safety analyses use the safety population.

Modified Intent-to-Treat (mITT) Population: All randomized participants who are vaccinated and have at least one post-injection anti-CHIKV human SNA assay result. Participants are counted in the group to which they were randomized. Primary and secondary immunogenicity analyses are repeated for the mITT population as a measure of robustness of the results.

Immunogenicity Evaluable Population (IEP): The IEP includes all participants in the mITT population who:

- Provide evaluable serum sample results for the relevant post-vaccination time points, and within the required time frames:
  - Day 22: Day 19 through Day 27, inclusive.
- Have no measurable (≥LLOQ) anti-CHIKV human SNA assay titer at Day 1 (baseline), i.e., seronegative at baseline. Note that participants with missing Day 1 (baseline) are excluded from IEP.
- Have no important protocol deviation deemed exclusionary or other reason to be excluded as defined prior to unblinding.

The IEP is the primary population for all immunogenicity analyses.

CHIKV Genotype Subset: The CHIKV genotype subset includes those IEP participants who received PXVX0317 and are selected for genotype analysis. See Section 8.4.3 for details.

5.4 Analysis Groups

Tables are displayed by treatment group (PXVX0317 and placebo) columns and overall, for selected tables only.

5.5 Analysis Time Points

For immunogenicity analyses, anti-CHIKV SNA samples are collected at Day 1 (baseline), Day 15 (-1/+3 days), Day 22 (-1/+3 days) and Day 183 EOS (-14/+7 days). For IEP membership, Day 22 has a wider window of Day 19 through Day 27, inclusive. For the time points other than the primary analysis (Day 22), all available data are included in the summaries according to the analysis set defined for a participant's inclusion.

Immunogenicity data are checked and, if another visit or unscheduled sample collection occurred closer to the nominal study day than the scheduled sample collection entered as the nominal visit, the visit data are replaced by the closer visit data when the analysis visit is assigned. In other words, the labeled database visit may not match the derived analysis visit; this procedure is necessary to mitigate the risk of data entered in an incorrect visit in the database. See also Section 5.7 describing handling of multiple sample collections in an analysis window.

Otherwise, unscheduled visit data are not presented in the by-visit summary analyses but are included in the summary tables by maximum toxicity grade or abnormality when applicable, and in data listings by participant.

5.6 Definition of Baseline

For all analyses, the baseline value for each measure is defined as the last non-missing value prior to IP administration. Note that, for some participants for whom randomization system errors delayed randomization by one calendar day, procedures performed the day before Day 1 were considered acceptable without being repeated on the actual Day 1.

5.7 Multiple Records in an Analysis Window

If more than one sample is collected for anti-CHIKV human SNA assay assessment for a given time point, the sample closest to the nominal time point is used for analysis tabulations. If there is a tie (i.e., the two samples are an equidistant number of days from the nominal time point), then the geometric mean of the two titers is used for analysis tabulations. All samples are reported with database visit and analysis visit in data listings by participant.

5.8 Coding Dictionaries

Medical history and AEs are coded to system organ class (SOC) and preferred term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 24.1.

Prior and concomitant medications and vaccines are coded according to the World Health Organization's (WHO) WHODrug Global Dictionary version C32021 to Anatomical Therapeutic Chemical (ATC) classification and preferred drug name.

5.9 Adverse Event Toxicity/Severity Grading

With the exception of redness and swelling, all solicited AEs are graded by the investigator according to severity grading scales from "mild" to "potentially life-threatening." The severity of redness and swelling, recorded as a diameter (mm) in the solicited adverse event diary, are summarized according to categories based on the largest-diameter linear measurement when a local reaction is present:

- Grade 0/absent = 0-24 mm.
- Grade 1/mild = 25-50 mm.
- Grade 2/moderate = 51-100 mm.
- Grade 3/severe = >100 mm.
- Grade 4/potentially life threatening = necrosis or exfoliative dermatitis.

Events reported as not present (0 mm is entered) are reported as Grade 0. Similarly, body temperatures recorded by the participant that are below 100.4° result in fever reported as Grade 0/absent.

Solicited AEs other than redness and swelling and unsolicited AEs are graded by the investigator for severity. The severity grading scales (Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = potentially life-threatening) that are used for safety assessment in this study are provided in Appendix I of this document and the protocol, based on the *FDA*

Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (2). Note that AEs that result in death are classified as Grade 4 and indicated as resulting in death.

6 STATISTICAL CONSIDERATIONS

6.1 Statistical Considerations

Data summaries are tabulated by appropriate grouping for each analysis population as specified in Section 5.4.

Continuous endpoints are summarized by descriptive statistics including number of non-missing observations (n), mean, SD, median, minimum, and maximum. In the analysis of the anti-CHIKV SNA data as a continuous variable, anti-CHIKV SNA values are logarithmically transformed (base10), and the GMTs and associated 95% CI for each treatment group are computed by exponentiating the corresponding log-transformed means and two-sided 95% CIs. Categorical variables are summarized by frequency counts (n) and percentages of participants (%) in each category, including missing or unknown when appropriate.

Unless otherwise specified, CIs and hypothesis tests are two-sided with 95% confidence (or one-sided with 97.5% confidence).

The reporting conventions to be applied to all tables, listings and figures are included in a living document that accompanies the table and listing shells. All derivations, statistical analyses, summaries, and listings are generated using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, United States).

