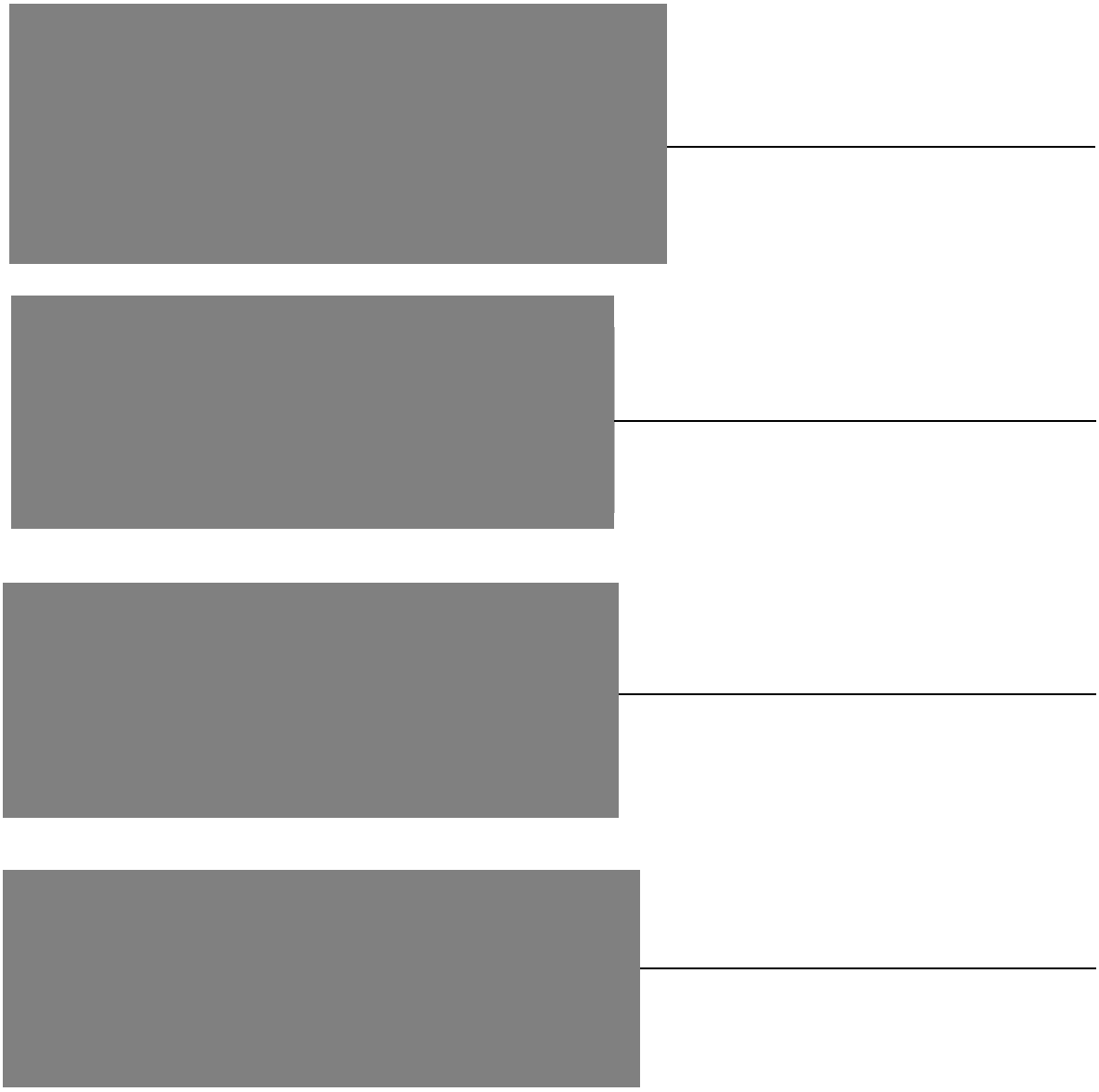
STATISTICAL ANALYSIS PLAN

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
Name of Test Drug:	PXVX0317 (CHIKV-VLP Vaccine)
Study Number:	EBSI-CV-317-002
Protocol Version:	4.0
Protocol Date:	25 Jan 2021
Phase of Study:	Phase 2
Analysis Plan Version:	Version 2.0
Analysis Plan Date:	01 March 2021
Analysis Plan Author:	Catalyst Clinical Research, LLC

Approvals:



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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CBC	Complete Blood Count
CHIKV	Chikungunya Virus
CHIKV-VLP	Chikungunya Virus Virus-Like Particle
CI	Confidence Interval
DC	Discontinuation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEEV	Eastern Equine Encephalitis Virus
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HBcAb	Antibody to Hepatitis B Virus Core Antigen
HBsAb	Antibody to Hepatitis B Virus Surface Antigen
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
ID	Identification
IEP	Immunogenicity Evaluable Population
IND	Investigational New Drug
LLOQ	Lower Limit of Quantification
LLT	Lowest Level Term
LOD	Limit of Detection
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified Intent-to-Treat
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
PT	Preferred Term
SAE	Serious Adverse Event

SOC	System Organ Class
ULOQ	Upper Limit of Quantification
USAMRIID	US Army Medical Research Institute for Infectious Diseases
VEEV	Venezuelan Equine Encephalitis Virus
WEEV	Western Equine Encephalitis Virus
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

1. INTRODUCTION

1.1. Background

1.1.1. Chikungunya Virus and Chikungunya Fever

Chikungunya virus (CHIKV) is an arthropod-borne alphavirus of the family Togaviridae. As of May 29, 2018, over 80 countries or territories have documented cases of CHIKV infection excluding those countries where only imported cases have been documented. Although mosquitoes are the primary mode of transmission of CHIKV, blood-borne transmission via needle stick is possible. Maternal-fetal transmission has been documented during pregnancy (Staples 2017). Following an incubation period of 2 to 12 days, acute clinical manifestations include high fever, rash, gastrointestinal complications, headache, muscle pain, nausea, fatigue, myalgia, and joint pain (Borgherini 2007, Taubitz 2007, Pialoux 2007). The most classic symptom of chikungunya is a debilitating polyarthralgia that is present in greater than 90% of cases. This acute phase resolves within several weeks, but joint pain and arthritis may persist for months or years in over 30% of infected individuals (Schilte 2013).

There are currently no approved vaccines to prevent CHIKV infection or disease. However, protection against subsequent infection has been shown to correlate with the presence of anti-CHIKV antibodies that neutralize the virus in vitro (Yoon 2015). Such antibodies are readily induced by this and other vaccine candidates. But a major challenge stands in the way of licensing any chikungunya vaccine: the virtual impossibility of conducting a field efficacy trial, because outbreaks of chikungunya are so sporadic and short-lived. From the time the first case is detected until the epidemic begins to subside is often less than two months (Beesoon 2008).

1.1.2. Venezuelan Equine Encephalitis Virus and Vaccines

Venezuelan equine encephalitis virus (VEEV) is an alphavirus related to CHIKV. Humans infected with VEEV develop a febrile illness, often with severe headache, averaging 1–5 days after exposure. Dissipation of febrile illness coincides with the production of neutralizing antibodies. The average case fatality rate of VEEV is <1%. Children who have more severe disease are more likely to develop encephalitis and can be left with severe neurological complications.

