BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125597/123
CBER Received Date	April 1, 2020
PDUFA Goal Date	January 1, 2020
Division / Office	DVRPA/OVRR
Priority Review	Yes
Reviewer Name(s)	Tina Khoie Mongeau, MD, MPH
Review Completion Date / Stamped Date	December 2, 2020
Supervisory Concurrence	R. Douglas Pratt, MD, MPH Associate Director for Medical Affairs, DVRPA/OVRR
	Lucia Lee, MD Team Leader CRB1/DVRPA/OVRR
Applicant	PaxVax Bermuda, Ltd.
Established Name	Cholera Vaccine, Live, Oral
Trade Name	Vaxchora
Pharmacologic Class	Vaccine
Formulation	A single dose contains $4x10^8$ to $2x10^9$ colony forming units live attenuated *Vibrio cholerae* strain CVD 103-HgR and excipients in buffer solution.
Dosage Form(s) and Route of Administration	Suspension administered orally. - Prepared by adding 1 packet of active component (lyophilized live attenuated *Vibrio cholerae* CVD 103-HgR) to 1 packet of buffer that is reconstituted in purified bottled or spring bottled water. The buffer packet contains lyophilized sodium bicarbonate (2.16-2.41 g), sodium carbonate (0.24-0.49 g), ascorbic acid (1.50-1.80 g), and dried lactose (0.18-0.22 g). For persons > 6 years of age, the active component is added to 100mL of buffer solution. For children 2 through 6 years of age, 50 mL of buffer solution is discarded before adding the active component to the buffer solution.
Dosing Regimen	Single dose. After preparation, a single dose is 100 mL in persons > 6 years of age and 50 mL in children 2 through 6 years of age.
Indication and Intended Population	*Indication*: Active immunization against disease caused by *V. cholerae* serogroup O1. *Intended population*: Individuals 2 through 17 years of age traveling to cholera-affected areas. Vaxchora is already approved for use in individuals 18 through 64 years of age.
Orphan Designated	No

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GLOSSARY

AE	Adverse Event
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CSR	Clinical Study Report
CVD	Center for Vaccine Development
CFU	Colony Forming Unit
CI	Confidence Interval
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
IEP	Immunogenicity Evaluable Population
IgA	Immunoglobulin alpha
IgG	Immunoglobulin gamma
IND	Investigational New Drug
LLOQ	Lower Limit of Quantification
mITT	Modified Intent-to-Treat
NCT	National Clinical Trial
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
PVP	Pharmacovigilance Plan
SAE	Serious Adverse Event
sBLA	Biologics License Application supplement
STN	Submission Tracking Number
SVA	Serum Vibriocidal Antibody
U.S.	United States
VRBPAC	Vaccines and Related Biologics Products Advisory Committee

1. EXECUTIVE SUMMARY

PaxVax Bermuda, Ltd. Has submitted a Biologics License Application supplement (sBLA) to support use of Cholera Vaccine, Live, Oral (Vaxchora) in children 2 years through 17 years of age traveling to cholera-affected areas. The indication, active immunization against disease caused by *Vibrio cholerae* serogroup O1, including El Tor Inaba, classical Inaba, El Tor Ogawa, and classical Ogawa subtypes, is unchanged. Vaccine effectiveness in children 2 years through 17 years was inferred via immunobridging of classical Inaba vibriocidal antibody responses in children and adolescents to vibriocidal antibody responses in the adult population in which efficacy of Vaxchora was previously established (STN 125597/0).

The safety and immunogenicity of Vaxchora in children 2 years through 17 years of age were evaluated in a single, phase 4, randomized, double-blind, placebo-controlled single-crossover study (PXVX-VC-200-006) conducted in the United States (U.S.). Study participants were randomized in a 6:1 ratio to receive a single oral dose of Vaxchora or a single oral dose of saline placebo. Enrollment was stratified by age: 12 to < 18 years (Cohort 1), 6 to < 12 years (Cohort 2), and 2 to < 6 years (Cohort 3). Eligible subjects had no prior history of cholera infection or cholera vaccination and had not traveled to a cholera-endemic area within the past 5 years.

The primary study objectives aimed to (1) compare classical Inaba vibriocidal antibody seroconversion rates at 10-days following Vaxchora vaccination in children 2 through 17 years of age to the corresponding seroconversion rates in adults 18 through 45 years of age who received a single Vaxchora vaccination in lot consistency study PXVX-VC-200-004, and (2) demonstrate that the seroconversion rate in study PXVX-VC-200-006 Vaxchora recipients 2 through 17 years of age was greater than or equal to 70% with 98.3% confidence. In order to ensure that the total Type I error for the study was capped at an alpha equal to 0.05, 2/3 of the alpha (0.033) was allotted to the primary objective of comparing seroconversion rates relative to study -004 and 1/3 of the alpha (0.017) was allotted to the primary objective of demonstrating a seroconversion rate that is ≥ 70%. The two primary objectives were evaluated independently. Within each primary objective, hypothesis testing in the different age cohorts proceeded sequentially beginning with the data for Cohort 1. Vibriocidal antibody seroconversion rates were assessed by age cohort, as it was hypothesized that subjects' immune responses could differ due to gastrointestinal maturity.

Both primary objectives were met for each of the three study cohorts. The lower limit of the 2-sided 96.7% confidence interval (CI) on the difference in seroconversion rates between Vaxchora recipients in each cohort of study PXVX-VC-200-006 and adult Vaxchora recipients in study PXVX-VC-200-004 was greater than -10% (the pre-specified immune-bridging success criterion). In addition, the lower limit of the 98.3% CI on the seroconversion rate in each of the 3 study cohorts was > 70%.