6.1.1 Seroresponse Rates

The superiority of the immune response to PXVX0317 vaccine over that to placebo is demonstrated at Day 22 by comparing seroresponse rates between the two treatment groups (the percentage of participants with an anti-CHIKV human SNA assay titer [redacted], considered the presumptive seroprotection rate). Percentages of participants with anti-CHIKV SNA [redacted] seroresponse rate and secondary response rates at ≥15 and 4-fold rise over baseline are reported with associated two-sided 95% Wilson score method CIs (keyword /BINOMIAL (WILSON) on tables statement). The difference in seroresponse rates between the PXVX0317 and placebo groups is calculated, along with the 95% CI for the difference based on the Newcombe hybrid score method (keyword /RISKDIFF (CL=NEWCOMBE)). The lower bound of the two-sided 95% CI on the difference in seroresponse rates between PXVX0317 and placebo must be [redacted]. Additionally, the null hypothesis of no difference between seroresponse rate percentages is tested using a two-sided chi-square test with alpha=0.05. No multiplicity adjustment is employed, and no covariate adjustment is performed. See Section 6.4 for statistical hypothesis, Section 6.9 for multiplicity considerations, and Section 8.4.1.1 for analysis outputs

Identical methods will be used for treatment group comparison of seroresponse rates at Days 15 and 183.

6.1.2 Geometric Mean Titers and Geometric Mean Fold Increase

The superiority of PXVX0317 vaccine immunogenicity over that of placebo is explored further by comparing Day 22 GMTs derived from a linear model with a one-sided alpha=0.025. The primary model is an analysis of variance (ANOVA), with log_{10}-transformed anti-CHIKV SNA titers (log_{10}) as the dependent variable and treatment group and study site as the fixed effects in the model. No interaction term is used. The adjusted least square means and their 95% CIs calculated based on the ANOVA are back transformed and reported as the group GMT values. No adjustment for multiplicity is applied. See Section 6.4 for statistical hypothesis, Section 6.9 for multiplicity considerations, and Section 8.4.1.2 for analysis outputs. Identical methods are used for treatment group comparison of GMTs at Days 15 and 183.

Geometric mean fold increase (GMFI) from baseline (Day 1) to Days 15, 22 and 183 is calculated using the difference from Day 1 in log_{10}-transformed titers as the dependent variable in the ANOVA model. The adjusted least square means and their 95% CIs calculated based on the ANOVA are back transformed and reported as the group GMFI values. The median, minimum and maximum titers and fold-increases are based on the non-transformed scale.

6.2 Units and Precision

No intermediate rounding is performed in SDTM datasets; only final values for TFLs are rounded as follows. Immunogenicity titers are reported with one decimal place or two significant digits (e.g., 0.032, 18.0). Ratios of GMTs are presented with two decimal places.

Vital sign data are reported using standard international units. Vital signs variables including derivations thereof are reported to the same precision as the source data. Parameters derived directly from source data (e.g., minimum, maximum) or first-order statistics (e.g., mean) are reported and analyzed with the same precision as the source data. Second-order statistics (e.g., SD) are reported with one more significant digit than the source data. Percentages are reported to one decimal place.

6.3 Derived Variables

This section provides definitions of the derived variables. In some cases, the definitions are provided in the relevant sections as noted.

AE, causing study discontinuation, is defined as a Yes response to the corresponding question on the AE eCRF.

AE, medically attended (MAAE), is defined as a Yes response to the corresponding question on the AE eCRF.

AE, related, is defined as one that is “probably” or “possibly” related to IP per investigator assessment on the eCRF. If the relationship is missing for one or more occurrences of an AE for a given participant, the closest relationship of the remaining occurrences of the AE for that participant is used; if the relationship is missing for the only occurrence of an AE for a given participant, then that event is assumed to be related in order to be conservative.

AE, resulting in death, is defined as a Yes response to the corresponding question on the AE eCRF and/or a fatal outcome.

AE, serious, is defined per the derived eCRF field for AE seriousness, based on the individual criteria that make an AE qualify as serious (results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect, or any event that may require medical or surgical intervention to prevent one of these outcomes).

AESI is defined in this study as new onset or worsening arthralgia that is medically attended, as noted by an AE having a Yes response to the corresponding AESI question on the AE eCRF.

AE, severity, is graded Grade 1 (mild) to Grade 4 (potentially life-threatening) as described in Section 5.9. If the severity is missing for one or more occurrences of an AE for a given participant, the maximum severity of the remaining occurrences of the AE for that participant is used; if the severity is missing for the only occurrence of an AE for a given participant, then that event is assumed to be severe in order to be conservative.

AEs, solicited, are defined as those collected in the electronic e-diary or paper diary. Solicited AEs include local (i.e., pain, redness, and swelling) and systemic reactions (i.e., fever, chills, fatigue, headache, myalgia, arthralgia, and nausea). ***Solicited AEs were to be entered on Day 1 through Day 8; solicited AEs starting on Day 9 or later will be excluded from tabulations, with the exceptions of AESI and SAEs (see Section 9.2.2 for solicited events collection details).***

The denominator for solicited AE tables comprises only those participants with at least one diary observation (i.e., any non-missing values but excluding "Not done/unknown"), at least one diary observation for a given symptom, or at least one diary observation for a given day, as applicable. ***Note that an elevated in-clinic temperature assessment as part of 30-min post-vaccination vital signs does not count as a solicited AE, as vital signs data are summarized separately.***

AE, treatment emergent. AE collection begins at Day 1 (baseline), the day of IP administration. AEs occurring after a participant has given informed consent, but before vaccination, are excluded from summaries. Only treatment-emergent AEs are summarized.

AEs, unsolicited, are defined as those AEs not listed in the e-diary or paper diary but collected in the EDC. ***Unsolicited AEs were to be collected though Day 29 unless they were SAEs, AESI, or MAAEs; unsolicited AEs starting on Day 30 or later that are not SAEs, AESI, or MAAEs are excluded from tabulations (see Section 9.2.2 for solicited vs. unsolicited events).***

Age at screening visit is automatically calculated by EDC based on date of birth versus date of informed consent. Age at baseline (Day 1) is be summarized in all outputs.

Age group strata are defined as ages ≥65 to <75 and ≥75 years as randomized. Note that, if a participant is randomized into a stratum and their age is later corrected such that they

should have been placed into a different age stratum, the participant is analyzed according to the corrected age stratum for immunogenicity analyses.

Analysis visits are defined in Section 5.5.

Analysis populations are defined in Section 5.3.

