

Statistical Review and Evaluation	
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Applicant	PaxVax, Inc.
Established Name	Cholera Vaccine, Live, Oral
Trade Name	Vaxchora™
Pharmacologic Class	Vaccine
Dosage Form(s) and Route(s) of Administration	For PXVX-VC-200-003: 5×10^8 CFU, Oral For PXVX-VC-200-004: 1×10^9 CFU, Oral For PXVX-VC-200-005: 1×10^9 CFU, Oral
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	Active immunization against disease caused by <i>Vibrio cholerae</i> serogroup O1 in adults 18 years of age and older

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1. Executive Summary

This submission includes the applicant's clinical study reports (CSRs) for one Phase 1 study (PXVX-VC-200-002), and three Phase 3 studies (PXVX-VC-200-003, PXVX-VC-200-004, and PXVX-VC-200-005). The applicant is seeking licensure for Cholera Vaccine, Live, Oral (Vaxchora™) for active immunization against disease caused by *Vibrio cholerae* serogroup O1 in adults 18 years of age and older. The statistical review of this submission will focus on the three Phase 3 studies.

PXVX-VC-200-003 is a Phase 3, randomized, double-blind, placebo-controlled, efficacy study of a single dose of live oral Cholera vaccine candidate PXVX0200 CVD 103-HgR strain, in preventing Cholera following challenge with *Vibrio cholerae* O1 El Tor Inaba 10 days or 3 months after vaccination. A total of 197 subjects were enrolled and randomized (95 in vaccine group and 102 in placebo group); 68 were challenged 10 days after vaccination (35 in vaccine group and 33 in placebo group), 66 were challenged 3 months after vaccination (33 in vaccine group and 33 in placebo group), and 63 were not challenged (27 in vaccine group and 36 in placebo group).

The primary objectives of this study were to

- (1) Demonstrate that the lower bound of the 2-sided 95% confidence interval on the vaccine efficacy (VE) of a single dose of PXVX0200 is >30% following a challenge with virulent *V. cholerae* O1 El Tor Inaba 10 days post-vaccination, when (a) associated primary endpoint is the occurrence of moderate or severe diarrhea (≥ 3.0 L purge), (b) PXVX0200 recipients challenged at 10 days are compared with a pooled group of placebo recipients challenged at either 10 days or 3 months
- (2) Demonstrate that the lower bound of the 2-sided 95% confidence interval on the vaccine efficacy (VE) of a single dose of PXVX0200 is >30% following a challenge with virulent *V. cholerae* O1 El Tor Inaba 3 months post-vaccination, when (a) associated primary endpoint is the occurrence of moderate or severe diarrhea (≥ 3.0 L purge), (b) PXVX0200 recipients challenged at 3 months are compared with a pooled group of placebo recipients challenged at either 10 days or 3 months.

Vaccine efficacy of one oral dose of PXVX0200 was 90.3% with 2-sided 95% CI of (68.8%, 99.2%) at 10 days and 79.5% with 2-sided 95% CI of (51.1%, 96.3%) at 3 months against moderate or severe diarrhea following challenge with 1×10^5 CFU of heterologous *Vibrio cholerae* O1 El Tor Inaba. Both co-primary objectives were met. Subgroup analyses by blood type (O and non-O), sex (female and male), and race (black and white) did not show any notable differences in efficacy results between subgroups.

PXVX-VC-200-004 is a Phase 3, randomized, double-blind, placebo-controlled, three-lot consistency study in healthy adult volunteers to assess immunogenicity of a single-dose of the live oral Cholera vaccine candidate PXVX0200, *Vibrio cholerae* O1 serotype Inaba

vaccine strain CVD 103-HgR. A total of 3,146 subjects were enrolled and randomized to lot A (927 subjects), lot B (933 subjects), lot C (935 subjects), or placebo (351 subjects).

