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Center for Biologics Evaluation and Research (CBER)
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TO: Biologics License Application Submission Tracking Number 125597/0

SUBJECT: Clinical Serology Assays Review of Biologics License Application
Number 125597

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APPLICANT: PaxVax Bermuda Limited

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1 General Information

PaxVax is seeking United States licensure of a live, attenuated cholera vaccine (PXVX0200) for active immunization against disease caused by *Vibrio cholerae* serogroup O1 in adults 18 years of age or older. The supporting information for safety and efficacy submitted to support licensure was obtained under investigational new drug (IND) application number 15010 originally submitted on 10 February 2012. The application received Fast Track designation on 20 December 2012. PaxVax proposes that the Biologic License Application (BLA) approval be based on safety and immunogenicity data from one Phase I study and three Phase III studies. PaxVax also proposes that the evidence for vaccine efficacy be based on the protection from cholera disease observed in a human challenge study.

The PXVX0200 vaccine candidate consists of a live, replication-competent, recombinant, attenuated *Vibrio cholerae* serogroup O1 classical Inaba 569B strain (CVD 103-HgR). The strain is attenuated by removal of a substantial portion (94%) of the catalytic domain of the cholera enterotoxin A subunit gene (*ctxA*). In addition, a mercury resistance marker (*mer* operon) is inserted into the hemolysin A (*hlyA*) locus. Insertion of the *mer* operon allows the vaccine strain CVD 103-HgR to be distinguished from the Wild-type 569B strain.

The vaccine formulation consists of a single dose package containing two multilayer foil sachets. One sachet contains 4×10^8 to 2×10^9 colony-forming units (CFU) of the lyophilized vaccine strain. The second sachet contains sodium bicarbonate and sodium carbonate buffer powder. The buffer sachet contents are reconstituted by mixing in 100 mL of bottled water. The contents of the sachet containing the lyophilized vaccine strain are then added to the resuspended buffer solution. The reconstituted vaccine is administered orally to recipients.

1.1 Review Identifiers and Dates

1.1.1 Biologics License Application (BLA) Submission Tracking Number (STN) #:
125597/0

1.1.2 Submission received by CBER: 16 October 2015

1.1.3 Review completed: 5 May 2016

1.1.4 Material reviewed

The following general module sections of the BLA were reviewed with regard to clinical serology assays

m1	Regional
m2	Common Technical Document Summaries
m5	Clinical Study Reports

A more detailed list of information in the BLA reviewed is provided below

Original submission dated 16 October 2015

m1.6	Meetings
m2.5	Clinical Overview
m2.7.2	Summary of Clinical Pharmacology Studies
m2.7.3	Summary of Clinical Efficacy
m5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies
m5.3.5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, PXVX-VC-200-002, PXVX-VC-200-003, PXVX-VC-200-004 PXVX-VC-200-005

1.1.5 Related Master File, INDs and BLAs

IND 15010

2 Executive Summary

The areas included in this review are the validated clinical serology assays and clinical serology data used to bridge vaccine efficacy from the challenge model to the general population and across populations. The benefit of the vaccine was demonstrated by direct human challenge of vaccinated individuals. The efficacy in the general population was then confirmed by demonstrating vaccine-induced immune responses in a larger adult population. In addition, the efficacy in older adults was demonstrated by immunologic noninferiority to the younger adults.

In this BLA, PaxVax has submitted immunogenicity data based on serum vibriocidal antibody (SVA) titers, serum anti-toxin antibody titers (b) (4) and memory B cell responses (b) (4) against cholera toxin B subunit and cholera lipopolysaccharide (LPS). The relevant clinical endpoints and criteria, as well as the quality of the vibriocidal and anti-toxin (b) (4) assays were discussed extensively with the applicant during the IND phase of clinical development. Prior to BLA submission, the applicant had submitted validation data to support adequate performance of the vibriocidal assays and (b) (4).

The anti-toxin B memory B cell (b) (4) assay was introduced by the applicant in the BLA submission as an exploratory endpoint in the clinical studies. However, this assay has only been qualified and no validation data have been submitted by the applicant. As the assay was used for exploratory endpoint only, it will not be formally reviewed here.