Baseline is defined in Section 5.6. Change from baseline is defined as (value at post-baseline assessment – value at baseline).

Baseline seropositive rate is defined as the percentage of participants with anti-CHIKV human SNA assay titer ≥LLOQ prior to IP administration.

Body mass index at screening visit is automatically calculated by EDC as a participant's weight in kg divided by height in m^2.

Anti-chikungunya virus (anti-CHIKV) human SNA assay NT_{80} (80% neutralizing titer) is defined as the dilution factor that corresponds to an 80% reduction of luciferase activity compared to virus-only control. Anti-CHIKV SNA titer values below LLOQ are replaced by LLOQ/2 in the immunogenicity analyses including GMT and GMFI. For the 4-fold rise over Day 1 (baseline), values below the LLOQ are replaced with the LLOQ.

Completion of study for an individual participant is defined as completion of the Day 183 EOS and any required safety follow-up (i.e., a disposition status of completed).

Early discontinuation for an individual participant is defined as completion of the Early Discontinuation/ Withdrawal Visit (i.e., a disposition status other than completed).

Enrolled/randomized is defined as receipt of a randomization number assignment within the EDC system.

Medical history items entered on the medical history eCRF are considered to predate the study regardless of onset date.

Medication, concomitant, is defined as one taken after start of IP administration on Day 1 (baseline) through the end of study. For analysis purposes, any medication which is ongoing or with a stop date that is on or after the start date of IP administration is categorized as a concomitant medication. Partial or missing concomitant medication start and/or end date are imputed according to Section 6.5.2.

Medication, prior, is defined as one with a stop date within 30 days prior to the screening visit (90 days for blood products) through the start of IP administration on Day 1 (baseline).

Protocol deviations are defined by inclusion in the EDC protocol deviation module (participant-level only, not site-level), including monitor-identified deviations as well as Sponsor- and EDC system-identified programmatic deviations. Protocol deviations are classified by category and type (important/not important).

Randomized participant not meeting entry criteria is defined using the protocol deviation dataset and not just the inclusion exclusion criteria dataset, because a project team decision was made to keep the inclusion exclusion criteria as entered at the time of randomization even if the participant was later found to have violated entry criteria. These violations are recorded as protocol deviations.

Rounding of values is described in Section 6.2.

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

Study Day 1 is defined as the day of IP administration on Day 1 (baseline). The day prior to Day 1 is Day -1. There is no Day 0. If the participant is not treated, then the Day 1 (baseline) is defined as the day of randomization.

Study day relative to Day 1 are calculated as:

- **Study Day** = (assessment date – date of Day 1 + 1) if the assessment is on or after Day 1.
- **Study Day** = (assessment date – date of Day 1) if the assessment is before Day 1.

For conversion of durations, 1 year = 365.25 days and 1 month = 365.25/12 = 30.4375 days.

Subgroups for sex (male and female), race (white and non-white) and ethnicity (Hispanic or Latino and Not Hispanic or Latino) are defined based on the corresponding demographic questions. Participants missing sex, race or ethnicity will be omitted from analyses by subgroup. Participants with "Not Reported" or Unknown" ethnicity are not included in ethnicity subgroups.

Summary statistics are described in Section 6.1.

Time duration (in days) between event A and event B is (date of event B – date of event A + 1). For conversion of durations, 1 year = 365.25 days and 1 month = 365.25/12 = 30.4375 days.

Treatment, actual, is defined as the treatment administered to the participant by the site (i.e., corresponding to the kit number used).

Treatment group is defined as PXVX0317 vaccine vs. placebo.

Treatment, randomized, is defined as the treatment assigned to the participant by the EDC (i.e., corresponding to the kit number assigned).

6.4 Statistical Hypotheses

6.4.1 Coprimary Immunogenicity Endpoints

The study is a multicenter, randomized, two-arm, active-controlled study to evaluate PXVX0317 vaccine vs. placebo. A successful trial means success on each of the coprimary endpoints: seroresponse (H_{A1}) and GMT (H_{A2}), both at Day 22 using the IEP. Statistical hypotheses for each of these endpoints are discussed in turn in this section. The familywise error rate is fixed at a two-sided alpha of 0.05 by the requirement that both coprimary endpoints must be met for a successful outcome.

In standard statistical notation, the null and alternative hypotheses are:

H_0: H_{A1} not met or H_{A2} not met

H_A: H_{A1} met and H_{A2} met

where H_{A1} and H_{A2} are the alternative hypotheses for each of the coprimary endpoints as defined below in this section.

The first coprimary endpoint is the treatment group-specific estimates and difference between treatment groups in anti-CHIKV SNA seroresponse rates using a titer of [redacted] at Day 22 in the IEP for both age strata pooled and is tested in two ways. First, the lower bound of the Newcombe hybrid score method two-sided 95% CI on the difference in seroresponse rates between PXVX0317 and placebo must be [redacted]. Secondly, the null hypothesis of no difference between seroresponse rate percentages is tested using a two-sided chi-square test with alpha=0.05. In standard statistical notation, the null and alternative hypotheses for the first coprimary endpoint are as follows:

H_{01}: ($P_{PXVX0317} - P_{placebo}$) [redacted] or ($P_{PXVX0317} - P_{placebo}$) ≤ 0 using a two-sided chi-square test

H_{A1}: ($P_{PXVX0317} - P_{placebo}$) [redacted] and ($P_{PXVX0317} - P_{placebo}$) >0 using a two-sided chi-square test

where $P_{PXVX0317}$ is the percentage of PXVX0317 participants and $P_{placebo}$ is the percentage of placebo participants with seroresponse at a titer of [redacted] at 21 days after vaccination in the IEP for both age strata pooled.