VEEV has been recognized as a potential biological weapon because of its high attack rate with a debilitating illness and its adaptability to aerosol dissemination. Accordingly, the US Army has invested much research in this pathogen and developed experimental vaccines to protect those who handle VEEV in the laboratory (Wolfe 2013).

Two vaccines for VEEV administered to laboratory workers at US Army Medical Research Institute for Infectious Disease (USAMRIID) under Investigational New Drug (IND) are a live attenuated virus vaccine (TC83) and an inactivated virus vaccine (TC84). TC83 is the most widely used but has a significant (26%) non-response rate. Non-responders who require immunity are generally offered the inactivated TC84 vaccine. Laboratory workers at USAMRIID may have also received investigational formalin-inactivated vaccines for Eastern

Equine Encephalitis (EEEV) and/or Western Equine Encephalitis (WEEV) Viruses (Reisler 2012).

1.1.3. Alphavirus Immune Interference

Over the many decades of experience with alphavirus vaccines at USAMRIID a number of studies have demonstrated immune responses to an alphavirus vaccine may be impaired among individuals who previously received a vaccine for a heterologous alphavirus. This phenomenon has been dubbed "alphavirus immune interference". While antibody responses to chikungunya were impaired in studies of prior recipients of TC83, there is no evidence that the non-responders were more susceptible to chikungunya. Challenge studies, though not consistently showing cross-protection, also do not show evidence that clinical outcomes are worse in prior recipients of heterologous alphavirus vaccines (Jochim 1974) or experimental infections (Byrne 1964).

1.2. Name and Description of Investigational Vaccine

PXVX0317 is the Sponsor's research name for this Chikungunya Virus-Like Particle Vaccine (CHIKV-VLP vaccine). PXVX0317 is a field-formulated vaccine with two components: CHIKV-VLP and Alhydrogel® adjuvant. The final concentration of the CHIKV-VLP is 40mcg per dose. CHIKV-VLP is essentially identical to the VRC-CHKVLP059-00-VP vaccine used in the nonclinical studies. Alhydrogel is a 2% (w/w) aqueous suspension of aluminum hydroxide.

1.3. Study Objectives

The goal of this study is to evaluate the safety and immunogenicity of the chikungunya vaccine candidate PXVX0317 when administered to prior recipients of experimental alphavirus vaccines versus alphavirus naïve gender and age-matched controls.

Safety Objectives

The primary safety objective is to evaluate the safety of PXVX0317 when administered to prior alphavirus vaccine recipients versus gender and age-matched controls. Safety will be assessed by measuring the incidence of local and systemic solicited adverse events (AEs), unsolicited AEs, and serious adverse events (SAEs).

Immunogenicity Objectives

Primary

- To evaluate the neutralizing antibody response to CHIKV induced by PXVX0317 when administered to prior alphavirus vaccine recipients versus gender and age-matched controls.

Secondary

- To evaluate the overall antibody responses to CHIKV and VEEV induced by vaccination with PXVX0317 when administered to prior alphavirus vaccine recipients versus gender and age-matched controls.

Exploratory

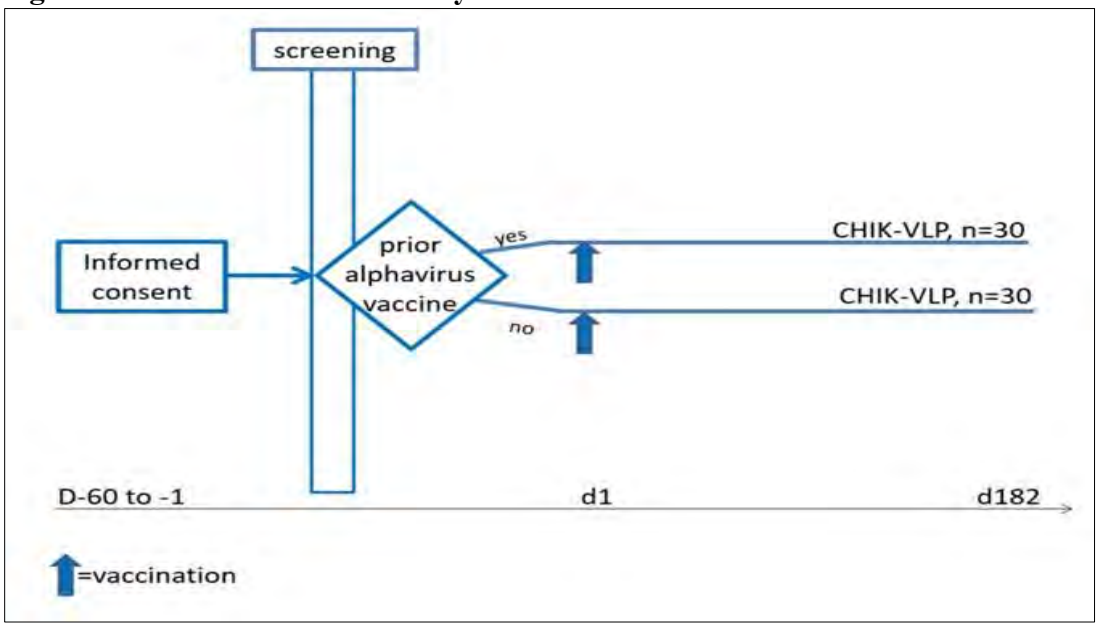
- To evaluate the cellular immune response to CHIKV induced by vaccination with PXVX0317 when administered to prior alphavirus vaccine recipients versus gender and age-matched controls.
- To evaluate the humoral immune responses to EEEV and WEEV induced by vaccination with PXVX0317 in selected subjects who previously received these vaccines versus alphavirus-naïve controls.

1.4. Study Design

This is a Phase 2 parallel-group, open label study in healthy adults 18-65 years of age. A total of 60 subjects are planned to be enrolled with up to 30 at each of two sites. Subjects who have previously received an investigational heterologous alphavirus vaccine and are enrolled at USAMRIID will be matched by age (±3 years) and gender (both birth and self-identified) with alphavirus-naïve subjects enrolled at Walter Reed Army Institute of Research (WRAIR). This matching is done to ensure that demographic characteristics are comparable between the groups, not to pair data between two specific individuals.

This study has a screening period of 60 days, a treatment and observation period from Day 1 to Day 29, and a follow-up period through Day 182 (±14 days) (Figure 1).

Figure 1: EBSI-CV-317-002 Study Schema



Study Duration

The maximum possible study duration for an individual subject is 256 days.

Inclusion Criteria:

1. Age 18 to 65 years old (inclusive)

2. For women of childbearing potential, a negative pregnancy test at screening and on vaccination day, practicing highly effective contraception for at least 30 days prior to vaccination, and willing to use a highly effective method of contraception through study completion.

3. Able and willing to provide informed consent for study participation prior to screening procedures.

4. Free of obvious health problems as established by medical history and clinical examination at screening and enrollment.