The primary objective of this study was to demonstrate consistency of three different production lots (A, B, and C) of PXVX0200 when (a) primary endpoint is serum vibriocidal antibody measured at Day 11, (b) consistency criterion is that the 2-sided 95% confidence interval (CI) around each pairwise ratio of GMTs be within [0.67, 1.5].

The 2-sided 95% CI around each pairwise ratio of geometric mean titers was (0.78, 1.08) comparing Lots A:B, (0.87, 1.20) comparing Lots B:C, and (0.80, 1.10) comparing Lots A:C, respectively. The primary objective of demonstrating consistency of three different production lots of PXVX0200 was met.

PXVX-VC-200-005 is a Phase 3, randomized, double-blind, placebo-controlled study in older adults (46-64 years) to assess immunogenicity of a single-dose of the live oral Cholera vaccine candidate PXVX0200 *Vibrio cholerae* O1 serotype Inaba vaccine strain CVD 103-HgR. A total of 398 subjects were randomized (299 in vaccine group and 99 in placebo group).

The primary objectives of this study were to

- (1) Demonstrate that seroconversion by classical Inaba vibriocidal antibody (defined as a ≥ 4 -fold rise over baseline titer) at Day 11 in older adults ages 46-64 years is non-inferior to seroconversion at Day 11 in younger adults ages 18-45 years following vaccination with PXVX0200, when the non-inferiority criterion is that the lower bound of the two-sided 95% confidence interval (CI) on the difference in seroconversion between older and younger adults be greater than -10 percentage points [The younger adult comparator group used for bridging analyses consisted of the Immunogenicity Evaluable Population from the PXVX-VC-200-004 lot consistency trial.]
- (2) Demonstrate acceptable immunogenicity of the vaccine among the older adults, when the acceptability criterion is that the lower bound of the two-sided 95% CI on seroconversion by classical Inaba vibriocidal antibody at Day 11 is greater than 70% in older adults ages 46-64 years following vaccination with PXVX0200.

Following vaccination, 90.4% [95% CI; 86.4%, 93.5%] of older subjects and 93.5% [95% CI; 92.5%, 94.4%] of younger subjects had seroconverted by classical Inaba vibriocidal antibody, and the lower bound of the two-sided 95% CI on the difference in seroconversion rate between older and younger adults was -7.2 percentage points. The primary objectives of this study were met.

2. Clinical and Regulatory Background

Please refer to this section in the medical officer's review.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues with respect to efficacy or safety were found.

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

5.1 Review Strategy

This submission includes the clinical study reports of PXVX-VC-200-003, PXVX-VC-200-004, and PXVX-VC-200-005. Statistical aspects of the efficacy, immunogenicity, and safety analyses were reviewed.

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

This submission (STN 125597/0) was received on 10/16/2015, and is located in the EDR. The Clinical Study Reports (CSR), electronic datasets, and Case Report Forms (CRF) for PXVX-VC-200-003, PXVX-VC-200-004, and PXVX-VC-200-005 are located in section 5.3.5.1 of this submission.

6. Discussion of Individual Studies/Clinical Trials

6.1 Clinical Trial #1: PXVX-VC-200-003

Title of the clinical trial: A Phase 3, randomized, double-blind, placebo-controlled efficacy trial of a single dose of live oral Cholera vaccine candidate, PXVX0200 CVD 103-HgR strain, in preventing Cholera following challenge with *Vibrio cholerae* O1 El Tor Inaba 10 days or 3 months after vaccination.

Date of study initiation: 9/13/2013
Date of study completion: 7/28/2014

6.1.1 Objective(s)

The primary objectives of this study were to

- (1) Demonstrate that the lower bound of the 2-sided 95% confidence interval on the vaccine efficacy (VE) of a single dose of PXVX0200 is >30% following a challenge with virulent *V. cholerae* O1 El Tor Inaba 10 days post-vaccination, when (a) associated primary endpoint is the occurrence of moderate or severe diarrhea (≥ 3.0 L purge), (b) PXVX0200 recipients challenged at 10 days are compared with a pooled group of placebo recipients challenged at either 10 days or 3 months
- (2) Demonstrate that the lower bound of the 2-sided 95% confidence interval on the vaccine efficacy (VE) of a single dose of PXVX0200 is >30% following a challenge with virulent *V. cholerae* O1 El Tor Inaba 3 months post-vaccination, when (a) associated primary endpoint is the occurrence of moderate or severe diarrhea (≥ 3.0 L purge), (b) PXVX0200 recipients challenged at 3 months are compared with a pooled group of placebo recipients challenged at either 10 days or 3 months.