The second coprimary endpoint tests for a significant difference in treatment group-specific Day 22 GMTs in the IEP for both age strata pooled, as derived from a one-sided alpha=0.025 ANOVA with $\log_{10}$-transformed anti-CHIKV SNA titers ($\log_{10}$) as the dependent variable and treatment group and study site as the fixed effects. The adjusted least square means and their 95% CIs calculated based on the ANOVA are back transformed and reported as the group GMT values. In standard statistical notation, the null and alternative hypotheses are:

H_{02}: ($GMT_{PXVX0317} - GMT_{placebo}$) ≤ 0

H_{A2}: ($GMT_{PXVX0317} - GMT_{placebo}$) >0

where $GMT_{PXVX0317}$ is the GMT 21 days after vaccination for IEP participants in both age strata pooled.

6.4.2 Key Secondary Immunogenicity Endpoints

A prespecified hierarchical approach is employed for the seroresponse key secondary immunogenicity endpoints to preserve the type I error rate without the need for further multiplicity adjustment. If the null hypotheses are rejected for both coprimary endpoints, only then are the key secondary endpoints for the seroresponse rate difference (H_{A3}) at Days 15 and 183 tested sequentially, in that order, each for the IEP across both age groups combined. At Days 15 and 183, the endpoint is tested for the success criterion of superiority to placebo using a two-sided chi-square test with alpha=0.05. When a nonsignificant test is reached formal testing stops, and the remaining endpoints are reported for information only.

1. Day 15 seroresponse at a titer of [redacted], including superiority to placebo.
2. Day 183 seroresponse at a titer of [redacted], including superiority to placebo.

In standard statistical notation, the null and alternative hypotheses are:

H_{03}: ($P_{PXVX0317} - P_{placebo}$) ≤ 0 using a two-sided chi-square test for Day 15 and ($P_{PXVX0317} - P_{placebo}$) ≤ 0 using a two-sided chi-square test for Day 183

H_{A3}: ($P_{PXVX0317} - P_{placebo}$) >0 using a two-sided chi-square test for Day 15 and ($P_{PXVX0317} - P_{placebo}$) >0 using a two-sided chi-square test for Day 183

After testing the coprimary immunogenicity endpoints and, if both met, the hierarchical key secondary immunogenicity endpoints, no other formal hypothesis testing is carried out. The remaining secondary immunogenicity endpoints involving GMTs, GMFI, other titers, the exploratory endpoint, and all safety endpoints are evaluated and reported for information only, thus no further Type I error control or multiplicity adjustment is needed.

6.5 Handling of Missing Data and Other Data Issues

Please see Section 6.3 for assumptions for AEs with missing relatedness and/or severity.

6.5.1 Missing or Partial Dates for Solicited Adverse Events

Solicited adverse events are collected from IP administration on Day 1 until Day 8 using an electronic diary (e-diary) or paper diary. In the case where a participant has all eight diary entries present and a single entry is missing a date (or has a partial date), then the missing date is assumed to be the date of the missing diary entry for that participant.

6.5.2 Missing or Partial Dates for Unsolicited Adverse Events and Concomitant Medications

Unsolicited AE collection begins at Day 1 (baseline), the day of IP administration. ***Consequently, all AEs will be considered treatment emergent regardless of onset date.***

For missing or partial dates for prior or concomitant medication/therapy, the following conventions are used for the purpose of determining whether the medication/therapy is concomitant or not. Original values are provided in the listings as is, without imputation.

- For start date missing completely or missing the year, impute the date to the date of first exposure to any study treatment.
- For start date missing both the month and the day, if the year is the same as the date of first exposure to any study treatment, impute the date to the date of first exposure to any study treatment, otherwise, impute the date to January 1st.
- For start date missing the day only, if the year and the month are the same as the date of first exposure to any study treatment, impute the date to the date of first exposure to any study treatment, otherwise, impute the date to the first of the month.
- For end date missing completely or missing the year, impute the date to the date of last contact.
- For end date missing both the month and the day, if the year is the same as the date of last contact, impute the date to the date of last contact, otherwise, impute the date to December 31st.
- For start date missing the day only, if the year and the month are the same as the date of last contact, impute the date to the date of last contact, otherwise, impute the date to the last day of the month.

6.5.3 Missing Outcome and Covariates

Participants are included in the analyses to the extent of their available data; missing immunogenicity data are not imputed. See Sections 5.5 and 5.7 and definition of anti-CHIKV human SNA assay titer in Section 6.3.

Participants with missing categorical data are counted in missing or unknown categories when appropriate. Participants with missing numeric data are treated as missing completely at random when calculating summary statistics. For likelihood-based analyses (e.g., regression), missing at random is assumed.

As sensitivity analyses for the coprimary endpoints **(**difference in anti-CHIKV SNA seroresponse rate between PXVX0317 and placebo at Day 22 and GMTs at Day 22)**,** missing immunogenicity outcome data at Day 22 are imputed conservatively as described below. Participants who have an out-of-window result at Day 22 (before Day 19 or after Day 27), are seropositive at baseline, or have an exclusionary PD are included in the mITT population but not the IEP population for these sensitivity analyses.

- Nonresponder analysis. Participants' missing Day 22 anti-CHIKV SNA titer value is imputed as the assay LLOQ/2, even for participants in the PXVX0317-vaccinated group.
- Last observation carried forward (LOCF) analysis. Participants' Day 15 immunogenicity value is substituted for the missing Day 22 anti-CHIKV SNA titer value.

The endpoints are recalculated using each method of conservative imputation and reported for the mITT population to assess the robustness of primary endpoint results to informative missingness.

6.5.4 Non-Quantifiable Laboratory Data

Not applicable.

6.5.5 Implausible Participant Reported Outcomes

Values measured and reported by the participant directly (e.g., via the electronic or paper diary) are not corrected in a reconciliation process. In cases where the reported values are clearly biologically implausible, the reported values and associated toxicity grades are set to missing and excluded from analysis. These reported values are included in listings.

Example: Body (oral) temperatures less than ≤33°C or ≥42°C.

6.6 Adjustment for Covariates

Beyond the inclusion of site in the immunogenicity ANOVA models described in Section 6.1, no further adjustment for covariates is performed. Immunogenicity analyses are conducted for both age strata pooled as well as by separate age strata.