A total of 468 Vaxchora recipients and 75 placebo recipients 2 through 17 years of age were included in the safety population. Overall, the safety profile of Vaxchora in this age group was consistent with the safety profile as described in Vaxchora prescribing information, and no safety concerns were identified. There appeared to be a general trend toward lower reporting rates of solicited adverse reactions in both study groups with decreasing age.

Since no safety signals were identified in this sBLA, routine pharmacovigilance (PVP) as proposed by the Applicant is adequate. A post-licensure U.S.-based pregnancy registry is ongoing with prospective collection of safety data on spontaneously reported exposures to Vaxchora occurring within 28 days prior to the last menstrual period or at any time during pregnancy.

The submission of this BLA supplement, which contains the final clinical study report for study PXVX-VC-200-006, fulfills the post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA) for children 2 through 17 years of age, as specified in the June 10, 2016 approval letter for the Vaxchora BLA (STN 125597/0). The Vaxchora prescribing information was updated to extend approved Usage to children 2 years through 17 years of age and to include safety and immunogenicity results from study PXVX-VC-200-006.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Among the 550 total randomized subjects, the median age was 9.0 years (ranging from 2-17 years). Overall, 52.0% of subjects were male. By race, 59.8% of randomized subjects identified as White, 31.1% as Black or African Americans,7.6% as multiple races, 0.9% as Asian, and 0.5% as American Indian or Alaskan Native. By ethnicity, 8.5% identified as Hispanic or Latino, and 91.5% identified as not Hispanic or Latino. Although the baseline demographics were generally balanced across the two treatment groups in the overall study, they differed within the age-based study cohorts by one or more demographic characteristics. The proportion of Black or African American subjects and the proportion of females in the Vaxchora group compared to the Placebo group were both higher in Cohort 2 and both lower in Cohort 3. In addition, a higher proportion of Cohort 1 subjects self-identified as White by race or Hispanic or Latino by ethnicity compared to Cohorts 2 and 3.

1.2 Patient Experience Data

Patient experience data was not submitted as part of this application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Cholera is an acute, secretory diarrheal disease caused by intestinal infection with toxin producing strains of *Vibrio cholerae* serogroups O1 and O139.[1,2] Cholera transmission is closely linked to resource limited settings where minimal requirements of clean water and sanitation are not met.[3] Dense populations (e.g., refugee camps) and populations affected by natural disasters are at a particular high risk.[1,2] The main reservoirs of *V. cholerae* are humans and environmental waters globally.[1,3] Transmission occurs through consumption of contaminated water or food[1] (i.e., food washed with contaminated water or exposed to contaminated irrigation water, or raw or undercooked shellfish from contaminated waters).[1]

The risk of illness is increased in persons with gastric hypochlorhydria, non breast-fed infants, young children, and travelers who drink untreated water or eat poorly cooked or raw seafood in disease-endemic areas.[4] In areas of high endemicity in Asia, the incidence of *V. cholerae* infection follows a seasonal distribution with peaks before and after rainy seasons. The incidence of cholera in cholera-affected areas is highest in children < 5 years of age[5,6], likely reflecting the lack of acquired protective immunity. In

populations with more limited immunity, massive epidemics may occur with similar attack rates in children and adults.[2]

Travelers who follow the usual tourist itineraries and who observe safe food and water recommendations and hygiene precautions while in countries reporting cholera have virtually no risk of acquiring cholera.[4] Although rare, several cases of cholera have been reported among U.S. health care workers caring for cholera patients in Haiti and in the U.S.[4] Travelers at highest risk are those who are visiting remote areas where access to safe food and water and medical care are likely to be limited. Risk is also higher among persons with underlying medical conditions that predispose them to increased morbidity due to moderate or mild diarrhea.

Most persons infected with *V. cholerae* are asymptomatic or have only mild diarrhea. When illness does occur, about 80-90% of cases are of mild or moderate severity and are difficult to distinguish clinically from other types of acute diarrhea. Less than 20% of ill persons develop typical cholera with signs of moderate-to-severe dehydration.[7,8]

Please refer to section 2.1 of the clinical review of the original BLA submission (STN 125597/0) for more detailed information.

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

Prevention strategies primarily include ensuring access to safe water (i.e., water for consumption, washing and preparing food, or brushing teeth), making food safe for consumption (i.e., peeling fruits and vegetables, thoroughly cooking high-risk foods, particularly seafood), improving sanitation and ensuring appropriate hand hygiene after defecating and before preparing or eating food. Water can be disinfected through chlorination or boiling. Foods such as fish, rice, or grain gruels should be refrigerated promptly after meals and thoroughly reheated before eating.[9] Cholera vaccines, in addition to the preventive strategies discussed above, can assist in cholera control.