6.1.2 Design Overview

The study was a Phase 3 randomized, double-blind, placebo-controlled three-center (in US) study to evaluate vaccine efficacy, immunogenicity, and safety of PXVX0200 compared with placebo following challenge with virulent *V. cholerae* at 10 days or 3 months post-vaccination in healthy volunteers aged 18 to 45 years.

PXVX0200 was provided as a lyophilized powder in a single-use sachet. It was reconstituted in bicarbonate buffer that was also provided in a single-use sachet. The batch used for this Phase 3 study had a titer of 5×10^8 CFU/dose at release. The placebo was physiological saline. The placebo was not matched to the vaccine visually or by taste, therefore subjects were dosed by an unblinded staff member not involved in post-vaccination assessments, in order to maintain the blind of staff performing post-vaccination assessments. Subjects were asked not to discuss the taste of the product with the clinic staff.

Eligible subjects for this study were healthy men and women aged 18 to 45 years. Planned enrollment was approximately 210 subjects (105 vaccine recipients; 105 placebo recipients). A total of 197 subjects (95 vaccine recipients; 102 placebo recipients) who completed informed consent and screening procedures, and met inclusion criteria and not exclusion criteria were randomized. All screening procedures were completed no more than 60 days before the Day 1 (Baseline) Visit. Screening procedures included medical

history, physical exam, vital signs, hepatitis B and C screen, HIV screen, ABO blood typing, urine pregnancy test (females of childbearing potential). The maximum total study duration for a given subject was approximately 241 days, including the screening period.

Subjects were randomly assigned according to a 1:1 ratio to receive either vaccine or placebo. The randomization procedure was stratified by study center. The subset of subjects to be challenged was selected from the pool of all subjects, using a random procedure stratified to ensure roughly equal balance between vaccine and placebo recipients so that at least 60% of subjects in each treatment group in the challenge had blood type O (Individuals with type O blood are less likely to be infected, but if infected, they are at greater risk for developing severe cholera).

A total of 197 subjects were enrolled and randomized (95 in the vaccine group and 102 in the placebo group); 68 were challenged 10 days after vaccination (35 in vaccine group and 33 in placebo group), 66 were challenged 3 months after vaccination (33 in vaccine group and 33 in placebo group), and 63 were not challenged (27 in vaccine group and 36 in placebo group). [Approximately 128 subjects (68 subjects for 10 day challenge; 60 subjects for 3 month challenge) were planned to be challenged. A random selection from a pool of available and eligible subjects was used to ensure balance across treatment maintaining a minimum of 60% blood group O subjects.]

6.1.3 Population

The key inclusion criteria for the enrollment of this trial were:

- Able to understand the study and give written consent.
- Healthy male and female adults, age 18 to 45 years (inclusive), without clinically significant medical history, physical or clinical laboratory abnormalities (as per protocol-defined acceptable ranges), and without protocol-defined abnormal ECG results at screening and pre-challenge.
- Women of childbearing potential must have had a negative pregnancy test at screening, prior to vaccination and challenge. Female subjects had to be of non-childbearing potential (as defined as surgically sterile or postmenopausal for more than 1 year), or if of childbearing potential had to be practicing abstinence or using an effective licensed method of birth control (e.g., hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), cervical sponges, diaphragms, condoms with spermicidal agents; or be in a monogamous relationship with a vasectomized partner) within 2 months of vaccination and had to agree to continue such precautions during the study and for 30 days post-challenge. Male subjects had to agree not to father a child for 30 days post-vaccination.
- Able to pass a written examination with at least a score of 70% correct in order to demonstrate their comprehension of the study procedures and possible side effects before inoculation with the challenge strain, *V. cholerae*. If the subject scored at least 50% correct, he/she could take the test a second time after undergoing re-education, but could not participate if the second score was less than 70%.