Initial safety and immunogenicity were assessed in a Phase I clinical study. Direct evidence of protection against cholera disease was derived from a Phase III placebo-controlled human challenge study in volunteers 18-45 years old. Protection was assessed by challenging volunteers 10 days (Day 11) or 3 months (Day 91) after vaccination. Data from this trial indicated that serum vibriocidal antibody titers against *V. cholerae* O1 classical Inaba measured at Day 11 correlated with protection. CBER and PaxVax agreed that seroconversion (defined as a ≥ 4 -fold increase over baseline titer) of classical Inaba vibriocidal antibody at Day 11 could be used as the primary clinical endpoint of vaccine efficacy in bridging studies. For subjects whose baseline titers are less than or equal to the lower limit of quantitation (LLOQ), the post-vaccination titer

must be greater than or equal to four times the LLOQ. For subjects whose baseline titers are greater than the LLOQ, the post-vaccination titer must be greater than or equal to four times the baseline titer.

Immunological equivalence of three different production lots was demonstrated in a Phase III clinical study in adults 18-45 years old by assessing the consistency of serum vibriocidal antibody responses across the three production lots. Additional safety and immunogenicity data were obtained in a third Phase III study in adults 46-64 years of age. The likely benefit of the vaccine in the older adults was assessed by noninferiority of the seroconversion rates of classical Inaba vibriocidal antibody at Day 11 post vaccination in the older adult group versus that in adults aged 18-45. Non-inferiority would be demonstrated if the lower bound of the two-sided 95% confidence interval on the difference in seroconversion rate between the older and younger adult groups was greater than -10 percentage points.

The performance of the cholera serum vibriocidal antibody titer assay and cholera toxin IgG (b) (4) quantitative assay was supported by validation and stability reports that were submitted to the BLA. The performance of the assays was found to be adequate for their intended use.

The data generated in each study was evaluated and no aberrant or unusual data were observed.

3 Review of Clinical Serology Assays

3.1 Serum Vibriocidal Antibody Assay

The following documents were submitted in support of the cholera serum vibriocidal assay used as a correlate of efficacy in clinical studies to bridge between populations of different ages. The summary information is taken from the original application Module 2.7.2, Table 3, Summary of Clinical Pharmacology Studies. All documents are found in BLA Section 5.3.1.4, Reports of Bioanalytical and Analytical Methods for Human Studies.

Vibriocidal Antibody against classical Inaba and classical Ogawa serotypes of *Vibrio cholerae*,

TSOP.119.0561E, AVAL.119.00064.01C, AVAL.119.00109A

Vibriocidal Antibody against El Tor Inaba and El Tor Ogawa serotypes of *Vibrio cholerae*,

TSOP.119.00743B, AVAL.119.00087A

QC Log Sheets for Serum Vibriocidal Antibody Assay,

C-Inaba-PXVX-VC-200-003, C-Inaba-PXVX-VC-200-004, C-Inaba-PXVX-VC-200-005, C-Ogawa-PXVX-VC-200-003, C-Ogawa-PXVX-VC-200-005, ET-Inaba-PXVX-VC-200-003, ET-Inaba-PXVX-VC-200-005, ET-Ogawa-PXVX-VC-200-005, C-Ogawa-PXVX-VC-200-005,

The cholera serum vibriocidal antibody assays were used to measure vibriocidal activity against *V. cholerae* O1 classical Inaba and Ogawa and El Tor Inaba and Ogawa in clinical samples from the Phase III studies. The assays were validated at (b) (4). The technical standard operating procedure (TSOP) documents as well as validation reports were submitted to IND 15010 and reviewed prior to the BLA submission. Following review and discussion of the submitted information with the sponsor, CBER accepted the currently reported lower limits of quantitation (LLOQs) that are based on the precision and accuracy data. The same information as that submitted to the IND was included in the BLA.

(b) (4)


The assay was initially developed at the (b) (4) and subsequently transferred to (b) (4). (b) (4) has been responsible for full validation of the assay as well as analyzing all clinical samples from the Phase III studies.

Summary of the assay validations at (b) (4)