Cholera can be treated with prompt and adequate rehydration and electrolyte replacement (i.e., correct the acidosis and potassium deficiency); antibiotic therapy can be initiated in moderate-to-severe cases.[1] Antibiotics can be used to reduce the volume of diarrhea and the length of time the organism is excreted in the stool.[1] The choice of antibiotic should be based on availability and local resistance patterns. Although *V. cholerae* strains remain susceptible to commonly used antibiotics, strains resistant to one or more antibiotics have been reported. In addition, unlike other enteric organisms, predominant strains often lose their resistance; so antibiotic resistance can vary from time to time and from place to place.[1]

Children in resource-limited areas may additionally benefit from supplementation with zinc.[4,10] Zinc supplementation has been shown to reduce the duration and volume of stool in children with cholera.[4,10,11]

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no other U.S.-licensed vaccines for the prevention of disease caused by *V. cholerae*. Please refer to section 2.3 of the clinical review of the original Vaxchora Biologics License Application (BLA) [STN 125597/0] for details regarding killed cholera

vaccines licensed outside of the U.S. and a live oral vaccine similar to Vaxchora (Orochol/Mutachol Berna] that was previously licensed outside of the U.S.

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

Vaxchora was first approved in the U.S. on June 10, 2016 for active immunization against disease caused by *Vibrio cholerae* serogroup O1 in adults 18 through 64 years of age traveling to cholera-affected areas. Vaxchora was evaluated in 4 randomized, placebo-controlled, clinical trials. A total of 3235 adults 18 through 64 years of age received one dose of Vaxchora and 562 received placebo. Overall, the most common adverse reactions (incidence > 3%) were tiredness (31%), headache (29%), abdominal pain (19%), nausea/vomiting (18%), lack of appetite (17%) and diarrhea (4%).

Vaccine efficacy was demonstrated in a randomized, double-blind, saline placebo-controlled *V. cholerae* challenge study conducted in the U.S. Vaccine efficacy was evaluated in adults 18 through 45 years of age with no prior history of cholera infection or travel to a cholera-endemic area in the previous 5 years. Vaccine efficacy against the occurrence of moderate-to-severe diarrhea at 10 days postvaccination was 90.3% [95% CI 62.7%, 100.0%] and at 3 months post-vaccination was 79.5% [95% CI 49.9%, 100.0%]. The effectiveness of Vaxchora for adults 46 through 64 years of age was inferred following comparisons of classical vibriocidal antibody seroconversion rates at 10-days post-vaccination in adults 46 through 64 years of age to the corresponding seroconversion rates achieved by 18 through 45-year-old Vaxchora recipients from the aforementioned efficacy study (immunobridging).

One additional non-IND foreign study was conducted in Mali. This randomized, placebo-controlled, double-blind Phase 2 trial evaluated Vaxchora when administered to adults 18 through 45 years of age at ≥ $2x10^8$ colony forming units (CFU) (n=49) and ≥ $2x10^9$ CFU (n=49) compared to placebo (n=99) and compared to an inactivated oral cholera vaccine (Shanchol; Shantha Biotechnics). No safety signals were detected following Vaxchora.

Please refer to Vaxchora prescribing information and/or the clinical review of the original Vaxchora BLA for more information regarding pre-licensure experience with Vaxchora.[12]

Following licensure in the U.S. in 2016, [redacted] doses were distributed through July 2019. A total of 123 adverse event reports were received via spontaneous post-marketing surveillance. No new safety reactions or other safety concerns were identified. Please refer to the CBER epidemiology review memo for more information.

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

On December 20, 2012, the investigation of Vaxchora for the prevention of disease caused by *V. cholerae* serogroup O1 in adults and children ages 2 years and older who will be visiting cholera endemic or epidemic areas was designated a Fast Track Development Program.

CBER received an initial pediatric study plan (iPSP) on June 7, 2013. CBER issued comments on the iPSP on September 6, 2013. An agreed final iPSP was received on November 25, 2013. On December 27, 2013, CBER issues a letter agreeing to the final iPSP. The agreed iPSP included a plan to request a deferral of the submission of

pediatric data/assessment for children ≥ 2 years of age to < 18 years of age (study PXVX-VC-200-006) and a partial waiver of the requirement for pediatric assessments for children < 2 years of age.

The original protocol for study PXVX-VC-200-006 (version 1) was received on 1/31/17. CBER issued comments regarding the original protocol on 3/31/17. Protocol version 2 (received 6/13/17) included revisions to the study design, primary objectives, enrollment strategy, safety monitoring, eligibility criteria, and statistical analyses in response to CBER comments. Additional data were also provided to justify the use of half the buffer volume in children 2 through < 6 years of age in addition to the (b) (4) vaccine. CBER issued additional comments on 10/10/17 regarding amendment 76.

Protocol version 3 and the statistical analysis plan were received on 12/18/17; protocol revisions satisfactorily addressed CBER comments dated 10/10/17. This included extending the safety follow-up of placebo cross-over subjects through 6-months after receipt of Vaxchora on study day 181. The protocol was also revised to include a new interim analysis after completion of cohorts 1 and 2 to facilitate regulatory submissions in Europe. The total study population planned for enrollment was also increased from at least 525 subjects to 595 subjects to accommodate for the observation that ~30% of cohort 3 subjects were not consuming a full study dose. CBER issued comments dated 1/5/18 addressing the planned interim analysis and the proposed unblinding strategy.

On January 25, 2018, CBER issued additional information requests regarding the (b) (4) vaccine for all study participants. The sponsor's responses submitted to amendment 81 were considered adequate. In amendment 86, the sponsor notified CBER of duplicate enrollments in study PXVX-VC-200-006. The sponsor's report and planned management of data for these subjects was considered acceptable.