- Agreeable not to participate in another investigational vaccine or drug trial during the duration of the study.
- Willing and able to comply with the study requirements and procedures.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study vaccine (Vaxchora™):

Single dose: each sachet of lyophilized vaccine contained nominally 5×10^8 CFU at release. The vaccine was reconstituted in 100 mL of bicarbonate buffer solution prior to oral administration.

6.1.6 Sites and centers

This study was conducted in 3 centers in Maryland, Ohio, and Vermont.

6.1.7 Surveillance/Monitoring

Please refer to this section in the medical officer's review.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the occurrence of moderate or severe diarrhea (≥ 3.0 L cumulative purge) post-challenge with virulent V. cholerae O1 El Tor Inaba 10 days (Day 11) and 3 months post-vaccination (Day 91) in two separate challenges. The co-primary objectives of the study were to demonstrate that the lower bound of the 2-sided 95% confidence interval on vaccine efficacy was $>30\%$ at both of these time points. Success at both the 10-Day and 3-Month Challenges was required to achieve success for the trial as a whole.

6.1.9 Statistical Considerations and Statistical Analysis Plan

Vaccine efficacy (VE) was estimated by comparing the attack rates of moderate/severe diarrhea in the two vaccinated challenge groups to those in the combined placebo group. Confidence intervals (CIs) for the VE estimates were calculated using the method of Farrington and Manning (1990).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Efficacy Endpoint

The analysis of primary efficacy endpoint was performed on the ITT Cohort for efficacy.

Table 1 shows the primary efficacy results that the applicant proposed to present in the Package Insert (PI).

Table 1: Vaccine Efficacy for 10-Day and 3-Month Challenge Groups

	VAXCHORA 10-Day (35 subjects)	VAXCHORA 3-Month (33 subjects)	Combined Placebo^a (66 subjects)
Parameter	n (%)	n (%)	n (%)
Attack Rate ^b : Moderate or Severe Diarrhea (≥ 3.0 L)	2 (5.7%)	4 (12.1%)	39 (59.1%)
Vaccine Efficacy ^c	90.3%	79.5%	

^a Combined placebo group comprised all placebo recipients who were challenged at either 10 days or 3 months following vaccination.

^b Attack Rate: Moderate or severe diarrhea severity, as noted by ≥ 3.0 L of overall diarrheal purge.

^c Vaccine Efficacy = [(Attack Rate in Placebo Group – Attack Rate in Vaccine Group)/Attack Rate in Placebo Group] x 100.

Reviewer's Comments:

1. The applicant performed the efficacy analyses as pre-specified.
2. One oral dose of PXVX0200 demonstrated vaccine efficacy of 90.3% with 95% CI of (68.8%, 99.2%) at 10 days against moderate or severe diarrhea following challenge with 1×10^5 CFU of heterologous *Vibrio cholerae* O1 El Tor Inaba. [The applicant's CI was (62.7%, 100.0%)]
3. One oral dose of PXVX0200 demonstrated vaccine efficacy of 79.5% with 95% CI of (51.1%, 96.3%) at 3 months against moderate or severe diarrhea following challenge with 1×10^5 CFU of heterologous *Vibrio cholerae* O1 El Tor Inaba. [The applicant's CI was (49.9%, 100.0%)]
4. Both co-primary objectives for efficacy were met.

6.1.12 Safety Analyses

Reactogenicity signs and symptoms after administration of study product were reported by 49.5% of vaccine recipients and 50.0% of placebo recipients. No notable difference in the frequency of any reactogenicity sign or symptom was identified between vaccine and placebo recipients.