6.7 Multicenter Study

This study is expected to enroll 400 participants at up to 10 sites in US. Data from all sites will be pooled, but site will be a covariate in the immunogenicity ANOVA models described in Section 6.1.

6.8 Subgroup Analyses

Summaries pool both age groups and are repeated separately for each age group. Analyses of the primary immunogenicity and safety endpoints are also summarized by sex, race, and ethnicity group along with treatment group. Summaries by baseline anti-CHIKV SNA serostatus are reported if the baseline (Day 1) seropositive rate is ≥10%.

6.9 Multiplicity Adjustment

6.9.1 Coprimary Immunogenicity Endpoints

The familywise error rate is fixed at a two-sided alpha of 0.05 by the requirement that both coprimary endpoints must be met for a successful outcome: seroresponse at a titer of [redacted] (H_{A1}) and GMT (H_{A2}). See Section 6.4 for formal statistical hypotheses.

For each individual coprimary endpoint, the primary time point is Day 22 and the primary analysis population is the IEP. For the seroresponse and GMT endpoints, the primary analysis is for the pooled age strata; no multiplicity adjustment is made for the analysis of the mITT population or of the separate age strata as the primary population is the combined age groups in the IEP.

6.9.2 Key Secondary Immunogenicity Endpoints

Seroresponse key secondary immunogenicity endpoints are tested using a prespecified hierarchical strategy to preserve the type I error rate without the need for further multiplicity adjustment. These endpoints are tested formally only if the null hypotheses are rejected for both coprimary endpoints and only until a nonsignificant test is reached. If a nonsignificant test is reached formal testing stops, and the remaining endpoints are reported for information only. The sequential order of the seroresponse rate difference key secondary endpoints (H_{A3}) is Day 15 and Day 183, each for the IEP across both age groups combined. At Days 15 and 183, the endpoint is tested for superiority to placebo using a two-sided chi-square test with alpha=0.05.

1. Day 15 seroresponse at a titer of [redacted], including superiority to placebo.
2. Day 183 seroresponse at a titer of [redacted], including superiority to placebo.

After testing the coprimary immunogenicity endpoints and, if both met, the hierarchical key secondary immunogenicity endpoints, no other formal hypothesis testing is performed. The remaining secondary immunogenicity endpoints involving GMTs, GMFI, other titers, the exploratory endpoint, and all safety endpoints are evaluated and reported for information only, thus no further multiplicity adjustment is needed.

7 STUDY POPULATION CHARACTERISTICS

7.1 Participant Disposition

Participant disposition over the course of the study is summarized for all randomized participants by treatment group, including number and percentages of participants still in the study each scheduled visit, competing the study, and reason for not completing the study. Screen failure reasons are listed by participant. The number and percentage of participants enrolled by site are provided by treatment group for all randomized participants.

Randomization details including site, stratum, date and time of randomization, kit number, randomized treatment group assignment, and actual treatment received including lot number are listed by participant. Participants randomized but not treated, those receiving the wrong treatment, or receiving an incorrect dose are listed. Participants who were randomized despite not meeting entry criteria and those who received an excluded concomitant medication are listed.

7.2 Protocol Deviations

Protocol deviations defined in Section 5.2 are categorized as important or not important and evaluated for exclusion of participants from analysis populations. Important protocol deviations are tabulated by category and by treatment group for the randomized population as well as listed by participant.

8 IMMUNOGENICITY ANALYSIS

8.1 Populations Analyzed

The number and percentage of participants in each analysis population (randomized, exposed, safety, mITT, IEP) are summarized by treatment group for all participants. Reasons for exclusion from analysis populations are summarized by treatment group for all randomized participants and listed by participant.

8.2 Demographics and Baseline Characteristics

8.2.1 Demographics

Demographic and baseline characteristics including age, age stratum, sex, race, ethnicity, baseline height, weight and body mass index, and baseline anti-CHIKV SNA serostatus (positive or negative) are tabulated by treatment group for the randomized, safety, mITT, and IEP populations for both age groups pooled and by age strata. Participant site assignment is evident from the unique participant identifier.

8.2.2 Baseline Disease Characteristics

This study enrolls healthy US adolescent and adult participants ≥65 years of age, so no baseline disease characteristics are collected.

8.2.3 Medical History

Medical history is coded to the MedDRA dictionary SOC and PT (see Section 5.8). A summary table and a listing of medical history are supplied by treatment group for the randomized population.

8.2.4 Prior and Concomitant Medications and Vaccines

Prior medications are defined as those taken within 30 days prior to the screening visit (90 days for blood products) through the start of IP administration on Day 1 (baseline). Concomitant medications are defined as those taken after start of IP administration on Day 1 (baseline) through the end of study. See definitions in Section 6.3. Partial dates are imputed according to Section 6.5.2.

Prior and concomitant medications and vaccines are coded to the WHODrug Global Dictionary ATC classification and preferred drug name (see Section 5.8). All prior and concomitant medications and vaccines are tabulated together by ATC classification, preferred drug name, and treatment group for the safety population; a second similar table contains only concomitant vaccines. A participant data listing of all prior and concomitant medications is generated.

8.3 Treatment Compliance

As the IP administration is a single 0.8 mL intramuscular injection performed by site personnel, measurements of treatment compliance are not applicable. A vaccine administration summary is provided and details listed.

8.4 Immunogenicity Analysis

Summary statistics for immunogenicity results by scheduled visit for each treatment group are provided for the IEP and mITT populations, unless otherwise specified. Anti-CHIKV SNA seroresponse rates and GMTs are tabulated by visit for each treatment group. Geometric mean fold increase as well as number and percentage of participants meeting anti-CHIKV SNA titers of ≥15 and 4-fold rise from baseline are also displayed by post-vaccination scheduled visit for each treatment group. Reverse cumulative distribution plots of anti-CHIKV SNA titer versus percentage of participants in each treatment group are generated by scheduled visit for the IEP. Anti-CHIKV SNA GMT are also plotted over time for each treatment group for the IEP.