On May 2, 2019, the Applicant's request for a deferral extension for the PMR established under PREA (study PXVX-VC-200-006) was granted to allow for additional time needed to complete the safety follow-up of Cohort 3 placebo-crossover subjects who received Vaxchora on study day 181, as recommended by CBER on 10/10/2017. The new target submission date was extended from June 30, 2019 to March 31, 2020 (STN 125597/81). On February 10, 2020, a second deferral extension request was granted to allow the additional time needed to prepare the study report and/or submission. The new target final report submission date was extended to September 30, 2020 (STN 125597/119).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Study PXVX-VC-200-006 was conducted in accordance with Good Clinical Practices and according to the requirement of 21 CFR Part 56 (Institutional Review Boards) and 21 CFR Part 50 (Informed Consent). A total of 9 sites participated in study PXVX-VC-200-006. Bioresearch Monitoring (BIMO) inspections were conducted at three principal

investigator sites participating in the conduct of the study (sites 7 in Atlanta, Georgia; site 14 in Wichita, Kansas; and site 30 in Columbus, Ohio), representing one third of all clinical sites. The inspections did not reveal substantive problems impacting the data submitted in the application. Please refer to CBER BIMO review memo for more details.

3.3 Financial Disclosures

Covered clinical study: PXVX-VC-200-006		
Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number (no.) of investigators identified: 9		
No. investigators who are sponsor employees (full-and part-time employees): 0		
No. investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
No. investigators with certification of due diligence (Form FDA 3454, box 3): 0		

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The CBER CMC reviewer concludes that the changes to the amount of buffer drug product and total volume of the Vaxchora suspension that will be delivered orally to children 2 to < 6 years of age are acceptable. The CMC reviewer also concluded that (b) (4)

(b) (4)

(b) (4)

The Applicant agreed and revised the prescribing information accordingly. Please refer to the CMC review for additional details.

4.2 Assay Validation

The CBER CMC/clinical serology assay reviewer evaluated the data submitted to support re-validation of the serum vibriocidal antibody (SVA) assay at a new facility ((b) (4)

(b) (4) . This assay was previously validated for use at the former (b) (4) The CBER clinical serology assay reviewer concluded that the data in this sBLA support transfer and re-validation of this assay for the strain Classical Inaba to (b) (4) , formerly known as (b) (4) .

4.3 Nonclinical Pharmacology/Toxicology

No nonclinical animal safety or toxicology studies are included in this license application, because *V. cholerae* is a strictly human pathogen with no valid animal model available to assess safety or predict mucosal immune response. Thus, Module 4 was omitted.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaxchora contains live attenuated cholera bacteria that replicate in the gastrointestinal tract of the recipient. Immune mechanisms conferring protection against cholera following receipt of Vaxchora have not been determined. However, rises in serum vibriocidal antibody 10 days after vaccination with VAXCHORA were associated with protection in a human challenge study (PXVX-VC-200-003).

4.5 Statistical

The CBER statistical reviewer verified that the safety and effectiveness analyses cited by the applicant were supported by the submitted data. No major statistical issues were identified in this submission.

4.6 Pharmacovigilance

The pharmacovigilance reviewer agrees with routine pharmacovigilance as proposed by the Applicant, with reporting as required under 21 CFR 600.80. The data reviewed did not indicate a need for a postmarketing requirement (PMR) study or a Risk Evaluation and Mitigation Strategy. Please refer to Dr. Ravi Goud's review for more details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This clinical review focuses on the single study submitted to this BLA (study PXVX-VC-200-006). There is no integrated summary of efficacy or integrated summary of safety.

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

The following modules (m) of the sBLA (submitted 4/1/2020) were reviewed:
m1.3 Administrative Information
m1.14 Labeling
m1.16 Risk Management Plan
m2 Common Technical Document Summaries
m5 Clinical Study Reports

Information reviewed by sBLA amendment number and submission date is listed below:

- Amendment 0: 4/1/2020, Original Submission
- Amendment 2: 5/26/2020, Response to 5/14/20 IR#1, Post-marketing safety analysis, safety based on current worldwide knowledge regarding Vaxchora

- Amendment 3: 5/29/2020, Prior correspondence regarding study PXVX-VC-200-006
- Amendment 4: 7/24/2020, Response to July 9th IR #2 regarding standardized datasets
- Amendment 5: 8/28/2020, Response to 8/3/2020 IR#3, Major clinical information amendment and updated datasets with data missing from original sBLA submission[1]
- Amendment 6: 8/28/2020, Response to 8/14/20 IR#5 regarding safety and immunogenicity data, subgroup analyses of the primary immunogenicity endpoints, and carton, buffer packet, and vaccine packet labels.
- Amendment 8: 9/4/2020, Response to PVP IRs and Updated Risk Management Plan
- Amendment 11: 10/5/2020, Responses to Labeling Comments
- Amendment 12: 10/23/2020, Response to 9/28/2020 IR#8, Update of affected analyses in CSR (based on information in amendment 5), as a CSR addendum.
- Amendment 13: 11/6/2020, Response to 11/2/2020 IR#11 regarding subgroup analyses for safety endpoints and additional points of clarification of info in CSR and in Amendment 12

5.3 Table of Studies/Clinical Trials

The clinical section of the sBLA contains one study report for one clinical study (Table 1).

Table 1. Clinical Study PXVX-VC-200-006 Design.

Study No.	Description	Vaccine Regimen	# Subjects Vaccinated
PXVX-VC-200-006 United States (multiple sites) 7/21/17-9/10/19 NCT03220737	Randomized, placebo-controlled, double-blind, single crossover study evaluating the safety and immunogenicity of a single dose of Vaxchora in healthy children 2 through 17 years of age in the United States	A single dose of approximately $1x10^9$ CFU[a] of live attenuated *V. cholerae* strain CVD 103-HgR per dose or a single dose of an oral saline solution, administered orally	543 total [468 vaccine, 75 placebo]

NCT: National Clinical Trial. CFU: colony forming units.