5. Available to participate for the duration of the study (approximately 8 months).

6. For the cohort of prior alphavirus vaccine recipients, a documented history of prior alphavirus vaccination.

Exclusion Criteria:

1. Acute disease or febrile illness at the time of enrollment.

2. Clinically significant cardiac, respiratory, rheumatologic or other medical or psychiatric condition that, in the opinion of the Investigator, places the subject at increased risk or affects their ability to understand and comply with study procedures.

3. Abnormal screening lab test results that, in the opinion of the investigator, obscures interpretation of the safety data or suggests a clinically significant cardiac, respiratory, rheumatologic or other medical condition that places the subject at increased risk.

4. Pregnant, lactating or planning to become pregnant during the study period.

5. Laboratory evidence of infection with Hepatitis B, C or HIV.

6. History of naturally (non-laboratory) acquired chikungunya or other alphavirus infection or travel to a WHO-designated chikungunya-endemic region within 30 days prior to Day 1.

7. History of acute allergic reaction to any component of CHIKV-VLP vaccine, or Alhydrogel®.

8. Current (30 days prior to Day 1) or anticipated use of systemic immunomodulatory or immunosuppressive medications.

9. History of splenectomy, immunosuppressive condition, autoimmune disease, or immunodeficient condition.

10. Family history of congenital or hereditary immunodeficiency.

11. Suspected or known current alcohol abuse that, in the opinion of the investigator, would interfere with their ability to understand and comply with study procedures.

12. Current intravenous drug use.

13. Prior receipt of an investigational chikungunya vaccine.

14. Receipt or planned receipt of any licensed vaccine from 30 days prior to Day 1 through the Day 29 study visit.

15. Participation in another clinical trial during the study period in which an investigational product is administered.

16. For the alphavirus naïve group, history of prior alphavirus vaccination is exclusionary.

Study Procedures

After signing the informed consent form, subjects will undergo screening procedures up to 60 days before the first injection. Subjects will be observed in clinic for 30 to 60 minutes after injection. Local and systemic solicited events occurring within 7 days after the injection will be recorded by the subject using a memory aid. Subjects will be specifically asked to record local injection site events (pain, redness, and swelling) and systemic events (fever with oral temperature ≥100.4 ºF, chills, fatigue, malaise, headache, myalgia, arthralgia, and nausea). Any other AEs and medications used through Day 29 will also be recorded. The reporting period for SAEs begins at the time of informed consent and continues for the duration of study participation. Concomitant medications associated with an SAE will be collected through the end of the study. Blood will be collected at Day 1 (before the injection) and Days 8, 22, 29, 57 and 182. See Table 1 on the following page for the complete schedule of study procedures and events.

Table 1: Schedule of Events

Study Event[1]	Screen	Day 1	Day 8	Day 22	Day 29	Day 57	Day 113	Day 182	Early DC
Compliance Ranges	-60 to -1	NA	+3 days	±3 days	±3 days	±7 days	±10 days	±14 days	
Informed Consent	X								
Vital signs	X	XX[8]	X	X	X	X[9]	X[9]	X[9]	X[9]
Review Inclusion/Exclusion Criteria	X	X							
Screening Medical History to include prior/concomitant medications	X								
Physical Examination	X								
Interim medical history, solicited[2] and unsolicited[3] AEs, and concomitant medications		X	X	X	X				X
Memory aid distribution		X							
Memory aid collection and review			X						If < D8
Clinical check[4]		XX[8]	X	X	X	X	X	X	X
CBC[5]	X	X	X						If < D8
Creatinine, AST, ALT[5]	X	X	X						If < D8
Anti-HIV-1/2, Anti-HCV, HBsAg, HBcAb, HBsAb	X								
Urine pregnancy test[6]	X	X			X				If < D29
Sera for antibody assays/future use[7]		X	X	X	X	X		X	X
Collection of blood for Peripheral Blood Mononuclear Cells (PBMCs)		X	X		X	X		X	
Minimum volume of blood required	24.5 mL	84.5 mL	84.5 mL	17 mL	57 mL	77 mL	0 mL	77 mL	0 to 20 mL
Cumulative volume of blood required (approximate mL)	30	120	210	230	290	370	370	450	n/a
Vaccination		X							

[1] SAEs will be collected throughout the study
[2] Solicited AEs collected through Day 8 only.
[3] Unsolicited AEs collected through Day 29 only.
[4] Clinical checks: targeted physical exams based on AEs/SAEs identified
[5] CBC, Creatinine, AST, ALT will be collected but the results will not be included in the database.
[6] Urine pregnancy tests only for women of child-bearing potential.
[7] Antibody assays vary with time point but include NT80 to CHIKV, PRNT80 to VEEV, total antibodies to CHIKV and VEEV, and exploratory assays of humoral immunity.
[8] On vaccination day, vital signs and clinical checks will occur twice: before and 30 to 60 minutes after vaccination.
[9] Vital signs may be collected at the discretion of the investigator past Day 29 but will not be included in the database.

1.5. Sample Size and Power

The sample size here was chosen based on the number of subjects in the Fort Detrick Special Immunization/Special Procedures Program (USAMRIID) who are available for screening. Of the approximately 60 available, 30 are expected to enroll in this trial along with an equal number of alphavirus naïve age- and gender-matched subjects. Based on an interim analysis of this vaccine lot and regimen in Study PXVX-CV-317-001, at least 95% of the alphavirus-naïve controls are expected to seroconvert in this trial. Assuming that the alphavirus-naïve group has a 95% seroconversion rate, a total sample size of 60 subjects affords 80% power to detect a significant difference between groups if the seroconversion rate in the prior alphavirus vaccine recipients is 65% or less. Or, in other words, power is 80% to detect a difference between groups if the seroconversion rate in the prior alphavirus recipients is 30 percentage points lower than in the alphavirus-naïve group. Compared to the previously cited studies in which decrements in the proportion of seroconversion of 64% (McClain 1998) and 100% (Harrison 1971) (DeMeio 1979) were seen, this study is adequately powered to detect immune interference on the order of one-half to one-third of what has previously been described. Further details of sample size and power estimation can be found in Section 9.1 of the protocol.

2. TYPE OF PLANNED ANALYSIS

This analysis plan describes the methods by which the data from this study will be analyzed. Completion of the Day 182 assessment for the final subject will mark the end of electronic data capture (EDC) data collection for the study. A final analysis of data collected throughout the study from all subjects will be performed after the last subject has completed the study and the immunogenicity and safety data have been locked. No interim analysis is planned for this study.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Continuous variables will be summarized in terms of the sample size, mean, standard deviation, median, minimum and maximum. The geometric mean and 95% confidence interval (CI) will be presented as appropriate. Calculation of the geometric mean will be performed by exponentiating the mean of the $\log_{10}$-transformed data to convert to the non-transformed scale. The calculation of the corresponding 95% CI will be performed in a similar manner. Categorical variables will be summarized using frequency counts and percentages. In general, data will be summarized by study arm (prior alpha vs. naïve alpha) and overall. Unless otherwise noted, the denominator for the percentages will include all subjects in the respective study arm.

The minimum and maximum values will be presented with the same number of decimal places as the raw data collected. The mean, median, standard deviation, and standard error will be presented using one additional decimal place.