Diarrhea, as a solicited symptom of reactogenicity defined as ≥ 4 loose stools per 24 hours, was reported in 1.1% of vaccine and 3.0% of placebo recipients as reactogenicity and in 2.1% of vaccine and 0% of placebo recipients as AEs.

One SAE was reported during this study. Placebo recipient 01047 was hospitalized for orthopedic surgery; the investigator considered this SAE to be unrelated to vaccination. This event occurred 57 days post-challenge. One potentially life threatening event post-challenge occurred in this study. Placebo recipient 03019 developed hyperkalemia 3 days post-challenge, which the investigator considered unrelated to vaccination.

Please refer to this section in the medical officer's review for more detailed analysis of safety.

6.1.13 Subgroup Analyses

Subgroup analyses by blood type (O and non-O), sex, and race (black and white) did not show differences in efficacy and safety results between subgroups. Among 197 randomized subjects, 133 (67.5%) subjects were black, 58 (29.5%) subjects were white, 2 (1.0%) were native American or Asian, and 4 (2.0%) were other race.

6.2 Clinical Trial #2: PXVX-VC-200-004

Title of the clinical trial: A Phase 3, randomized, double-blind, placebo-controlled three-lot consistency study in healthy adult volunteers, to assess immunogenicity of a single-dose of the live oral Cholera vaccine candidate PXVX0200, *Vibrio cholerae* O1 serotype Inaba vaccine strain CVD 103-HgR.

Date of study initiation: 5/12/2014

Date of study completion: 2/23/2015

6.2.1 Objective(s)

The primary objective of this study was to demonstrate consistency of three different production lots (A, B, and C) of PXVX0200 when (a) primary endpoint was serum vibriocidal antibody measured at Day 11, (b) consistency criterion was that the 2-sided 95% confidence interval (CI) around each pairwise ratio of GMTs was within [0.67, 1.5].

6.2.2 Design Overview

The study was a Phase 3 randomized, double-blind, placebo-controlled study with a planned enrollment of up to 2,964 subjects 18 to 45 years old (inclusive) randomized to receive either PXVX0200 (2,634) or placebo (330) at approximately 40 sites. Subject eligibility was determined during an up-to-45-day screening period and subjects were vaccinated on Day 1.

Each subject was scheduled for at least three visits: the vaccination visit (could be combined with screening visit) on Day 1, and post-vaccination visits on Day 11 and Day 29. Total study duration for a given subject was approximately 226 days, including the screening visit which could occur on Day 1. A phone follow-up was scheduled for Day 181.

Subjects were randomly assigned to receive a single dose from one of three lots of PXVX0200 or placebo according to an 8:8:8:3 ratio (A:B:C:P) using randomized permuted blocks of 27.

A total of 3,146 subjects were enrolled and randomized to lot A (927 subjects), lot B (933 subjects), lot C (935 subjects), or placebo (351 subjects).

6.2.3 Population

The key inclusion criteria for the enrollment of this trial were:

- Able to understand the study and give written consent.
- Healthy male and female adults, age 18 to 45 years (inclusive) without significant medical history and physical examination findings at screening.
- Women of childbearing potential must have a negative urine pregnancy test at screening prior to vaccination. Female subjects must be of non-childbearing potential (defined as surgically sterile or postmenopausal for more than 1 year), or if of childbearing potential must be practicing abstinence or using an effective licensed method of birth control (e.g., hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, intrauterine devices [IUDs], cervical sponges, diaphragms, condoms with spermicidal agents; or must have a vasectomized partner) within 2 months of vaccination and must agree to continue such precautions during the study.
- Willing and able to comply with the study requirements and procedures.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Study vaccine (Vaxchora™):

Single dose: each sachet of lyophilized vaccine contained nominally 1×10^9 CFU at release. The vaccine was reconstituted in 100 mL of bicarbonate buffer solution prior to oral administration.

6.2.6 Sites and centers

This study was conducted in 25 sites in the U.S. (19 sites) and Australia (6 sites).

6.2.7 Surveillance/Monitoring

Please refer to this section in the medical officer's review.