[a]This is the same Vaxchora dose used in the PXVX-VC-200-004 lot consistency study in 18 through 45-year-old adults (STN 125597/0). As in study -004, Vaxchora was prepared in study -006 by emptying the contents of the vaccine sachet into 100 mL of buffer solution for children 6 through 17 years of age. For children 2 through 5 years of age, 50 mL of the buffer suspension was discarded before reconstituting the contents of the vaccine sachet into the buffer solution.

> ***Reviewer Comment:*** *During clinical development and prior to licensure, Vaxchora was known by its constituent V. cholerae strain, CVD 103-HgR.*

1 Body temperature, number of episodes for vomiting, and number of episodes for diarrhea were not collected in the datasets. These values were converted to absence or presence (of fever) and severity grading (for each based on the protocol-specified toxicity grading scale). In response to FDA's August 3, 2020 request for this missing information, the Applicant contacted study sites and collected electronic copies of the memory aids. The datasets were updated to enter the requested data from these documents. The Applicant also performed an impact assessment of the records where entered data in the memory aid for temperature, diarrheal episodes and vomiting episodes values disagreed with the severity (or presence of the event) in the electronic data capture (EDC). There were 10 cases where there was disagreement of which eight were downgrades in severity and two were upgrades. The CSR was updated in amendment 12.

5.4 Consultations

5.4.1 Advisory Committee Meeting

Our review of information submitted in this sBLA did not raise concerns or controversial issues that would have benefited from public discussion at a Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting.

5.4.2 External Consults/Collaborations

There were no external consultations or collaborations during the review of this BLA.

5.5 Literature Reviewed

1. Clemens JD, Shin S, Sah BK, Sack DA. Cholera *Vaccines*. In: Plotkin SA, Orenstein WA, Offit PA eds. *Vaccines*. 6th ed. Elsevier;2013:[141-152].
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5. Lopez AL, Gonzales MLA, Aldaba JG, et al. Killed oral cholera vaccines: history, development and implementation challenges. *Ther Adv Vaccines*. 2014;2(5):123-136.
6. Ali M, Lopez AL, You YA et al. The global burden of cholera. Bulletin of the World Health Organization. 2012;90:209-218A. Available at: http://www.who.int/bulletin/volumes/90/3/11-093427/en/ [accessed Nov 3, 2020].
7. World Health Organization [Internet]. Cholera. Available at: http://www.who.int/topics/cholera/about/en/ [accessed Nov 3, 2020].
8. World Health Organization [Internet]. Cholera Fact Sheet. Geneva: WHO;2015.
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11. Roy SK, Hossain MJ, Khatun W et al. Zinc supplementation in children with cholera in Bangladesh: randomized controlled trial. *BMJ*.2008;336(7638):266-271.
12. Emergent BioSolutions Inc. Vaxchora Prescribing Information. Available at: https://www.fda.gov/media/128415/download.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study PXVX-VC-200-006 (NCT03220737)

Study PXVX-VC-200-006: A Phase 4 Study to Assess the Safety and Immunogenicity of Vaxchora (Cholera Vaccine, Live, Oral) in Children 2 to < 18 Years of Age

Study enrollment began on July 21, 2017 (first consent form signed), and the last subject completed the last study visit or contact on September 10, 2019. The final clinical study report, dated March 19, 2020, submitted in this supplementary BLA includes final, locked data through study day 730.

6.1.1 Objectives

Primary Immunogenicity Study Objectives:

1. To demonstrate that the seroconversion rate at Day 11 in Vaxchora recipients 2 through 17 years of age in study PVXV-VC-200-006 is non-inferior to the seroconversion rate at Day 11 in adults between the ages of 18 and 45 years who participated in the lot consistency study PVXV-VC-200-004.

2. To demonstrate that the seroconversion rate in pediatric subjects 2 through 17 years of age who participated in study PXVX-VC-200-006 is greater than or equal to 70% with 98.3% confidence.

   Seroconversion rate was defined as the percentage of subjects with a ≥ 4-fold rise over baseline Day 1 Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of *V. cholerae* at Day 11 following one dose of Vaxchora.

Secondary Immunogenicity Objectives:

- To evaluate the immunogenicity of Vaxchora in Cohort 1 (12 through 17 years) using the following endpoints:
  - Seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Days 29, 91 and 181 for all subjects.
  - Seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Days 365, 547, and 730 for all subjects participating in the optional sub-study.

- To evaluate the immunogenicity of Vaxchora in Cohort 2 (6 through 11 years) and Cohort 3 (2 through 5 years) using the following endpoint:
  - Seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Day 29 following one dose of Vaxchora.

Exploratory Immunogenicity Objective:
To explore memory B cell response to Vaxchora vaccination at each time point in Cohort 1 using the following endpoint:

- Anti- O1 lipopolysaccharide memory B cell concentration at Days 1, 91 and 181 for the subjects in the active treatment group and Days 365, 547 and 730 for the subjects in the active treatment group who participate in the sub-study.