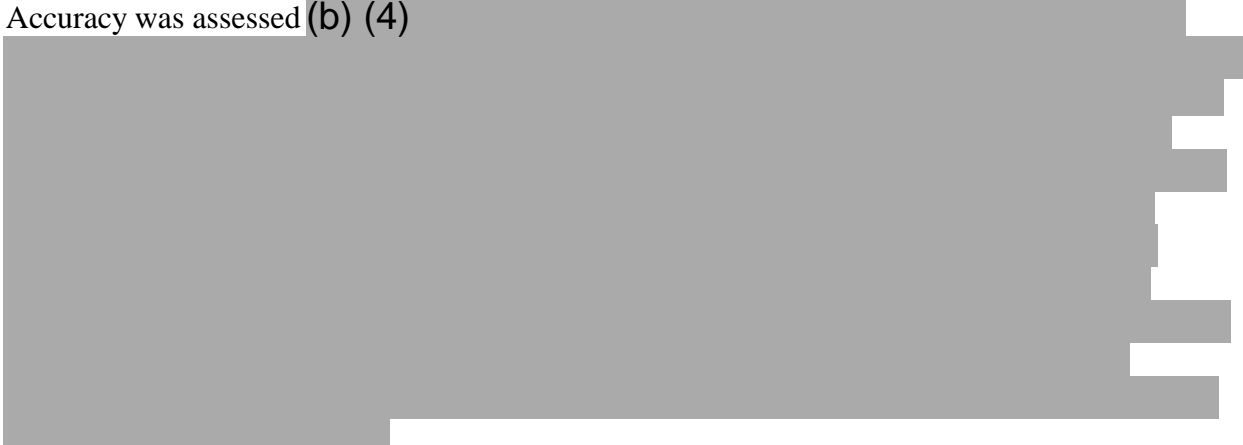
Three validation reports were submitted to support the performance of the serum vibriocidal assay. Prior to the start of the Phase III clinical studies, PaxVax submitted validation reports to support the performance of the SVA in evaluating vibriocidal activity against classical Inaba and Ogawa strains of *V. cholerae* O1. Validation evaluated precision, accuracy/dilutability, specificity, sample stability, LLOQ, and robustness. Following review of the validation results, CBER requested that the acceptance criteria for precision be based on the coefficient of variation (%CV) rather than a qualitative criterion such as a 2-fold change from the median of reported titer values. CBER also requested additional testing of samples diluted down to and beyond the LLOQ and limit of detection (LOD) to demonstrate accuracy across the range of the assay and to assess the rates of false negative and false positive results. In addition, CBER requested that incurred samples be tested during validation to reflect assay performance with clinical samples from the pivotal Phase III trials. PaxVax submitted a validation report addendum that included the requested additional precision and accuracy evaluations. PaxVax also submitted a validation report to support the adequate performance of the SVA in measuring vibriocidal activity against El Tor Inaba and Ogawa strain of *V. cholerae*.

Precision was assessed (b) (4)


(b) (4)




Accuracy was assessed (b) (4)



Assay specificity was evaluated (b) (4)



PaxVax included robustness as a validation parameter for the SVA. Robustness was evaluated for the (b) (4)



The applicant provided data to support the stable performance of the assay over time. Assay stability was supported by data from assay controls that were recorded and tracked for pass/fail criteria and for trending on a monthly basis. No trends were observed over time.

In summary, the cholera serum vibriocidal assays performed at (b) (4) are considered adequately validated for the detection and measurement of antibacterial antibodies to *Vibrio cholerae* O1 classical and El Tor biotypes in test sera derived from the clinical studies.

3.2 Cholera Toxin Quantitative IgG (b) (4)

The following documents were submitted in support of the cholera toxin IgG (b) (4) used to measure immune response to Vaxchora to support bridging between populations of different ages. The summary information is taken from the original application Module 2.7.2, Table 3, Summary of Clinical Pharmacology Studies. All documents are found in BLA Section 5.3.1.4, Reports of Bioanalytical and Analytical Methods for Human Studies.

Anti-Cholera Antibody (b) (4)

TSOP.119.00562D, AVAL.119.00065A, AVAL.119.00108A

The anti-cholera toxin (CT) antibody assay measures serum IgG antibodies against cholera toxin. Validation of the assay was conducted at (b) (4). The TSOP documents as well as validation reports were submitted to IND 15010 and reviewed prior to the BLA submission. Following review and discussion of the submitted information with the sponsor, CBER accepted the currently reported lower limits of quantitation (LLOQs) that are based on the precision and accuracy data.


The assay is a (b) (4) that begins with (b) (4)

The assay was initially developed at the (b) (4) and subsequently transferred to (b) (4). In addition to validating the CT antibody (b) (4) was also responsible for analyzing all clinical samples from the Phase III studies.

Summary of the assay validations at (b) (4)

Two validation reports were submitted to the BLA to support the performance of the CT antibody assay. PaxVax submitted a validation report to IND 15010 prior to the initiation of the Phase III clinical studies to support the performance of the assay in evaluating serum IgG antibody levels against cholera toxin. CBER requested that the acceptance criteria for precision be based on the coefficient of variation (%CV) rather than a qualitative criterion such as a 2-fold change from the median of reported titer values. CBER also requested that an LLOQ, based demonstrated accuracy and precision, be established for the assay, and that additional testing of samples diluted down to and beyond the LLOQ and limit of detection (LOD) be done to demonstrate accuracy across the range of the assay and to assess the rates of false negative and false positive results. In addition, CBER also requested that incurred samples be tested during validation to reflect assay performance with clinical samples from the pivotal Phase III trials. PaxVax submitted a validation report addendum that included additional precision and accuracy evaluations.