6.2.8 Endpoints and Criteria for Study Success

The primary immunogenicity endpoint used to demonstrate consistency of three different production lots of PXVX0200 was serum vibriocidal antibody measured at Day 11 using consistency criteria in the Immunogenicity Evaluable Population. The 2-sided 95% CI around each pairwise ratio of GMTs was required to be within [0.67, 1.5].

6.2.9 Statistical Considerations and Statistical Analysis Plan

The primary analysis consisted of three between-lot equivalence tests of serum vibriocidal antibody titer measured at Day 11. The GMT of each lot (μ_A , μ_B , and μ_C) was calculated by log-transforming (base 10) the serum vibriocidal antibody titers, computing the means of the transformed data by lot, and then exponentiating the log-scale means to return to the original, untransformed scale. The resulting GMTs were combined to form three ratios: μ_A/μ_B , μ_A/μ_C , and μ_B/μ_C .

The CIs for the ratios of GMTs were calculated following similar logic. First, a CI was determined for the mean difference between two lots of log-transformed data. The CI was calculated using the formula for the two-sample t-test but since there are three lots instead of just two, an analysis of variance (ANOVA) model was used to obtain an estimate of the residual variance needed for the formula. Once the CI was determined in the log scale, the CI in the original scale was obtained by exponentiation.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Immunogenicity Endpoint

The analysis of the primary immunogenicity endpoint was performed on the Immunogenicity Evaluable Population.

The 2-sided 95% CI around each pairwise ratio of geometric mean titers was (0.78, 1.08) comparing Lots A:B, (0.87, 1.20) comparing Lots B:C, and (0.80, 1.10) comparing Lots A:C, respectively.

Reviewer's Comments:

1. The applicant performed the efficacy analyses as pre-specified.
2. As shown above, the primary objective of demonstrating immunologic equivalence (lot consistency) of three different production lots of PXVX0200 was met.

6.2.12 Safety Analyses

Reactogenicity signs and symptoms after vaccine administration were reported by 51.9% of vaccine recipients and 43.2% of placebo recipients. Reactogenicity signs and symptoms of at least moderate severity were reported by 23.8% of vaccine recipients and 18.4% of placebo recipients. Especially, headache was reported in 28.9% of vaccine recipients and 23.6% of placebo recipients. Also, diarrhea (defined as ≥ 4 loose stools per 24 hours) was reported in 3.9% of vaccine recipients and 1.2% of placebo recipients.

Adverse events post-vaccination through Day 29 were reported by 23.0% of vaccine recipients and 24.0% of placebo recipients and were mostly mild in severity. There was one death (in the vaccine group) during the study due to suicide (Onset Day 85; Subject R4-251356) that seemed to be not related to study product. Nineteen subjects reported 23

SAEs other than death during this study. None of the SAEs were considered (by the applicant) related to the study product, and all but two had resolved by Day 181. The 2 events that had not resolved were exacerbation of depression and fracture of left patella in 2 subjects (both in the vaccine group) who were lost to follow up.

Two subjects (both in the vaccine group) reported grade 4 events, considered probably related to study product, that did not meet the definition of an SAE (fever of 104.7°F and diarrhea that resulted in an emergency room visit).

Please refer to this section in the medical officer's review for more detailed analysis of safety.

6.2.13 Subgroup Analyses

Subgroup analyses [by blood type (O and non-O), sex, and race of immunogenicity data were not relevant to the trial's main objectives of demonstrating consistency among vaccine lots.