Reviewer Comment: *The Applicant plans to submit the analysis of memory B cells in a future clinical study addendum.*

Primary Safety Objective:
Evaluate the safety and tolerability of Vaxchora using the following endpoints:

1. Incidence and severity of solicited Adverse Events (AE) through Day 8: abdominal pain, headache, lack of appetite, tiredness, diarrhea, nausea, vomiting and fever, by age cohort and overall. This includes data from placebo crossover subjects between Days 181 and 188.2
2. Incidence and severity of unsolicited AEs through Day 29, by age cohort and overall. This includes data from placebo crossover subjects between Days 181 to 209.
3. Incidence of Serious Adverse Events (SAE) through Day 181, by age cohort and overall. This includes SAEs recorded through Day 365 (for placebo crossover subjects) or Day 730 (for sub-study subjects).

Exploratory Palatability Objective:
To evaluate Vaxchora palatability (after 30-min observation) using the following endpoints:

- Palatability assessed by subject using a 5-point Hedonic scale[3] in Cohorts 1 and 2.
- Palatability assessed by the caregiver using a 5-point Hedonic scale in Cohort 3.

Exploratory Acceptability Objective:
To evaluate the acceptability of Vaxchora based on the percent of subjects in each age cohort who were able to complete the dosing according to protocol. Acceptability is defined as the entire volume of dose consumed within 15 minutes after reconstitution.

6.1.2 Design Overview

Study PXVX-VC-200-006 was conducted using a randomized, double-blind, placebo-controlled single-crossover design. Within each of three age cohorts, subjects ages 2 through 17 years were randomized in a 6:1 ratio to receive a single oral dose of Vaxchora or saline placebo (Table 2). Eligible subjects had no prior history of cholera infection or cholera vaccination and had not traveled to a cholera-endemic area within the past 5 years. To maintain blinding, subjects were asked not to discuss the taste of the administered dose with other study participants. Subjects were followed through 6 months post-vaccination (Day 181). Randomized treatment assignments were unblinded individually as each subject completed his/her Day 181 clinic visit. Subjects in the placebo crossover group who chose to receive Vaxchora after unblinding (on Day 181) had additional follow up visits through Day 365. After completion of the main study (Day 181), subjects assigned to the Vaxchora group in Cohort 1 were given the option of participating in a long-term follow-up sub-study with study visits on Days 365, 547, and 730. The primary comparator group for all age cohorts consists of healthy adult subjects 18 through 45 years of age who received a single dose of Vaxchora while participating in the PXVX-VC-200-004 lot-to-lot consistency study.

2 For Placebo-Crossover subjects, solicited AEs were evaluated from Day 181 through Day 188; unsolicited AEs from Day 181 through Day 209; and SAEs from Day 181 through Day 365. For Sub-Study subjects, SAEs were evaluated through Day 730.
3 The 5-point Hedonic scale consisted of palatability score values ranging from 1-5 for “super bad”, “bad”, “maybe good or maybe bad”, “good” and “super good”, respectively.

Table 2. PXVX-VC-200-006 Study Treatment by Cohort and Treatment Group

Cohort	Age (years)	Treatment Group	N (Planned)	Day 1 Treatment (blinded)	Day 181 Treatment (Placebo Crossover)
1	12 to < 18	Active	150	Vaxchora	None
1	12 to < 18	Placebo-Crossover	25	Placebo	Vaxchora
2	6 to < 12	Active	150	Vaxchora	None
2	6 to < 12	Placebo-Crossover	25	Placebo	Vaxchora
3	2 to < 6	Active	150	Vaxchora	None
3	2 to < 6	Placebo-Crossover	25	Placebo	Vaxchora
		Total	525		

Source: STN 125597/123.0. Module 5.3.5.1, Appendix 16.1.1, Study PXVX-VC-200-006 protocol version 3, Table 2, p26.

Subjects, clinical site personnel and the sponsor were blinded to treatment assignments. Only the pharmacist/designee and dose administrator as well as the study monitor and Sponsor representative (who provided real-time review of unblinded data and resolving deviations with unblinded site staff) were unblinded. Double-blinding was maintained until each subject completed his/her Day 181 visit. Each subject was unblinded individually at Day 181 and at that time, their active/placebo status was recorded. To reduce the possible bias introduced by individual unblinding, the following steps were taken prior to subject unblinding: protocol deviations were identified during review and important protocol deviation status and exclusions from analysis decisions were made; all queries on data through Day 29 were written and addressed; and the sites confirmed that SAEs had been reviewed with the subjects' caretakers.

6.1.3 Population

Inclusion criteria

1. Male or female in general good health aged 2 to <18 years of age on Day 1.
2. For females of childbearing potential, uses acceptable method of contraception through Day 29.
3. Subject or primary caregiver is able and willing to provide informed consent.

Exclusion criteria

1. Current acute gastrointestinal illness or loose stools within 3 days of Day 1 visit.
2. Current acute febrile illness.
3. History of cholera infection.
4. For females of childbearing potential, pregnant or nursing or planning to become pregnant or nurse during the study.
5. History of cholera vaccination.
6. History of severe allergic reaction to any component of Vaxchora.
7. Congenital or acquired immunodeficiency.
8. Any other condition that creates an unacceptable risk to the subject or that will interfere with the conduct of the study or the validity of the data.
9. Abnormal stool pattern of > 2 weeks duration (i.e., < 3 stools/week or > 2 stools/day) in the past 6 months.
10. Regular use of laxatives in the past 6 months.
11. History of enterotoxigenic *E. coli* infection.
12. Travel to a cholera-endemic area in the previous 5 years.