For subject counts/frequencies, percentages will generally be shown to one decimal place. The denominator will be the total size of the sample, N, unless otherwise noted. Counts of 0 will be shown but 0% will be shown as blank. A percentage of 100% will be reported as 100%.

3.1. Analysis Populations

Analysis populations define which subjects are included in an analysis. A summary of the number and percent of subjects in each analysis population will be provided by study arm and in total.

3.1.1. Enrolled Population

The enrolled population, referred to as the study population in the protocol, is comprised of all screened subjects who provide informed consent and provide demographic and other baseline screening measurements, and are assigned a study subject identification (ID) number.

3.1.2. Exposed Population

All subjects in the enrolled population who receive study vaccination.

3.1.3. Safety Population

All subjects in the enrolled population who receive study vaccination and provide safety assessment data. This generally includes anyone who was not lost to follow-up at Day 1 as they will be at risk for reporting an SAE.

3.1.4. Modified Intent-to-Treat (mITT) Population

The mITT population includes all subjects in the exposed population who have evaluable immunogenicity results from both Day 1 and at least one later on-study sample.

3.1.5. Immunogenicity Evaluable Population (IEP)

The IEP includes all subjects in the exposed population who:

- Have no important protocol deviation or other reason to be excluded as defined prior to database lock.
- Have not received a prohibited medication.
- Provide evaluable serum sample results for baseline and the primary immunogenicity endpoint within the required time frames:
    - Baseline: Day 1 or within 60 days before study vaccine administration
    - Day 22: Day 19 through Day 25, inclusive

In addition, all subjects in the alphavirus-naïve group are required to be seronegative for both CHIKV and VEEV at baseline, where seronegativity is defined as:

- Anti-CHIKV neutralizing antibody levels below the limit of detection (LOD) of 15, determined by luciferase-based assay (NT80)
- Anti-VEEV neutralizing antibody levels below the LOD of 20, determined by Plaque-Reduction Neutralization Test (PRNT80) assay,

3.2. Missing Data and Outliers

Missing Data

A missing datum for a given study visit may be due to the fact that:

1. data were not collected for the visit or were unusable, or
2. a subject permanently discontinued from the study before reaching the assessment.

There are no plans to impute values for missing data points except for imputing missing relationship to study drug for AEs as related.

3.3. Data Handling Conventions and Transformations

By-subject listings will be presented for all enrolled subjects sorted by subject ID number, study arm, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within subject.

Baseline is defined as the Day 1 value. If the Day 1 value is missing, then the last non-missing value prior to Day 1 will be used as the baseline value.

Data that are less than the limit of detection (LOD) or above the upper limit of assay reporting will be imputed as follows:

- Antibody titer assay results that are reported as less than the LOD will be imputed as the LOD/2 when calculating geometric mean titer (GMT) and geometric mean ratio (GMR). For example, if the LOD is 15 and a result is noted as "<15", a titer of 15/2 (=7.5) will be imputed.

- For fold increase over baseline in antibody titer, if a value is < LOD, it will be imputed as the LOD. For example, if the LOD is 15 and a result is noted as "<15", a titer of 15 will be imputed.

- A value that is one unit above the upper limit of assay reporting will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the limit of quantitation). Values with decimal points will follow the same logic as above.

3.4. Visit Windows

For determination of Baseline visit and all other visits, an analysis visit will be derived to summarize the data by the proper visit window interval.

The following algorithm will be used for the study day determination:

- Day 1 = Day of Vaccination;

- If Date of Assessment/Visit >= Date of Vaccination then Study Day = (Date of Assessment/Visit - Date of Vaccination) + 1;

- If Date of Assessment/Visit < Date of Vaccination then Study Day = (Date of Assessment/Visit - Date of Vaccination).

4. SUBJECT DISPOSITION

4.1. Study Arms

All subjects who do not fail screening will fall into one of two study arms based on their prior exposure to an investigational heterologous alphavirus vaccine. The group of subjects who had prior exposure will be referred to as the "prior alpha" study arm and the group of subjects who had no prior exposure will be referred to as the "naïve alpha" study arm throughout the remainder of this document. Regardless of pre-exposure status, subjects will receive one injection of the study drug (PXVX0317) on Day 1.

4.2. Summary of Subjects by Site

The number and percent of subjects will be summarized by site for each study arm (prior alpha vs. naïve alpha) and overall. The percentage calculations will be based on the number of subjects in the exposed population.

4.3. Disposition of Subjects

A summary of subject disposition will be provided by study arm and overall. This summary will present the number of subjects who completed through Day 182 and discontinued from the study early along with the primary reason for discontinuing the study early. No p-values or inferences based upon comparison of disposition in the study arms will be generated.

A data listing of reasons for early study discontinuation will be provided as well as a listing of reasons for screen failure.

5. BASELINE DATA

5.1. Demographics

Subject demographic and baseline data (e.g., age, age group (18-31, 32-45, 46-55, and 56-65 years), sex, ethnicity, race, weight, height, body mass index (BMI), time since prior alphavirus vaccine, and prior alphavirus vaccine titer) will be summarized by study arm and overall using descriptive statistics for continuous data and by the number and percent of subjects for categorical data. Age and time since prior alphavirus vaccine will be calculated in years at the time of vaccination. No p-values or inferences regarding comparisons of baseline demographics between the two study arms will be provided.

The summary will be provided for the safety, immunogenicity evaluable, and mITT populations. A listing of demographic data will be provided for the enrolled population.

5.2. Medical History

Medical history will be coded using version 20.1 of the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized by system organ class (SOC), preferred term (PT), study arm, and overall for the safety population. Medical history will also be listed for the exposed population.

6. PRIMARY, SECONDARY, AND EXPLORATORY ANALYSES

The treatment period begins and ends at the time of vaccination at baseline (Day 1). The observation period spans Day 1 post-vaccination through Day 29, and follow-up period spans the time following the Day 29 visit through Day 182.

The primary and secondary analyses will be performed once all data have been collected from all subjects through their Day 182 follow-up visit and all EDC and laboratory data records have been cleaned and signed off by the PI.

6.1. Primary Immunogenicity Endpoint

The primary immunogenicity endpoint is the anti-CHIKV seroresponse at Day 22 in prior alpha versus naïve alpha subjects, where seroresponse is defined as a 4-fold rise over baseline in anti-CHIKV neutralizing antibodies as determined by a luciferase-based assay (NT80). Note that seroresponse is referred to as seroconversion in the protocol and in the list of endpoints excerpted from the protocol below.

6.1.1. Analysis Methods for Primary Immunogenicity Endpoint

The primary immunogenicity analysis will compare the proportion of prior alpha subjects to the proportion of naïve alpha subjects with seroresponse by anti-CHIKV neutralizing antibody at Day 22. The significance of the comparison of the two groups will be assessed using a Fisher's exact test. The percentage with seroresponse in each group will be presented along with a 95% CI calculated using the Wilson method (Agresti 1998). The difference and a 95% CI for this difference calculated based on Newcombe hybrid score method will also be presented. The primary immunogenicity analysis will be performed on both the IEP and mITT population.