6.3 Clinical Trial #2: PXVX-VC-200-005

Title of the clinical trial: A Phase 3 randomized, double-blind, placebo-controlled study in older adults (46 to 64 years of age) to assess immunogenicity of a single-dose of the Live Oral Cholera Vaccine Candidate PXVX0200 *Vibrio cholerae* O1 Serotype Inaba Vaccine Strain CVD 103-HgR

Date of study initiation: 5/19/2014

Date of study completion: 1/15/2015

6.3.1 Objective(s)

The primary objectives of this study were to

- (1) Demonstrate that seroconversion (defined as ≥ 4 -fold rise over baseline titer) by classical Inaba vibriocidal antibody at Day 11 in older adults aged 46-64 years was non-inferior to seroconversion at Day 11 in younger adults aged 18-45 years following vaccination with PXVX0200. The non-inferiority criterion was that the lower bound of the two-sided 95% confidence interval (CI) on the difference in seroconversion between older and younger adults must be greater than -10 percentage points,
- (2) Demonstrate that the lower bound of the two-sided 95% CI on seroconversion by classical Inaba vibriocidal antibody at Day 11 was greater than 70% in older adults aged 46-64 years following vaccination with PXVX0200.

6.3.2 Design Overview

The study was a Phase 3 randomized, double-blind, placebo-controlled study that planned to screen approximately 480 healthy older adult subjects aged 46-64 years (inclusive) and enroll approximately 400 subjects. Subjects were to be randomized in a 3:1 ratio to receive one oral dose of either vaccine (n~300) or placebo (n~100). Subject eligibility was determined during a 45-day screening period and subjects were vaccinated on Day 1. Each subject was scheduled for at least four visits: a Screening Visit, a vaccination visit on Day 1, and post-vaccination visits on Day 11 and Day 29. Telephone follow-up contacts were scheduled for Day 91 and Day 181.

A total of 398 subjects were randomized, 299 to vaccine and 99 to placebo (physiological saline) at 16 investigational sites in the U.S.

6.3.3 Population

The key inclusion criteria for the enrollment of this trial were:

- Able to understand the study and give written consent
- Healthy male and female adults, age 46-64 years (inclusive) without significant medical history, physical, or abnormal screening laboratory test results at screening
- Women of childbearing potential must have had a negative urine pregnancy test at screening, prior to vaccination. Female subjects must be of non-childbearing potential (as defined as surgically sterile or postmenopausal for more than 1 year), or if of childbearing potential must be practicing abstinence or using an effective licensed method of birth control (e.g., use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, intrauterine devices [IUDs], cervical sponges, diaphragms, condoms with spermicidal agents; or must have a vasectomized partner) within 2 months of vaccination and must agree to continue such precautions during the study
- Willing and able to comply with the study requirements and procedures.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Study vaccine (Vaxchora™):

Single dose: each sachet of lyophilized vaccine contained nominally 1×10^9 CFU at release. The vaccine was reconstituted in 100 mL of bicarbonate buffer solution prior to oral administration.

6.3.6 Sites and centers

This study was conducted in 16 sites in the U.S.

6.3.7 Surveillance/Monitoring

Please refer to this section in the medical officer's review.

6.3.8 Endpoints and Criteria for Study Success

The immunogenicity endpoint was seroconversion by vibriocidal antibody (defined as ≥ 4 -fold rise over baseline titer) against the classical Inaba biotype of *V. cholerae* at Day 11 post-vaccination.

Non-inferiority would be demonstrated if the lower bound of the two-sided 95% CI on the difference in the percentage of seroconverters between older and younger adults was greater than -10 percentage points.

Additionally, the lower bound of the two-sided 95% CI on seroconversion by classical Inaba vibriocidal antibody at Day 11 was required to be greater than 70% in older adults aged 46-64 years.

6.3.9 Statistical Considerations and Statistical Analysis Plan

The difference between older and younger adults in the Day 11 seroconversion rate was calculated and a 95% Wald CI on the difference was estimated. The lower limit of the CI had to be greater than -10 percentage points for the first primary objective to be met.

The Day 11 seroconversion rates for both older and younger adults were reported along with their Clopper-Pearson two-sided 95% CIs. The lower bound of the CI on the older adults' seroconversion rate was required to exceed 70% to meet the second primary objective.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Immunogenicity Endpoint

The immunogenicity analyses were performed on the Immunogenicity Evaluable Population from the lot consistency study and the Immunogenicity Evaluable Population from the current study.