13. Received or plans to receive the following from 14 days prior to the study vaccination through 11 days after vaccination:
    a. Any other licensed vaccines
    b. Antibiotics or chloroquine or any other investigational agents.
14. Received or plans to receive any other investigational agent from Day 1 to Day 181.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects in the main study were randomized to receive either Vaxchora or placebo (saline solution) on study Day 1. Study treatment was to be taken orally and was administered by an unblinded administrator following reconstitution.

Vaxchora (Cholera Vaccine, Live, Oral): Vaxchora is a live attenuated bacterial vaccine for single-dose oral administration. The *V. cholerae* strain CVD 103-HgR was constructed from the serogroup O1 classical Inaba parent strain 569B by deleting the catalytic domain sequence of both copies of the *ctxA* gene. Vaxchora was provided as two packets containing a single dose of buffer and a single dose of active component. After reconstitution in purified bottled water, VAXCHORA contains 4×10^8 to 2×10^9 colony forming units (CFU) of live attenuated *V. cholerae* strain CVD 103-HgR. Each dose also contains sucrose, sodium chloride, Hy-Case SF (casein acid hydrolysate, from bovine milk), ascorbic acid, dried lactose, sodium bicarbonate, and sodium carbonate. The resulting suspension, which is slightly cloudy and may contain white particulates, was administered in an opaque sealed container. In study PXVX-VC-200-006: Vaxchora lots P700.610-7000005 and P700.610-7000008 were used. The potency range was ~ 8.9×10^8 CFUs to 7.7×10^8 CFUs. In the prior Vaxchora lot consistency study PXVX-VC-004, Vaxchora maintained a potency range of ~ 1.4×10^9 CFUs to 9.0×10^8 CFUs.

Placebo: The placebo was normal (0.9%) oral saline solution. It was not matched to Vaxchora visually or by taste, but it was administered in an opaque sealed container.

6.1.5 Directions for Use

The study product was intended to be administered within 15 minutes of reconstitution. Reconstitution was to be performed within 15 minutes of removing the study product from the (b) (4) and involved mixing the study product with 100 mL of purified bottled water in an opaque sealed cup (mixing was advised for a minimum of 30 second). Subjects were asked to not discuss the taste of their assigned treatment with other subjects.

Subjects were to take no food or drink for 60 minutes before or after vaccine administration. Subjects or healthcare providers had the

Subjects in cohorts 1 and 2 were monitored to ensure that all 100 mL of reconstituted product or placebo were consumed. For Cohort 3, the vaccine was prepared by suspending the contents of the buffer sachet into an opaque sealed container containing 100 mL of purified bottled water, then discarding 50 mL of the buffer suspension. This halved the volume of buffer administered to the youngest children. The vaccine sachet was then emptied into the opaque sealed container containing 50 mL of buffer solution, and the mixture was stirred for at least 30 seconds. These subjects were monitored to ensure that all 50 mL of reconstituted study product or placebo was consumed.

6.1.6 Sites and Centers

A total of 550 subjects were enrolled and randomized into the study across 9 study sites (site 02 failed to enroll any subjects).

6.1.7 Surveillance/Monitoring

All participants were observed for 30 minutes after vaccination for immediate reactions. Solicited adverse reactions were recorded daily on days 1 through 8 (and days 181 through 188 for placebo crossover subjects) on a memory aid by subjects 12 to < 18 years of age and by parents of subjects < 12 years of age. Symptoms continuing beyond day 8 (or day 188 for placebo crossover subjects) were recorded as an unsolicited AE. Solicited adverse reactions included the following: abdominal pain, nausea, vomiting, diarrhea, headache, anorexia (loss of appetite), fatigue (tiredness) and fever. Severity grading scales are specified below.

- Diarrhea grading scale: 1 (mild): 4 loose stools/24 hours; 2 (moderate): 5 loose stools/24 hours; 3 (severe): ≥ 6 loose stools/24 hours; 4 (potentially life-threatening): ER visit or hospitalization.
- Fever grading scale: 1 (mild): ≥ 38.0 – 38.4^{o}C; 2 (moderate): ≥ 38.5 – 38.9^{o}C; 3 (severe): ≥ 39.0-40.0^{o}C; 4 (potentially life-threatening): > 40.0^{o}C.
- Vomiting grading scale: 1 (mild): 1-2 episodes/24 hours; 2 (moderate): > 2 episodes/24 hours; 3 (severe): requires IV hydration; 4 (potentially life-threatening): ER visit or hospitalization for hypotensive shock.
- General grading scale for anorexia, abdominal pain, fatigue, headache, myalgia, nausea and other unsolicited events are as shown below.
    - Mild (Grade 1) – No interference with activity
    - Moderate (Grade 2) – Some interference with activity
    - Severe (Grade 3) – Significant; prevents daily activity
    - Potentially Life-Threatening (Grade 4) – ER visit or hospitalization
    - Fatal (Grade 5)

Unsolicited AEs were collected through Day 29 for Active treatment groups and from day 181 through Day 209 for Placebo crossover subjects. SAEs were collected for the duration of study participation. In < 12-year-olds, events occurring after Day 29 were assessed initially by telephone.

AEs and SAEs were classified according to the Medical Dictionary for Regulatory Activities (Version 15.0) system organ class or preferred term.

Use of medications taken from 30 days prior to vaccination and within 28 days post-vaccination (through Day 29) were recorded. A listing of medications associated with a SAE was also collected through Day 181 (Day 730 for long-term sub-study subjects).

The study included a safety monitoring committee composed of two independent physicians and one independent statistician. Blinded safety reports were reviewed on a 6-month basis and when a study stopping rule was met. The blind was not broken at any time for a safety event.