The primary analysis of all immunogenicity endpoints utilizes the IEP across both age groups combined. As specified for individual endpoints below, primary and secondary immunogenicity analyses of anti-CHIKV SNA seroresponse rates and GMTs are repeated using the mITT population as a measure of robustness of results. All immunogenicity analyses are repeated in the separate age strata for the IEP, and primary and secondary immunogenicity analyses of anti-CHIKV SNA seroresponse rates and GMTs are repeated in the separate age strata for the mITT population as well. No multiplicity adjustment is made for the analysis of the mITT population or of the separate age strata as the primary population is the combined age groups in the IEP.

In addition, the primary immunogenicity endpoints using the IEP across both age groups combined are repeated by sex, by race group (white and non-white), and by ethnicity group (Hispanic or Latino and Not Hispanic or Latino). If the baseline (Day 1) seropositive rate is ≥10%, then subgroup analyses will be performed by baseline serostatus (positive or negative) for coprimary immunogenicity endpoints as well as key secondary seroresponse rate endpoints.

Finally, two types of sensitivity analysis for the coprimary endpoints **(**difference in anti-CHIKV SNA seroresponse rate between PXVX0317 and placebo at Day 22 and GMTs at Day 22) are performed as described in Section 6.5.3. These endpoints are recalculated using the conservative imputation methods for missing immunogenicity outcome data at Day 22 (i.e., nonresponder analysis and LOCF analysis) and reported for the mITT population to assess the robustness of primary endpoint results to informative missingness.

8.4.1 Coprimary Immunogenicity Endpoints

8.4.1.1 Day 22 Treatment Group Estimates and Difference in Anti-CHIKV SNA Seroresponse Rates

The superiority of PXVX0317 vaccine immunogenicity over that of placebo is illustrated at Day 22 by estimating the treatment-specific seroresponse rates and by calculating the difference in seroresponse rates between the two treatment groups (the percentage of participants with an anti-CHIKV SNA titer [redacted]; PXVX0317 minus placebo) and associated 95% CI. See Section 6.1 for statistical details.

This endpoint is summarized for both age strata pooled and for individual age strata in the IEP, as well as by sex, by race group (white and non-white), and by ethnicity group (Hispanic or Latino and Not Hispanic or Latino) for both age strata pooled in the IEP. The analysis, both for the pooled age strata and for individual age strata but not for subgroups, is repeated using the mITT population as a measure of robustness of results. Additionally, sensitivity analyses of this endpoint are performed using the mITT population as described in Section 6.5.3.

A forest plot is generated to represent seroresponse rate differences between treatment groups at Day 22 for the IEP, both for pooled age strata and for individual age strata.

8.4.1.2 Day 22 Anti-CHIKV SNA GMT by Treatment Group

Day 22 anti-CHIKV SNA GMTs and associated 95% CIs are compared between PXVX0317 and placebo treatment groups to demonstrate superiority of PXVX0317 vaccine. See Section 6.1 for statistical details.

This endpoint is summarized for both age strata pooled and for individual age strata in the IEP, as well as by sex and by race group (white and non-white) and ethnicity group (Hispanic or Latino and Not Hispanic or Latino) for both age strata pooled in the IEP. The analysis, both for the age strata pooled and for individual age strata but not for subgroups, is repeated using the mITT population as a measure of robustness of results. Additionally, sensitivity analyses of this endpoint are performed using the mITT population as described in Section 6.5.3.

A graph of anti-CHIKV SNA GMTs by visit is presented for the IEP population. As well, a reverse cumulative distribution plot of titers by visit is displayed for the IEP population.

8.4.2 Secondary Immunogenicity Endpoints

8.4.2.1 Key Secondary Immunogenicity Endpoints: Treatment Group Estimates and Difference in Anti-CHIKV SNA Seroresponse Rates at Day 15 and Day 183, in that order

The key secondary endpoint of treatment specific anti-CHIKV SNA seroresponse rates and treatment group difference in seroresponse rates (PXVX0317 minus placebo) and associated 95% CI based on antibody titers measured at Day 15 and Day 183 will be analyzed as described above for Day 22. For each time point, the null hypothesis of no difference between seroresponse rate percentages in the PXVX0317 vs. placebo group is tested using a chi-square test with alpha=0.05.

This endpoint is summarized for both age strata pooled and for individual age strata using the IEP. The analyses are repeated using the mITT population as a measure of robustness of results. Additionally, sensitivity analyses of these endpoints are performed using the mITT population as described in Section 6.5.3.

8.4.2.2 Anti-CHIKV SNA GMT at Day 15 and Day 183 by Treatment Group

The secondary endpoint of anti-CHIKV SNA GMT and associated 95% CIs for PXVX0317 and placebo based on antibody titers measured at Day 15 and Day 183 is analyzed as described above for Day 22.

This endpoint is summarized for both age strata pooled and for individual age strata using the IEP. The analyses are repeated using the mITT population as a measure of robustness of results.

8.4.2.3 GMFI in Anti-CHIKV SNA Titer from Day 1 to Days 15, 22 and 183 by Treatment Group

Geometric mean fold increase over Day 1 (baseline) titer is analyzed as described for GMTs for each post-vaccination time point (Days 15, 22 and 183) by treatment group. See Section 6.1 for statistical details and definition of anti-CHIKV SNA assay in Section 6.3 for handling of anti-CHIKV SNA titer values below LLOQ.

This endpoint is summarized for both age strata pooled and for individual age strata using the IEP population. Geometric mean fold increase is plotted by visit for the IEP, and a reverse cumulative distribution of fold-rise from baseline by visit is also presented for the IEP.

8.4.2.4 Participants with Anti-CHIKV SNA Titer ≥15 and 4-fold Rise over Baseline at Days 15, 22 and 183 by Treatment Group

Number and percentage of participants with an anti-CHIKV SNA titer ≥15 and 4-fold rise over Day 1 (baseline) at Days 15, 22 and 183 are analyzed by treatment group as described for Day 22 seroresponse. See Section 6.1 for statistical details.