The primary objectives of demonstrating (a) seroconversion by classical Inaba vibriocidal antibody on Day 11 was non-inferior to seroconversion in younger adults, defined as the lower bound of the two-sided 95% CI on the difference in seroconversion rate being greater than -10 percentage points, and (b) the lower bound of the two-sided 95% CI on seroconversion was greater than 70% in older adults, were met.

Following vaccination, 90.4% [95% CI; 86.4%, 93.5%] of older subjects and 93.5% [95% CI; 92.5%, 94.4%] of younger subjects had seroconverted by classical Inaba

vibriocidal antibody. The lower bound of the two-sided 95% CI on the difference in seroconversion between older and younger adults was -7.2 percentage points [The applicant's LB was -6.7 percentage points]. The lower bound of the two-sided 95% CI on seroconversion in older adults was 86.4%.

Reviewer's Comments:

1. The applicant performed the efficacy analyses as pre-specified.
2. As shown above, the primary objectives of demonstrating non-inferior immunogenicity in the older adult population (compared to younger adults) and acceptable immunogenicity among older adults were met.

6.3.12 Safety Analyses

Reactogenicity signs and symptoms after vaccine administration were reported by 36.3% of vaccine recipients and 50.5% of placebo recipients. The percentage of placebo recipients with tiredness was higher (36.4% vs. 20.0%) compared with vaccine recipients.

Unsolicited AEs were reported by 20.6% of vaccinees and 27.3% of placebo recipients, with no clear differences in the frequency and severity of AEs between vaccine and placebo recipients.

Three subjects in the vaccine group experienced SAEs during this study. None of the SAEs (atrial fibrillation, myocardial infarction, and spinal compression fracture) were considered (by the applicant) to be related to the study product.

Please refer to this section in the medical officer's review for more detailed analysis of safety.

6.3.13 Subgroup Analyses

Subgroup analyses by blood type (O and non-O), sex, and race (black and white) did not reveal differences in immunogenicity results between subgroups. Among 398 randomized subjects, 87 (21.9%) subjects were black, 298 (74.9%) subjects were white, 10 (2.5%) were native American, Pacific Islander or Asian, and 3 (0.7%) were other race.

7. Integrated Overview of Efficacy

N/A. [Study PXVX-VC-200-003 was an efficacy study following a challenge with virulent *V. cholerae* O1 El Tor Inaba. Study PXVX-VC-200-004 was a three-lot consistency study in healthy adult volunteers (18-45 years of age), and study PXVX-VC-200-005 was a study for older adults (46-64 years) to assess immunogenicity.]

8. Integrated Overview of Safety

N/A. Please see section 7.

10. Conclusions

Based on study PXVX-VC-200-003, vaccine efficacy of one oral dose of PXVX0200 was 90.3% with 2-sided 95% CI of (68.8%, 99.2%) at 10 days and 79.5% with 2-sided 95% CI of (51.1%, 96.3%) at 3 months against moderate or severe diarrhea following challenge with 1×10^5 CFU of heterologous *Vibrio cholerae* O1 El Tor Inaba. Both co-primary objectives of demonstrating that the lower bound of the 2-sided 95% confidence interval on vaccine efficacy was >30% at both of these time points were met.

Based on study PXVX-VC-200-004, the 2-sided 95% CI around each pairwise ratio of geometric mean titers was (0.78, 1.08) comparing Lots A:B, (0.87, 1.20) comparing Lots B:C, and (0.80, 1.10) comparing Lots A:C, respectively. The primary objective of demonstrating consistency of three different production lots of PXVX0200 was met.

Based on studies PXVX-VC-200-004 and PXVX-VC-200-005, 90.4% [95% CI; 86.4%, 93.5%] of older subjects and 93.5% [95% CI; 92.5%, 94.4%] of younger subjects had seroconverted by classical Inaba vibriocidal antibody, and the lower bound of the two-sided 95% CI on the difference in seroconversion rate between older and younger adults was -7.2 percentage points. The primary objectives of this study were met.