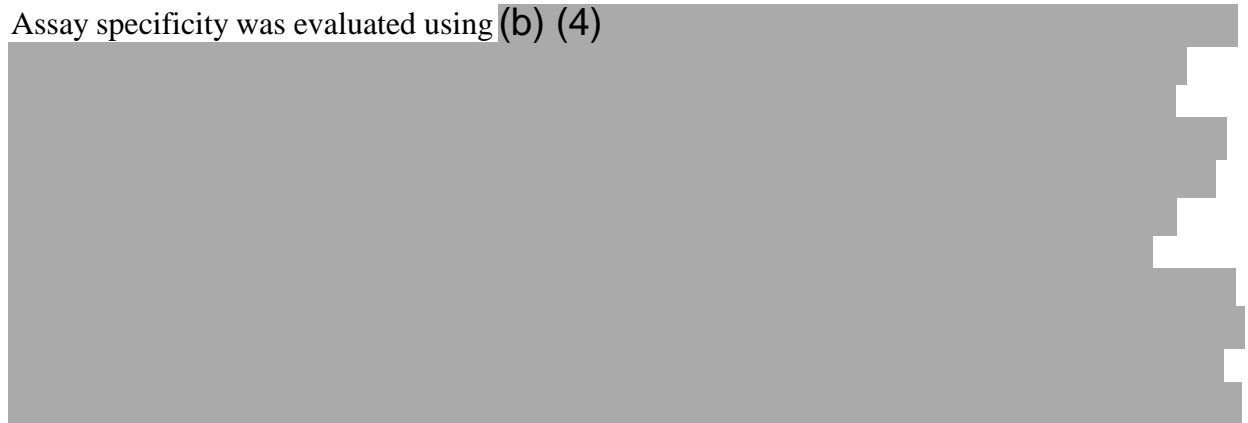
Precision was assessed (b) (4)



Accuracy was assessed by (b) (4)



Assay specificity was evaluated using (b) (4)



Evaluation of assay robustness was done by (b) (4)



In summary, the cholera toxin IgG (b) (4) quantitative assay performed at (b) (4) is

considered adequately validated for the detection and measurement of serum IgG antibodies against cholera toxin.

4 Review of Clinical Serology Data

In this BLA, PaxVax submitted summary data on four randomized, double-blinded, and placebo-controlled clinical trials of the PXVX0200 cholera vaccine. The trials were conducted in healthy subjects of both sexes aged 18-64 years old. Study PXVX-VC-200-002 was a Phase I study designed to evaluate the safety and immunogenicity of PXVX0200. Vaccine efficacy was demonstrated in a Phase III US human cholera challenge trial (PXVX-VC-200-003). Another Phase III clinical lot study (PXVX-VC-200-004) was carried out to demonstrate immunologic equivalence of three vaccine lots. A third Phase III study (PXVX-VC-200-005) evaluated immunogenicity in older adults. Only the data from the Phase III studies are reviewed here.

Each of the Phase III clinical studies is listed below with a summary review.

PXVX-CV-200-203: A Phase III 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* 01 El Tor Inaba 10 Days or 3 Months after Vaccination

Study Groups

Group 1 received a single dose of vaccine (N=95); 35 in day-10 challenge, 33 in 90-day challenge, and 27 not challenged

Group 2 received a single dose of placebo (N=102); 33 in day-10 challenge, 33 in day-30 challenge, and 36 not challenged

Primary Objectives

The co-primary objectives of this study were to demonstrate that the lower 95% confidence bound on the protective efficacy of a single dose of PXVX0200 was at least 30% following challenge at both 10 days (Day 11) and 3 months (Day 91) post-vaccination.

Secondary Objectives

To evaluate the impact of vaccination on disease severity based on total weight of diarrheal stools, incidence of fever, and incidence of shedding of wild-type *V. cholerae* post-challenge.

Exploratory Endpoints

To explore the relationship between pre-challenge, post-vaccination vibriocidal and/or anti-CT antibody and the incidence of moderate/severe diarrhea, mild

diarrhea, any diarrhea, or measures of diarrhea severity such as total number or total volume of diarrheal stools.