6.2. Secondary Immunogenicity Endpoints

Secondary immunogenicity endpoints include:

- Anti-CHIKV neutralizing antibodies, determined by luciferase-based assay (NT80), in prior alpha subjects vs. naïve alpha subjects, assessed by
  - Seroconversion rates on Days 8, 29, 57 and 182
  - GMT and GMR on Days 1, 8, 22, 29, 57 and 182
  - The proportion of subjects with titers of at least 40, 100, 160 or 640 on Days 1, 8, 22, 29, 57 and 182

- Anti-CHIKV total antibodies, determined by immunoassay, in prior alpha subjects vs. naïve alpha subjects, assessed by
  - Seroconversion rates on Days 22 and 29 where seroconversion is a 4-fold rise in titer over baseline
  - GMT and GMR on Days 1, 22 and 29

  - The proportion of subjects with titers of at least 40, 100, 160 or 640 on Days 1, 22 and 29

- Anti-VEEV neutralizing antibodies, determined by Plaque-Reduction Neutralization Test (PRNT80) assay, in prior alpha subjects vs. naïve alpha subjects, assessed by
  - Seroconversion rate on Days 22 and 29 where seroconversion is a 4-fold rise in titer over baseline
  - GMT and GMR on Days 1, 22 and 29
  - The proportion of subjects with titers of at least 40, 100, 160 or 640 at Days 1, 22 and 29

- Anti-VEEV total antibodies, determined by immunoassay, in prior alpha subjects vs. naïve alpha subjects, assessed by
  - Seroconversion rate on Days 22 and 29 where seroconversion is a 4-fold rise in titer over baseline
  - GMT and GMR on Days 1, 22 and 29
  - The proportion of subjects with titers of at least 40, 100, 160 or 640 at Days 1, 22 and 29

6.2.1. Analysis Methods for Secondary Immunogenicity Endpoints

The same method used for the primary immunogenicity analysis, excluding the estimated difference, will also be used for the secondary analysis of seroresponse rate, comparing the proportion of prior alpha subjects to the proportion of naïve alpha subjects having seroresponse by anti-CHIKV neutralizing antibodies on Days 8, 29, 57 and 182 and by anti-CHIKV total antibodies and anti-VEEV total and neutralizing antibodies on Days 22 and 29.

For the secondary analysis of GMT and GMR, the GMTs and GMRs at the specified time points will be compared for differences between the two study arms (prior alpha vs. naïve alpha) for each type of antibody listed above.

The primary model used for the immunogenicity evaluable population is an analysis of variance (ANOVA), with logarithmically-transformed (log_{10}) titers as the dependent variable and study arm, age, and gender as the predictor variables in the model. The primary model used for the mITT population is the same except that log_{10} baseline titer will be added as a predictor if there are subjects with measurable titers in the naïve alpha group at baseline. If any baseline titer is equal to zero, then one will be added to all baseline titers prior to taking the log. The least square means estimated from the ANOVA (or ANCOVA) and their 95% CIs will be back-transformed and reported as the group GMT values. The geometric mean ratio of the prior alpha group to the naive alpha group, and its 95% CI, will be calculated by specifying a linear contrast between the groups in the model. Since the linear contrast yields a difference between groups in log-transformed space, the difference will be exponentiated to produce a geometric mean ratio of one group to the other. The p-value associated with each model comparison will also be reported. Additionally, the median, minimum and maximum will be summarized based on the non-transformed scale.

An additional analysis of geometric mean of the fold-increase in titer over baseline will be provided. The geometric mean and median fold-increase in titer over baseline will be presented at each visit. To calculate the geometric mean fold-increase and 95% CI, the fold-increase results will be $\log_{10}$-transformed, the mean and 95% CI of these transformed data will be calculated and then exponentiated to convert to the non-transformed scale. A t-test will be used to compare the $\log_{10}$-transformed fold increase between the prior alpha and naive alpha subjects. The median, minimum and maximum of the fold-increase in titer over baseline will be summarized based on the non-transformed scale.

The percentage of subjects achieving specified thresholds (40, 100, 160, and 640 anti-CHIKV neutralizing antibody titers), and associated Wilson 95% CIs, will be summarized at Days 1, 8, 22, 29, 57 and 182 for anti-CHIKV neutralizing antibodies and at Days 1, 22 and 29 for anti-CHIKV total, anti-VEEV total, and anti-VEEV neutralizing antibodies. The groups will be compared by pairwise Fisher's exact tests on the percentage achieving each threshold. An additional summary will be provided for the cumulative percentage of subjects reaching the specified thresholds of anti-CHIKV neutralizing antibody titers.

All secondary analyses will be performed for the IEP. The secondary analysis of anti-CHIKV neutralizing antibodies as determined by luciferase-based assay will be repeated on the mITT population.

6.3. Exploratory Endpoints

Exploratory endpoints include:

- Cellular immune responses to chikungunya antigens: PBMCs will be collected on Days 1, 8, 29, 57 and 182 in order to determine the nature and stability of the cellular immune response to PXVX0317.

- Humoral immune responses at other time points, to other pathogens (including EEEV and WEEV) and using other thresholds than those specified above may be performed in selected subjects.

6.3.1. Analysis Methods for Exploratory Endpoints

As part of an exploratory analysis, the chikungunya-specific cellular immune (IFN-g ELISpot) response of prior alpha subjects will be compared to that of naïve alpha subjects. Assay results will be reported as the number of spot-forming cells per 1 million PBMC (SFC / 10^6 PBMC). The sample size, mean, median, 25^{th} and 75^{th} percentiles, and minimum and maximum SFC / 10^6 PBMC will be summarized for each study arm at each visit. A p-value from a comparison of the two groups using a Wilcoxon Rank Sum test will be provided for each visit.

The percentage of subjects achieving specified thresholds (2, 4, 8, and 16 fold increase over Day 1 in SFC / 10^6 PBMC), and associated Wilson 95% CIs, will be summarized at each visit. The groups will be compared by pairwise Fisher's exact tests on the percentage achieving each threshold.

Analogous methods will be used to summarize VEEV-specific IFn-g.

Any exploratory humoral antibody data will be summarized using similar methods as those used to summarize the secondary antibody endpoints. All exploratory analyses will based on the IEP and only valid sample results will be included in the analyses.

6.4. Immunogenicity Subgroup Analysis

Subgroup analyses by race group – white or non-white – and gender will be conducted for the following endpoints:

- Anti-CHIKV neutralizing antibodies, determined by luciferase-based assay (NT80), in prior alpha subjects vs. naïve alpha subjects, assessed by
  - Seroconversion rates on Days 8, 22, 29, 57 and 182
  - GMT and GMR on Days 1, 8, 22, 29, 57 and 182
  - The proportion of subjects with titers of at least 40, 100, 160 or 640 on Days 1, 8, 22, 29, 57 and 18

Statistics and p-values for all sub-group analyses will be calculated using the same methods as described for the endpoint except for GMT and GMR analyses. The mean of the $\log_{10}$-transformed titers will be calculated and then exponentiated to convert to the non-transformed scale to estimate the GMT. 95% CIs for the GMT will be calculated by constructing a *t*-interval for the mean of the transformed titers and then back-transformed. The GMR of the prior alpha group to the naive alpha group, and its 95% CI, will be calculated by taking the difference between groups in log-transformed space and then exponentiating the difference. *T*-tests will be used to compare $\log_{10}$-transformed titer data between the prior alpha and naive alpha subjects. The median, minimum and maximum will be summarized based on the non-transformed scale.