This endpoint is summarized for both age strata pooled and for individual age strata using the IEP.

8.4.3 Exploratory Immunogenicity Endpoint

8.4.3.1 Geometric Mean Titers for Neutralizing Antibodies against Various CHIKV Genotypes at Day 22

For a subset of participants in the PXVX0317 group (CHIKV genotype subset, see Section 5.3), baseline (Day 1) and Day 22 samples are tested for neutralizing antibodies against various CHIKV genotypes. GMTs and associated two-sided 95% CIs are reported for this participant subset, along with fold change relative to the LR2006 OPY-1 strain. This analysis may be performed as a Clinical Study Report Addendum.

8.5 Pharmacokinetic and Pharmacodynamic Analysis

Not applicable.

9 SAFETY ANALYSIS

All safety data are presented in the form of tabulations and participant listings, based on the safety population.

9.1 Extent of Exposure

The frequencies and percentages of participants receiving IP administration are summarized by treatment group for the randomized population, along with whether or not the dose was administered per protocol (yes/no).

9.2 Adverse Events

The safety of PXVX0317 in healthy adult participants ≥65 years of age is evaluated using solicited AEs occurring from IP administration on Day 1 through Day 8, unsolicited AEs through Day 29, and AESI and SAEs and MAAEs though Day 183 EOS. AEs are coded to SOC and PT according to the MedDRA dictionary per Section 5.8. They are coded for severity according to Section 5.9 and Appendix II. Only treatment-emergent AEs are summarized (i.e., excluding those after a participant has given informed consent, but before vaccination). See Section 6.3 for definitions.

Solicited AEs, unsolicited AEs, AESI and SAEs and MAAEs are summarized separately by treatment group and maximum severity for the safety population for both age strata combined. Separate participant data listings of solicited and unsolicited AEs sorted by participant identifier and AE start date are generated.

9.2.1 Overall Summary of Solicited and Unsolicited Adverse Events

A high-level summary of solicited and unsolicited AEs combined reviews the frequency counts and percentages of participants by treatment group reporting AEs in each of the following categories:

- Any AE and any AE ≥Grade 3
- Any solicited AE and any solicited AE ≥Grade 3
- Any treatment-related solicited AE and any treatment-related solicited AE ≥Grade 3
- Any unsolicited AE and any unsolicited AE ≥Grade 3
- Any treatment-related unsolicited AE and any treatment-related unsolicited AE ≥Grade 3
- Any SAE
- Any treatment-related SAE
- Any AE leading to study discontinuation
- Any fatal AE
- Any AESI (see definition in Section 6.3)
- Any MAAE and any treatment-related MAAE

In addition, summaries of combined solicited and unsolicited AEs by SOC, PT and highest reported severity are provided for the following populations:

- Safety population, both age groups
- Safety population by age strata
- Safety population by sex
- Safety population by race group
- Safety population by ethnicity

9.2.2 Solicited Adverse Events from Day 1 until Day 8

Solicited AEs recorded daily in the e-diary or paper diary until Day 8 include local (i.e., pain, redness, and swelling) and systemic reactions (i.e., fever, chills, fatigue, headache, myalgia, arthralgia, and nausea). In addition, solicited AEs ongoing after seven days post-injection (Day 8) and those that are serious or MAAEs are also recorded as unsolicited AEs. Severity of solicited AEs is assessed by the investigator in the same manner as unsolicited AEs.

Frequencies and percentages of participants experiencing each solicited AE are presented by maximum severity and by treatment group. The following summaries of solicited AEs are produced:

- Solicited AEs by maximum event severity, for each event and for any event
- Solicited AEs of severe (Grade 3) or higher severity, for each event and for any event

- Treatment-related solicited AEs by maximum event severity, for each event and for any event
- Day of first onset of solicited AEs, for each event and any event
- Duration of solicited AEs, for each event and any event
- Solicited AEs by day post-injection for each event and for any event

Occurrence of at least one AE by category (local, systemic) for solicited AEs are also included.

The denominator for solicited AE tables comprises only those participants with at least one diary observation (i.e., any non-missing values but excluding "Not done/unknown"), at least one diary observation for a given symptom, or at least one diary observation for a given day, as applicable. ***Note that an elevated in-clinic temperature assessment as part of 30-min post-vaccination vital signs does not count as a solicited AE, as vital signs data are summarized separately.***

9.2.2.1 Electronic or Paper Diary Compliance

Participant compliance with e-diary or paper diary solicited adverse event entry is not summarized.

9.2.3 Unsolicited Adverse Events from Day 1 through Day 29

All unsolicited AEs occurring during the specified collection period in the study are recorded, regardless of their assessment of relatedness by the investigator. Unsolicited AEs include also those solicited AEs ongoing after seven days post-injection (Day 8), AESI, and SAEs.

All reported unsolicited AEs are summarized by treatment group according to MedDRA SOC, PT and highest reported severity. When an unsolicited AE occurs more than once for a participant, the maximum severity and closest relationship to treatment is counted. The unsolicited AE analysis includes unsolicited AEs judged by the investigator as at least possibly related to IP.

9.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

9.3.1 Deaths from Day 1 to Day 183 End of Study Visit

Deaths are not expected in this study with healthy participants. A tabulation and participant data listing of AEs leading to death are provided.

9.3.2 Serious Adverse Events from Day 1 to Day 183 End of Study Visit

SAEs are tabulated by treatment group according to MedDRA SOC, PT and highest reported severity for both age groups and by age group stratum. A separate tabulation is limited to treatment-related SAEs only. A participant data listing of all SAEs is provided.

9.3.3 Adverse Event of Special Interest from Day 1 to Day 183 End of Study Visit

AESI (see definition in Section 6.3) are tabulated by treatment group according to MedDRA SOC, PT and highest reported severity. In addition, solicited and unsolicited AESI are tabulated together.