Results

In this study, subjects in the vaccine group received a single dose of PXVX0200 containing 5×10^8 CFU of the vaccine strain. This dose is 10-fold lower (based on CFUs) than that used in the other Phase III clinical studies. The purpose of this lower dose of vaccine was to obtain evidence of efficacy of a low dose to support setting of product specifications.

The vaccine strain is derived from a strain of the *V. cholerae* O1 classical Inaba serotype. However, the challenge strain (N16961) in this study is of the El Tor Inaba serotype. The challenge strain is the only clinical-grade strain available for human challenge studies. In addition the applicant indicated that the study would provide some evidence of vaccine cross protection against biotypes of the O1 serogroup.

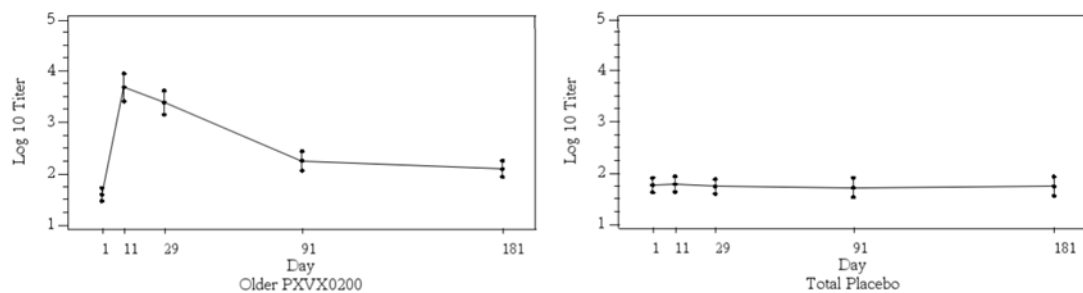
Analysis of the challenge data performed by the applicant indicated that a single dose of PXVX0200 had a protective efficacy of 90.3% [62.7%, 100.0%] at 10 days and of 79.5% [49.9%, 100.0%] at 3 months against moderate or severe diarrhea post-challenge. Therefore, the applicant concluded that both co-primary objectives were met because the lower 95% confidence bound on protective efficacy was greater than 30% for the challenge groups.

In an effort to define potential correlates of protection, exploratory analyses were performed to determine the relationship between immunogenicity measured by vibriocidal and/or anti-CT antibody titers and the incidence of moderate/severe cholera in the Day 11 and Day 91 cohorts in the challenge study.

The two validated serological assays, vibriocidal antibody assay and anti-CT antibody assay, were used to obtain immunogenicity data from clinical samples collected at Days 1, 8, 11, 29, and 181. Vibriocidal titers were assessed against classical Inaba and Ogawa and El Tor Inaba and Ogawa.

The figure below shows vibriocidal geometric mean titers against classical Inaba measured at Days 1, 11, 29, 91 and 181 following vaccination.

Figure 1
Time course plot of the vibriocidal geometric mean titer (95% CI)
Against *V. cholerae* classical Inaba (from figure 11.4.3 Integrated Summary of Efficacy)

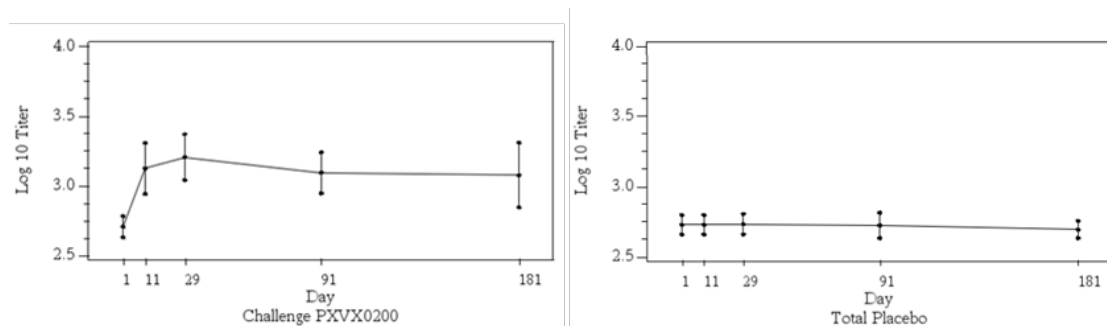


Note: For classical Inaba *V. cholerae* in Challenge trial, only 3-Month Challenge group is measured at Day 91, and only non-challenge group is measured at day 181.

The geometric mean titers increased rapidly after vaccination and peaked at day 11 and subsequently declined. However, post day 11 GMTs in the vaccinated group were still significantly higher than the placebo group GMTs. Similar rates of kinetics were observed for all *V. cholerae* serotypes and for all vaccinated groups in the 3 Phase III clinical studies.