7. SAFETY ANALYSES

7.1. Extent of Exposure

Vaccine administration data, including date/time of vaccination and injection site location, will be provided in a listing for all subjects in the exposed population.

All safety analyses will be based on the safety population.

7.2. Adverse Events

An AE is any untoward medical occurrence in a study participant, regardless of the suspected causal relationship with study vaccine. An AE can therefore be a new-onset symptom or disease, an exacerbation of a pre-existing symptom or disease, a new-onset laboratory abnormality considered by the Investigator to be clinically significant, a new-onset symptom or disease that occurs as a result of a protocol-specified procedure.

The reporting period for SAEs begins at the time of informed consent and continues for the duration of study participation. The reporting period for solicited AEs begins after study vaccine administration on Day 1 and continues through Day 8. The reporting period for unsolicited AEs begins after study vaccine administration on Day 1 and continues through Day 29.

Solicited AEs are assigned to two different categories of events, systemic and local, with the following pre-specified signs and symptoms:

1. Systemic events: fever with oral temperature ≥ 100.4 °F, chills, malaise, fatigue, headache, myalgia, arthralgia, and nausea

2. Local events: pain, redness, and swelling at the injection site

Solicited AEs from Day 1 through Day 8 will be recorded on the solicited AE electronic case report form (eCRF). Symptoms experienced on Day 8 and continuing beyond Day 8 will be recorded on the AE eCRF with a start date corresponding to the first date the symptom was continuously experienced through Day 8.

An unsolicited AE is defined as an AE that is spontaneously reported by the subject or discovered by the Investigator.

Adverse Event Dictionary

AEs will be coded using the MedDRA version 20.1. SOC, High Level Group Term (HLGT), High Level Term (HLT), PT, and Lowest Level Term (LLT) will be attached to the clinical database.

All solicited AEs will be summarized according to severity grading scales defined in Sections 6.2 and 9.5.1 of the protocol; these range from "mild" to "potentially life-threatening."

The analyses of solicited AEs (categorized as systemic or local) will be tabulated by maximum severity and study arm. In addition, solicited AEs ongoing after 7 days post-injection will be also recorded as unsolicited AEs. Frequencies and percentages of subjects experiencing each solicited AE will be presented by maximum severity.

All the unsolicited AEs occurring during the study that occur during reporting periods will be recorded, regardless of their assessment of relatedness by the Investigator. The original verbatim terms used by the Investigator to identify AEs in the eCRF will be mapped to preferred terms using the MedDRA dictionary. The unsolicited AEs will then be grouped by MedDRA preferred terms into frequency tables according to SOC. All reported AEs, as well as AEs judged by the Investigator as at least possibly related to study vaccine, will be summarized by study arm, according to SOC and preferred term within SOC. When an unsolicited AE occurs more than once for a subject, the maximum severity and strongest relationship to the study arm will be counted. Only treatment-emergent AEs will be summarized, i.e., excluding those after a subject has given informed consent, but before vaccination. The selection of unsolicited AEs and their assignment to time intervals will be done by day of onset and not by days ongoing/persisting.

7.2.1. Adverse Event Severity

AEs (inclusive of all solicited and unsolicited AEs) are graded by the Investigator or designee as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (potentially life-threatening) according to toxicity criteria specified in the study protocol (see Appendix B of study protocol). The severity grade of events for which the Investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation (will sort to the top).

7.2.2. Relationship of Adverse Events to Study Drug

AEs and SAEs are determined to be related or unrelated to study product by study Investigators or their designees. The Investigators or designees will evaluate the relatedness of an AE to vaccine treatment using three categories: Not Related, Possibly Related, and Probably Related. Related AEs are those for which the Investigator or designee answers "Possibly Related" or "Probably Related". Events for which the Investigator or designee did not record relationship to study drug will be considered related to study drug for the purposes of analysis. Data listings will show relationship as missing in this case.

7.2.3. Serious Adverse Events

SAEs are those identified in the clinical database as serious by the Principal Investigator or designee. Further information on the definition of a SAE is provided in Section 6.1.4 of the study protocol.

7.2.4. Summaries of Adverse Events and Deaths

A single summary table of AEs will tabulate, by study arm, the number and percentage of subjects who had any (1) solicited or unsolicited AE, (2) solicited AE, (3) solicited systemic AE, (4) solicited local AE, (5) unsolicited AE, (6) treatment-related solicited or unsolicited AE, (7) solicited treatment-related AE, (8) solicited systemic treatment-related AE, (9) solicited local treatment-related AE, (10) unsolicited treatment-related AE, (11) SAE, (12) treatment-related SAE, (13) solicited or unsolicited AE leading to permanent discontinuation from the study, and (14) death during study.

Summaries (number and percent of subjects) of AEs will be provided by SOC and PT and study arm as follows:

- All AEs (inclusive of all solicited and unsolicited AEs)
- All unsolicited AEs
- Treatment-related unsolicited AEs
- AEs that caused permanent discontinuation from study,
- Unsolicited AEs by maximum severity grade,
- Treatment-related unsolicited AEs by maximum severity grade.

For subjects with multiple events, only one event will be counted in each summary. For data presentation, SOCs will be ordered alphabetically, with PT sorted by decreasing total frequency. Solicited AEs will be presented by decreasing total frequency. For summaries by maximum severity grade, only the event with the highest severity will be presented. For summaries by relatedness, only one event per relatedness category will be presented. Summaries will be provided by study arm and for the Safety Population.

In addition to the by-treatment summaries, data listings will be provided for the following:

- All unsolicited AEs
- All solicited events
- AEs leading to discontinuation from study
- SAEs
- Deaths

7.3. Safety Endpoints

The safety and tolerability endpoints include local and systemic post-injection solicited events and other AEs collected during the 7 days following the injection. Safety endpoints also include the occurrence of any unsolicited AEs through Day 29, and SAEs and AEs leading to withdrawal at any time during the study. All safety data will be tabulated according to study arm and at the time points of assessment.

7.3.1. Analysis Methods for Safety Endpoints

The number and percentage of subjects who experience a solicited AE recorded during Days 1 through 8 will be summarized according to maximum severity grade by study arm and decreasing total frequency. For subjects with multiple events of the same type, only the event of the highest severity will be counted in each summary. Events with missing severity grades will be handled according to Section 7.1.1. A Fisher's exact test will be used to compare the frequency of the corresponding solicited event between the two groups. The 95% CI for the subject percentages will be calculated using the Wilson method. This summary will be repeated for treatment-related solicited AEs and solicited AEs during Days 1 through 8 of at least severe (Grade 3) severity or higher.

Day of onset post-injection will be summarized with descriptive statistics for each type of solicited AE by study arm. The median and its 95% CI will be estimated by Kaplan-Meier analysis. The log-rank test will be used to compare day of onset between the two study arms. This summary will be repeated for treatment-related solicited AEs.