9.3.4 Medically Attended Adverse Events from Day 1 to Day 183 End of Study Visit

MAAEs (see definition in Section 6.3) are tabulated by treatment group according to MedDRA SOC, PT and highest reported severity for both age groups and by age group stratum.

9.3.5 Adverse Events Leading to Study Discontinuation from Day 1 to Day 183 End of Study Visit

A participant data listing of all AEs leading to study discontinuation (see definition in Section 6.3) is provided.

9.3.6 Day 1 Adverse Events

A participant data listing of all AEs occurring post-vaccination on Day 1 is generated.

9.4 Clinical Laboratory Tests

Not applicable.

9.4.1 Pregnancy Testing

Not applicable.

9.4.2 Viral Serology Testing at Screening

Viral serology testing results are supplied in a participant listing.

9.5 Vital Signs, Physical Findings and Other Variables Related to Safety

9.5.1 Vital Signs

Observed values in vital signs include temperature, blood pressure, respiratory rate, and heart rate at the screening visit and pre- and post-vaccination on Day 1. All vital sign records are displayed in the participant data listings.

9.5.2 Physical Examinations

Physical examinations by body system include a complete examination at screening and directed examinations at Days 1, 15, 22 and 183 only if indicated in order to determine if an AE needs to be recorded. Physical examination findings are listed by participant.

10 DATA MONITORING AND INTERIM ANALYSIS

10.1 Safety Monitoring Committee

The SMC reviews aggregated, blinded safety data after the first 50 participants have completed at least seven days of safety follow-up and periodically thereafter as per SMC recommendation according to the SMC Charter.

10.2 Interim Analysis

10.2.1 Preliminary Safety and Immunogenicity Analysis after Day 29 Visit

After required data entry and cleaning has been completed, there is a preliminary analysis of safety and immunogenicity on data for all participants through the Day 29 Visit to facilitate health authority presubmission preparation. The analyses are performed by an unblinded third-party vendor and results are reported to the Sponsor only at the treatment group summary level, preserving the double-blind status on the participant level. No p-value penalty is assessed because the Day 22 primary immunogenicity endpoint data are final at the time of preliminary analysis and no action regarding the study is made based on these findings. The Sponsor, participants, and site personnel are not unblinded at the participant level until all follow-up visits are completed for the study through Day 183 EOS.

11 REFERENCES

1. CBER (2018) *Guidance for Industry: Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review*, Technical Specification Document.
2. CBER (2007) *Guidance for Industry: Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*.
3. ICH E3 (1996) *Guidance for Industry: Structure and Content of Clinical Study Reports*.

APPENDIX I LIST OF TABLES, FIGURES, AND LISTINGS

Note the list of TFLs is a living document and subject to changes during the study.

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Baseline	
14.1.1	Participant Enrollment by Site – Randomized Population
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14.2.1.1.2	Anti-CHIKV SNA Seroresponse Rate by Treatment Group and Visit – Immunogenicity Evaluable Population, Both Ages Pooled by Sex Subgroups
14.2.1.1.3	Anti-CHIKV SNA Seroresponse Rate by Treatment Group and Visit – Immunogenicity Evaluable Population, Both Ages Pooled by Race Subgroups
14.2.1.1.4	Anti-CHIKV SNA Seroresponse Rate by Treatment Group and Visit – Immunogenicity Evaluable Population, Both Ages Pooled by Ethnicity Subgroups
14.2.1.1.5	Anti-CHIKV SNA Seroresponse Rate by Treatment Group and Visit – Immunogenicity Evaluable Population, Both Ages Pooled by Baseline Serostatus Subgroups *Note: Only needed if baseline seropositive rate is ≥10%.*
14.2.1.2.1	Anti-CHIKV SNA Seroresponse Rate by Treatment Group and Visit – mITT Population, Both Ages Pooled and by Age Group
14.2.1.2.2	Anti-CHIKV SNA Seroresponse Rate by Treatment Group and Visit, Sensitivity Analyses – mITT Population, Both Ages Pooled and by Age Group
14.2.2.1.1	Anti-CHIKV SNA GMT by Treatment Group and Visit – Immunogenicity Evaluable Population, Both Ages Pooled and by Age Group
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Table	Title
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Figure	Title
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Figure	Title
14.4.2.3.2	Reverse Cumulative Distribution of Geometric Mean Fold Increase in Anti-CHIKV SNA Titers by Visit – Immunogenicity Evaluable Population, Both Ages Pooled

Listing	Title
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APPENDIX II TOXICITY GRADING SCALE

EVENT	MILD (Grade 1)	MODERATE (Grade 2)	SEVERE (Grade 3)	POTENTIALLY LIFE THREATENING (Grade 4)
Fever	≥100.4-101.1°F (≥38.0-38.4°C)	≥101.2-102°F (≥38.5-<39°C)	≥102.1°F-104°F (≥39°C-40°C)	>104°F (>40°C)
Headache	No interference with activity	Some interference with activity, may require repeated use of non-narcotic pain reliever for more than 24 hours	Significant, prevents daily activity, any use of narcotic pain reliever	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Nausea	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization for hypotensive shock
Vomiting	1–2 episodes/24 hours	>2 episodes/24 hours	Requires IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 g/24 hours	4-5 stools or 400-800 g/24 hours	6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Injection site pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Use of any narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Injection site erythema/redness	25-50 mm	51 mm-100 mm	>100 mm	Necrosis or exfoliative dermatitis
Injection site induration/swelling	25-50 mm and does not interfere with activity	51 mm-100 mm or interferes with activity	>100 mm or prevents daily activity	Necrosis

Document Approvals
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Document Approval Task Verdict: Approve	[redacted] Sr Director, Biostatistics & Data Sciences
Document Approval Task Verdict: Approve	[redacted] Sr. Manager, Clinical Trials
Document Approval Task Verdict: Approve	[redacted] Director, Biostatistics
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