The anti-CT antibody titers did not show similar kinetics as the vibriocidal titers and instead peaked at day 29 and decreased only slightly thereafter as shown below.

Figure 2
Time course plot of anti-CT geometric mean titer (95% CI)
(from figure 11.4.12 Integrated Summary of Efficacy)



Note: For Anti-CT in Challenge trial, only 3-Month Challenge group is measured at Day 91, and only non-challenge group is measured at day 181.

The cumulative rates of seroconversion, defined as a 4-fold increase over baseline, in vibriocidal antibody titer at the peak (Day 11) of the immune response in vaccine recipients were determined for the classical and El Tor biotypes. These data are summarized in the table below (Table 23).

Table 23 Day 11 Vibriocidal 4-Fold Rise, All Biotypes and Serotypes - Immunogenicity Evaluable Population

Cholera Strain	PXVX0200 N=94	Placebo N=102	P-value ^a
Classical Inaba	89.4%	2.0%	<0.0001
El Tor Inaba	90.4%	3.9%	<0.0001
Classical Ogawa	86.2%	2.9%	<0.0001
El Tor Ogawa	88.3%	4.9%	<0.0001

Note: Statistics describe the cumulative number and percentage of subjects who had at least a 4-fold rise in titer over the titer measured by Day 1.

a P-value was calculated using Fisher's exact test comparing number of vaccine recipients with a 4-fold rise with placebo recipients.

Source: Table 14.4.2, Table 14.4.5, Table 14.4.8, Table 14.4.11.

The cumulative rates of seroconversion at Day 11 were comparable against the different *V. cholerae* O1 serotypes studied. In contrast, the cumulative rates of seroconversion based on anti-CT antibody titers reached a maximum of 38.3% at Day 181.

Analysis of the immunogenicity results in the challenge group to determine potential correlates of protection revealed that seroconversion at Day 11 in vibriocidal antibody titer, had a significant correlation with protection against moderate/severe cholera in both the Day 11 and Day 91 challenge studies. The rates of seroconversion were 94% for the Day 11 challenge group and 88% for the Day 91 challenge group. In contrast, the seroconversion rates for the placebo group (challenged) was only 2%.

The relationship between seroconversion and rates of protection against moderate/severe cholera is shown in the table below (Table 28).

Table 28 Protection Against Moderate/Severe Cholera and Vibriocidal Seroconversion^a by Day 11

	N	Mod/Sev Diarrhea in Seroconverters	Mod/Sev Diarrhea in Non- Seroconverters	Rate of Protection among Seroconverters	95% CI on Rate of Protection
Vaccine - Day 11 Challenge	35	1/33 (3%)	1/2 (50%)	97%	[84% , 100%]
Vaccine - Day 91 Challenge	33	1/29 (3%)	3/4 (75%)	97%	[82% , 100%]

Note: Vaccinees only; N=68. Across the two challenge groups, 1 placebo subject out of 66 seroconverted at Day 11, and this subject did not develop moderate/severe cholera.

Source: PXVX STAT-VIB-003, Table 2.

In contrast to the strong association between vibriocidal antibody seroconversion and protection, the anti-CT antibody titer data was not strongly associated with prevention of moderate/severe cholera. Of the 33 vaccine recipients in the 3 month challenge study,

only 48% (16 of 33) had seroconverted prior to challenge. The data support the use of seroconversion at Day 11 as a correlate for inferring protection and for bridging to non-challenged vaccine recipients.

PXVX-CV-200-204: A Phase III Randomized, Double-Blind, Placebo-Controlled Three-Lot Consistency Study in Healthy Adult Volunteers to Assess Immunogenicity, and Clinical Acceptability of a Single Dose of the Live Oral Cholera Vaccine Candidate, PXVX0200, *Vibrio cholerae* O1 Serotype Inaba Vaccine Strain CVD 103-HgR

Study Groups

Group 1 received a single dose of vaccine (N=2789)
Group 2 received placebo (N=351)

Primary Objectives

The primary immunologic objective of this Phase 3 trial was to demonstrate the immunologic equivalence of three different production lots of PXVX0200 at Day 11 post-vaccination in healthy volunteers 18-45 years of age. The criteria to demonstrate equivalence was that the geometric mean antibody titer (GMT) of each lot must be within $\pm 50\%$ of each other lot with 95% confidence. In addition the 95% confidence interval (CI) around each pairwise ratio of GMTs must be between 0.67 and 1.5.