The number of days a subject experiences each solicited AE will be summarized by descriptive statistics (number of subjects with each solicited AE, mean, median, minimum and maximum) by study arm. The days may not be consecutive. The 95% CI of the mean will be based on t-statistics assuming a normal distribution. The 95% CI of the median will be a distribution-free estimate based on order statistics. A Wilcoxon rank sum test on the number of days of symptoms will be used to compare both groups. This summary will be repeated for treatment-related solicited AEs.

The percentage of subjects reporting solicited AEs will also be summarized for each event category and sign and/or symptom by study arm and day on study.

A summary of the number and percentage of subjects who experience an unsolicited AE during Days 1 through 29 by SOC and PT will be presented. Similarly, a summary of the number and percentage of subjects who experience a treatment-related AE during Days 1 through 29 by SOC and PT will be provided.

In addition, a summary of the number and percentage of subjects who experience an SAE during Days 1 through 182 by SOC and PT will be presented. Similarly, a summary of the number and percentage of subjects who experience a treatment-related SAE during Days 1 through 182 by SOC and PT will be provided.

7.3.2. Safety Subgroup Analysis

A summary of the number and percentage of subjects who experience a solicited and unsolicited AE during Days 1 through 29 by SOC and PT will be presented by race group – white or non-white – and gender.

7.4. Prior and Concomitant Medications

Only medications taken from 30 days prior to vaccination through study termination will be recorded.

Any medications started and stopped prior to or on the date of vaccination will be considered prior medications. If a partial stop date is entered and the month and year (if day is missing) or year (if day and month are missing) of the stop date are before the date of vaccination, the medication will be considered a prior medication.

Any medications started prior to or on the date of vaccination and continued to be taken after vaccination, or started after the date of vaccination, will be considered a concomitant medication. If a partial stop date is entered and the month and year (if day is missing) or year (if day and month are missing) of the stop date are after the date of vaccination, the medication will be considered a concomitant medication.

Concomitant medications (i.e., medications other than study vaccine that are taken while receiving study vaccine) and prior medications (medications started and ended before receiving study vaccine) will be coded using the World Health Organization (WHO) Drug Dictionary version September 2017. The WHO preferred name and drug code will be attached to the clinical database. All concomitant medications associated with unsolicited AEs will be documented through Day 29. Concomitant medications associated with SAEs will be documented through Day 182.

Use of concomitant and prior medications up to and including Day 29 will be summarized (number and percentage of subjects) by study arm, WHO drug class (ATC level 4), and WHO generic name. Multiple drug use (by preferred name) will be counted once only per subject. The summary will be sorted alphabetically by drug class and then by decreasing total frequency within a class. Concomitant medications reported with start dates after Day 29 through Day 182 for all subjects will be listed.

Summaries of prior and concomitant medications will be provided for the safety population. No p-values or inferences regarding comparisons of the usage of concomitant medications in the two study arms will be generated.

A listing of prior and concomitant medications will be provided, with a column indicating if a medication is prior, Y or N. Any exposed subjects who received an excluded concomitant medication will be provided in a separate listing.

7.5. Vital Signs

Vital signs will be listed by subject and time point for the exposed population.

7.6. Physical Examination

A data listing will be provided for physical examination results based on the exposed population.

7.7. Other Safety Measures

A data listing of all pregnancy test results as well as a data listing of HBV, HCV and HIV test results will be provided for exposed subjects.

8. CHANGES TO STATISTICAL METHODS IN THE PROTOCOL

The population labeled "Study Population" in the protocol has been renamed the "Enrolled Population."

In response to an issue raised by the FDA following a review of the study protocol, the following requirement was added to the definition of the immunogenicity evaluable population:

> In addition, all subjects in the alphavirus-naïve group are required to be seronegative for both neutralizing CHIKV and VEEV antibodies at baseline.

A titer of [redacted] was added to the summaries of the secondary immunogenicity endpoints identified as the proportion of subjects with titers of at least [redacted]. This addition was made to provide better profiling of the distribution of titers and to match data from other studies.

Fisher's exact tests were specified in the protocol as the primary method for comparing alphavirus-naive subjects to alphavirus-prior subjects. Logistic regression models that incorporated age and gender were also specified as sensitivity analyses for these endpoints. However, the models proved problematic, and in some cases impossible, to fit because of the high seroconversion rate in both groups. Thus, the logistic regression analyses were eliminated.

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10. SOFTWARE

SAS Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

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STATISTICAL ANALYSIS PLAN

ADDENDUM Number # 1

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 Number/Product: EBSI-CV-317-002 (CHIKV VLP vaccine)

Plan Prepared by: [redacted]

Version and Date: Version 1: 17 NOV 2021

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

CSR	Clinical Study Report
IEP	Immunogenicity Evaluable Population
mITT	Modified Intent-to-Treat
SAP	Statistical Analysis Plan
TOC	Table of Content

1. BACKGROUND AND RATIONALE

This addendum is to officially document the removal of certain tabular summaries from the final Clinical Study Report Tables.

2. STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) called for the following secondary endpoints:

Anti-CHIKV total antibodies, determined by immunoassay, in prior alpha subjects vs. naïve alpha subjects, assessed by

- The proportion of subjects with titers of at least [redacted] on Days 1, 22 and 29

Anti-VEEV total antibodies, determined by immunoassay, in prior alpha subjects vs. naïve alpha subjects, assessed by

- The proportion of subjects with titers of at least [redacted] at Days 1, 22 and 29

It was determined post database lock, that the threshold analysis of the anti-CHIKV total and anti-VEEV total antibodies had no valuable meaning with respect to historical sero-epidemiologic protection. Therefore, the CSR team decided that these summaries should be eliminated from the final set of tables.

Also included in the original TOC for the mock tables were cumulative percentages of subjects reaching 4-fold. Because all subjects experienced 4-fold rise by the second timepoint and the groups remained at 100% throughout the study, these tables (mITT and IEP) were considered moot and not produced (they exactly mimic the by-visit summary table).

3. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The following tables specified in the SAP mock table TOC, corresponding to the removed deleted analyses, have been removed.

14.2.1.7.1	Cumulative Percentage of Subjects with Anti-Chikungunya Neutralizing Activity At or Above Selected Thresholds by Time Point; Immunogenicity Evaluable Population
14.2.1.7.2	Cumulative Percentage of Subjects with Anti-Chikungunya Neutralizing Activity At or Above Selected Thresholds by Time Point; mITT Population
14.2.2.4	Percentage of Subjects with Anti-Chikungunya Total Antibody Activity At or Above Selected Thresholds by Time Point; Immunogenicity Evaluable Population
14.2.4.4	Percentage of Subjects with Anti-VEEV Total Antibody Activity At or Above Selected Thresholds by Time Point; Immunogenicity Evaluable Population

STATISTICAL ANALYSIS PLAN

ADDENDUM Number # 2

Protocol EBSI-CV-317-002

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

23 Feb 2024

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
CDISC	Clinical Data Interchange Standards Consortium
CSR	Clinical Study Report
IEP	Immunogenicity Evaluable Population
PRNT	Plaque-reduction Neutralizing Titer
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
TOC	Table of Contents

1. BACKGROUND AND RATIONALE

This addendum is to document both the addition and updating of the following:

- The study data tabulation model (SDTM) structures for the AE (adverse events) and CE (clinical events; the solicited data from the diaries) domains changed to follow the Office of Vaccines Research and Review (OVRR) guidance to provide consistency across studies

- To add the analyses associated with the following exploratory objective:

  Exploratory Objective: Evaluate the ability of anti-CHIKV antibodies to CHIKV VLP vaccine to neutralize diverse (other arthritogenic and encephalitic) alphavirus strains.

  The endpoints assessed as part of this statistical analysis plan addendum are associated with the analyses of plaque reduction neutralizing test ($PRNT_{50}$) titers associated with non-vaccine[1] (heterologous) CHIKV genotype strains measured at three time points (Day 1 (pre-vaccination), Day 22, and Day 182) to explore cross-neutralization activity.

2. STATISTICAL CONSIDERATIONS

Analysis Methods for Exploratory Immunogenicity Endpoints

All exploratory analyses will be performed for the IEP.

Heterologous CHIKV genotypes GMT:

The primary model used for the immunogenicity evaluable population is an analysis of variance (ANOVA), with logarithmically-transformed (log_{10}) titers as the dependent variable and study arm, age, and gender as the predictor variables in the model. The least square means estimated from the ANOVA and their 95% CIs will be back-transformed and reported as the group and overall GMT values. The ANOVA model will be used to determine the significance of the difference between the naïve and prior alphavirus groups.

Percentage of participants with seroconversion to the heterologous CHIKV genotype strains:

[1] CHIKV VLP vaccine is comprised of three recombinant CHIKV structural proteins (capsid, envelope 1 and envelope 2) derived from CHIKV Senegal West African strain 37997.

The percentage of participants with a $PRNT_{50}$ titer ≥20 (the lower limit of quantitation in the PRNT assay) and associated Wilson 95% CIs, will be summarized at Days 1, 22, and 182 for each CHIKV strain. The groups will be compared by pairwise Fisher's exact tests on the percentage with seroconversion.

Raw mean fold rise and geometric mean fold rise as compared to CHIKV strain 181/25:

Of particular interest is the ability of serum anti-CHIKV antibodies collected from individuals immunized with CHIKV VLP vaccine in the clinical study, to neutralize other CHIKV strains that are genotypically diverse from the vaccine strain (CHIKV Senegal strain 37997), as measured by $PRNT_{50}$ titers.

A validated Human SNA Assay was used to measure anti-CHIKV serum neutralizing antibodies (SNA) in the primary endpoint in this study, and throughout CHIKV VLP vaccine clinical development. The Human SNA Assay uses a modified version of CHIKV strain 181/25 engineered to express a luciferase transgene (*luc*) encoding bioluminescent luciferase enzyme (CHIKV-luc) and is based on the capacity of serum antibodies to neutralize (NT_{80}) the CHIKV-luc reporter virus *in vitro*. To explore the relative ability to neutralize the other CHIKV strains, a comparison back to strain 181/25 was performed.

For the comparison against 181/25, for each participant at each time point, the raw heterologous strain titer will be divided by the 181/25 strain titer to provide a raw fold difference. Descriptive statistics will be provided and statistical significance between the treatment groups will be based on a t-test.

As the titers and fold differences are not necessarily normally distributed, an additional analysis of geometric mean of the fold-increase in titer versus strain 181/25 will be provided. To calculate the geometric mean fold-increase and 95% CI, each strain titer will be log_{10}-transformed and the difference versus 181/25 strain computed (other strain minus 181/25 strain). The mean and 95% CI of the differences in the logs will be calculated and then exponentiated to convert to the non-transformed scale. A t-test will be used to compare the log_{10}-transformed difference in log titers between the prior alpha and naïve alpha subjects.

Changes to the safety dataset structures

The original CDISC datasets were based on a flat structure (each symptom per day per participant was its own record). The FDA OVRR guidance requires that the CE dataset for the data based on the diaries have a summary structure similar to the AE data (start and stop of the event) and that any event that carried past the diary collection be summarized with the diary data rather than as an AE. Per the protocol directions, if an event recorded on the diary continued past day 8, the event was to also be recorded as an AE. These data need to be copied to the CE data to reflect the full extent of the diary symptom duration.

As a result, the datasets that comprise the adverse event CDISC domains (AE and CE), need to be updated to reflect the FDA's guidance.

The changes needed are:

AE data

- STDM - leave the diary records in AE.
- Copy the events that start before Day 8 post injection to FACE (turn into flat structure - one record per event per day)
- Set flag in SUPPAE that this is record that was moved.
- Add same flag to ADaM ADAE dataset to exclude this data from the AE summaries to avoid double counting.

CE data

- Copy flat structure from CE to FACE domain.
- Combine the transferred AE data with the 'new' FACE data (see above) to produce a new summary CE record.
- CEDUR should consist of the dates from the CE and AE records combined (per pre-BLA response from FDA) to provide the full duration across the diary collection and into the AE collection time period.

As a result of these structural changes, the tables based on the solicited and unsolicited adverse events will be rerun.

3. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The following new and updated tables specified in the SAP addendum 2 mock table TOC will be:

New tables and listing:

Table/Listing	Title
14.2.6.1	Geometric Mean PRNT Titer Against Heterologous Chikungunya Strains
14.2.6.2	Percentage of Subjects with Seroconversion in Anti-Chikungunya PRNT Titer Against Heterologous Chikungunya Strains by Time Point
14.2.6.3	Raw Mean Fold Increase in PRNT Titer of Heterologous Chikungunya Strains Against 181/25 Homologous Strain by Time Point
14.2.6.4	Geometric Mean Fold Increase in PRNT Titer of Heterologous Chikungunya Strains Against 181/25 Homologous Strain by Time Point
16.2.6.4	Anti-Chikungunya PRNT50 Neutralizing Antibody Titers Against Non-vaccine Strains

Revised tables:

Table	Title
14.3.1	High Level Summary of All Solicited and Unsolicited Events
14.3.1.1	Solicited Events by Highest Reported Severity
14.3.1.2	Solicited Events of at Least Severe (Grade 3) Severity
14.3.1.3	Treatment-related Solicited Events by Highest Reported Severity
14.3.2.1	Day of Onset for Subjects who Reported Solicited Events
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14.3.4	Percentage of Subjects with Solicited Events by Day on Study
14.4.4.1	Unsolicited Adverse Events by Preferred Term in Descending Order of Incidence Through Day 29
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14.4.5.2	Solicited and Unsolicited Adverse Events Through Day 29 by System Organ Class and Preferred Term
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14.4.6	Unsolicited Adverse Events Through Day 29 by System Organ Class, Preferred Term, and Highest Reported Severity
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14.4.9.1	Treatment-related Unsolicited Adverse Events Through Day 29 by System Organ Class and Preferred Term
14.4.9.2	Treatment-related Solicited and Unsolicited Adverse Events Through Day 29 by System Organ Class and Preferred Term
14.4.10	Treatment-related Unsolicited Adverse Events Through Day 29 by System Organ Class, Preferred Term, and Highest Reported Severity