Secondary Objectives

Estimate the seroconversion rate by serum vibriocidal antibody by Day 11 (Immunogenicity Evaluable Population).
Estimate the antibody response profile up to 6 months post-vaccination (Immune Sub-study Population).

Results

Three different lots of final vaccine product were administered to study participants. Lot A (P700-550-1CA03) was administered to 925 subjects, lot B (P700-550-3CA03) to 933 subjects, and lot C (P700-550-6BA03). Subjects (n=351) in the placebo group received physiological saline.

Assessments of vibriocidal activity against the classical Inaba biotype of *V. cholerae* were performed on blood samples collected from all subjects on Days 1 and 11. For an immune sub study group, vibriocidal antibody and anti-CT antibody assessments were made at Days 1, 11, 29, 91 and 181. The rates of vibriocidal seroconversion were 94% for the vaccine group and 4% for the placebo group. Results of the analysis of GMT ratios in the lot consistency study are summarized in Table 1.

Table 1
Geometric mean ratios (GMR) between vaccine lots and 95% CI on GMR
(Source: Post Hoc Analysis Report No. PXVX-STAT-HOC-OVR)

Comparison	Geometric Mean Ratio	95% CI on GMR	Pre-Defined Equivalence Interval
Lot A vs. Lot B	0.92	[0.78, 1.08]	[0.67, 1.5]
Lot B vs. Lot A	1.02	[0.87, 1.20]	
Lot A vs. Lot C	0.94	[0.80, 1.10]	

These results indicate that the criteria to demonstrate immunologic equivalence of the three lots based on the GMR between lots being within $\pm 50\%$ of each other and the 95% CI around each pairwise ratio of GMTs of [0.67, 1.5] were met.

PXVX-CV-200-205: A Phase III Randomized, Double-Blind, Placebo-Controlled Study in Older Adults to Assess Immunogenicity and Clinical Acceptability of a Single dose of the Live Oral Cholera Vaccine Candidate, PXVX0200 *Vibrio cholerae* O1 Serotype Inaba Vaccine Strain CVD 103-HgR

Study Groups

Group 1 received a single dose of vaccine (N=296)
Group 2 received placebo (N=99)

Primary Objectives

The primary objectives of this trial were to demonstrate that the post vaccination seroconversion rate measured by classical Inaba vibriocidal antibody titers at Day 11 in older adults ages 46–64 was non-inferior to the rate at Day 11 in younger adults ages 18–45, and that the lower bound of the two-sided 95% CI on seroconversion was greater than 70% in older adults. Non-inferiority margin: 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.

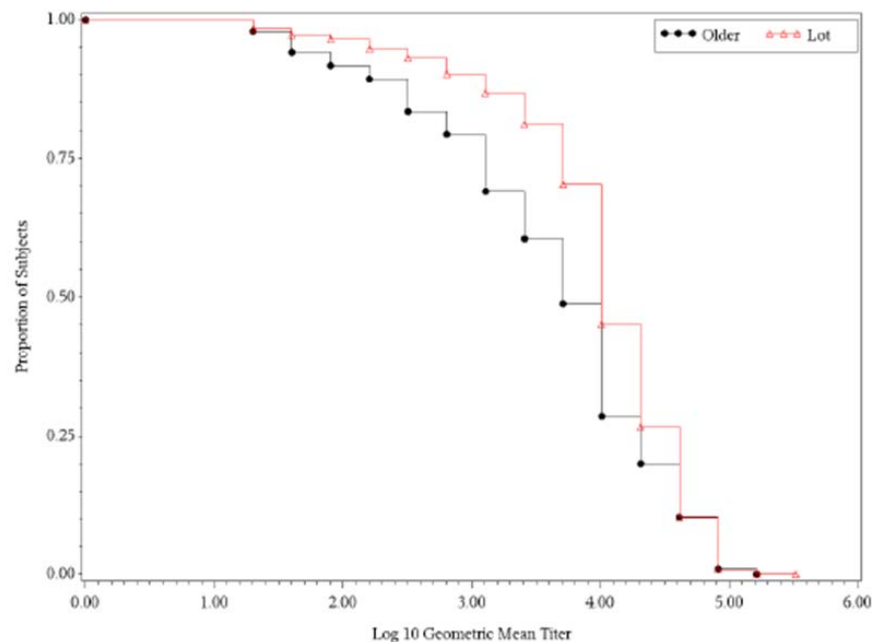
Secondary Objectives

The secondary objective was to compare the classical Inaba vibriocidal geometric mean titer (GMT) attained by older adults ages 46-64 years to the GMT of younger adults ages 18-45 years following vaccination with PXVX0200

Results

Serum vibriocidal antibody titers and seroconversion rates against classical Inaba were compared between the older adult group in this study and the younger adult group of the lot consistency study. Differences in the immune responses can be observed in the following reverse cumulative distribution plots shown in Figures 3 and 4 below.

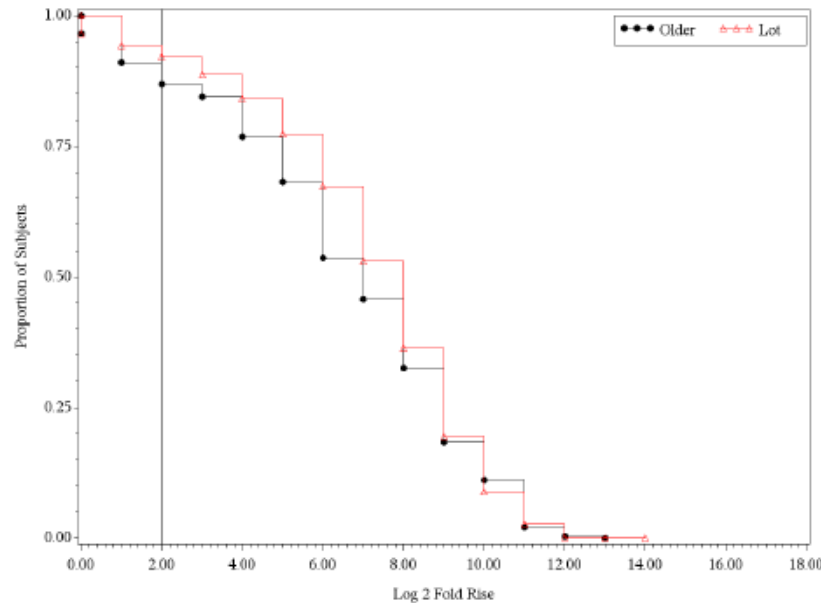
Figure 3
Reverse Cumulative Distribution Curves on Geometric Mean Titer
Against Classical Inaba *V. cholerae* at Day 11 (Lot Consistency and Older Adult Trials)
(Figure 11.4.16 from Integrated Summary of Efficacy)



Analysis of immune responses based on vibriocidal antibody titers between the younger adults in the lot consistency study and older adults shows that the immune responses detected in the older adults were lower than those in the younger adult population (Figure 3). However, as Figure 4 shows, a distribution of the vibriocidal antibody fold-rise following vaccination shows a much closer agreement between the two populations. This is consistent with the close agreement seen when the two populations are compared based on vibriocidal seroconversion (≥ 4 -fold rise over baseline).

Figure 4
Reverse Cumulative Distribution of Vibriocidal Fold-Rise Against

Classical Inaba *V. cholerae* at Day 11 (Lot Consistency and Older Adult Trials)
(Figure 11.4.17 from Integrated Summary of Efficacy)



The observed rates of seroconversion against classical Inaba following vaccination were 90.4% [86.4, 93.5%] in the older subjects and 93.5% [92.55, 94.45] in younger subjects. The lower limit on the two-sided 95% CI on seroconversion at Day 11 for the older adults was 86.4%. The lower bound of the two-sided 95% CI on seroconversion differences between the two groups was -6.7 which satisfies the pre-specified requirement that it must be greater than -10 percentage points.

Clinical serology assay review summary

The validated clinical serologic assays appear to perform adequately for their intended use. Immunogenicity of the vaccine product was assessed based on serum vibriocidal antibody titers and anti-CT antibody titers. Vibriocidal seroconversion, defines as a ≥ 4 -fold rise over baseline at Day 11, was shown to be an acceptable correlate of vaccine efficacy for the purpose of bridging responses in adult populations to the responses in vaccinated individuals shown to be protected in the challenge study. Vibriocidal antibody titers were also used to demonstrate immunologic equivalence across three production lots of vaccine. Non-inferiority of immune responses between the older adults (46-64 year olds) and the younger adults (18-45 year olds) was also demonstrated based on vibriocidal antibody seroconversion. The data provide reasonable evidence of the likely benefit of the vaccine.

5 Recommendation

The validation data on the clinical serology assays submitted by PaxVax demonstrate that the assays perform adequately for their intended use. Seroconversion based on a four-fold increase

over baseline in the vibriocidal antibody titers measured at day 11 post vaccination is an acceptable correlate of vaccine efficacy for the purpose of bridging responses in the lot consistency study to the responses in vaccinated individuals shown to be protected in the challenge study.

Based on the data I reviewed, I recommend approval of the product.