> ***Reviewer Comment:*** *The grading scale used for grading solicited adverse reactions was based on FDA's Guidance entitled Toxicity Grading Scale for Healthy Adult and Adolescent Subjects Enrolled in Preventative Vaccine Clinical Trials. However, the scale was modified to accommodate the historical definition*

of diarrhea in cholera vaccine studies. Diarrhea post-vaccination was defined as ≥ 4 loose stools/24 hours rather than ≥ 2 loose stools/24 hours. This is consistent with the grading scale used in adult Phase 3 pre-licensure studies.

Reviewer Comment: *The Applicant explained in STN 125597/123.5 that if a memory aid was not completed by the subject, the sites were instructed to document the missing memory aid in the source document. In addition, in the case of a missing or partially completed memory aid, the principal investigator (PI) interviewed the subject/parent/guardian and asked them to recall if the subject experienced any solicited symptoms from Day 1 through Day 8. For solicited events noted as present on the memory aid, the PI assessed the event's severity and relationship to study vaccine as per the grading scale in Appendix B of the protocol. The PI's assessment was entered into the electronic database capture (EDC) and the sites were instructed to source document any discrepancies between the assessments and the memory aids. This practice of recall of solicited safety information was described in neither the protocol nor the statistical analysis plan. Ten discrepancies between information on severity grading for fever, diarrhea, and vomiting were also noted to be corrected in amendment 5 of this supplement; these were discrepancies based on what was entered in the EDC vs what was found to be documented in the corresponding subject's memory aid upon re-review in response to CBER information request #3.*

The study schedule of events for Cohorts 1, 2 and 3 are shown in Tables 3, 4 and 5, respectively.

Table 3. Cohort 1 (12 to < 18 Years) Schedule of Events

Study Day	Screening	1	11	29	91	181	Early D/C	181[PC]	191 PC	209 PC	271 PC	365 PC	365[a]	547	730
Window (days)	-30 to 0	0	0	± 2	± 7	± 7	n/a	± 7	0	± 2	± 7	± 7	± 14	±14	±14
Informed Consent/ Assent	X							X							
Medical History	X	X[d]													
Inclusion/Exclusion	X	X													
Physical Exam	X	X[d]													
Vital Signs	X	X						X[PC]							
Con Med Eval	X	X[d]	X	X	X	X	X	X[PC]	X[PC]	X[PC]	X[PC]	X[PC]	X	X	X
Urine Pregnancy test[b]	X	X						X[PC]							
Vaccination		X						X[PC]							
Acceptability/Palatability		X						X[PC]							
Memory Aid[c]		X	X				X[e]	X[PC]	X[PC]						
Solicited AEs		X					X[e]	X[PC]							
AE Evaluation		X	X	X	X	X	X	X[PC]	X[PC]	X[PC]	X[PC]	X[PC]	X	X	X
Serum Vibriocidal Antibody		X	X	X	X	X	X						X	X	X
Blood Collection for Memory B Cell Test		X			X	X	X						X	X	X

X = All subjects; PC = placebo crossovers; D/C = discontinuation

[a] Days 365+ required separate informed consent forms; these visits did not apply to all subjects. [b] For females of child-bearing potential

[c] All subjects were issued a Memory Aid at Day 1. Memory aids were reviewed at Day 11. [d] Updated as necessary.

[e] Only if between Day 1 and Day 11 (all subjects)

Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 5, page 24 of 107.

Table 4. Cohort 2 (6 to < 12 Years) Schedule of Events

Study Day	Screening	1	11	29	91	181	Early D/C	181[PC]	191 PC	209 PC	271 PC	365 PC
Window (days)	-30 to 0	0	0	± 2	± 7	± 7	n/a	± 7	0	± 2	± 7	± 7
Informed Consent/ Assent	X											
Medical History	X	X[c]										
Inclusion/Exclusion	X	X										
Physical Exam	X	X[c]										
Vital Signs	X	X						X[PC]				
Con Med Eval	X	X[c]	X	X	X	X	X	X[PC]	X[PC]	X[PC]	X[PC]	X[PC]
Urine Pregnancy test[a]	X	X						X[PC]				
Vaccination		X						X[PC]				
Acceptability/Palatability		X						X[PC]				
Memory Aid[b]		X	X				X[d]	X[PC]	X[PC]			
Solicited AEs		X					X[d]	X[PC]				
AE Evaluation		X	X	X	X	X	X	X[PC]	X[PC]	X[PC]	X[PC]	X[PC]
Serum Vibriocidal Antibody		X	X	X			X					

X = All subjects; PC = placebo crossovers; D/C = discontinuation

[a] For females of child-bearing potential. [b] All subjects were issued a Memory Aid at Day 1. Memory aids were reviewed at Day 11.

[c] Updated as necessary. [d] Only if between Day 1 and Day 11 (all subjects)

Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 5, page 25 of 107.

Table 5. Cohort 3 (2 to < 6 Years) Schedule of Events

Study Day	Screening	1	11	29	91	181	Early D/C	181[PC]	191 [PC]	209 [PC]	271 [PC]	365 [PC]
Window (days)	-30 to 0	0	0	± 2	± 7	± 7	n/a	± 7	0	± 2	± 7	± 7
Informed Consent/ Assent	X											
Medical History	X	X[b]										
Inclusion/Exclusion	X	X										
Physical Exam	X	X[b]										
Vital Signs	X	X						X[PC]				
Con Med Eval	X	X[b]	X	X	X	X	X	X[PC]	X[PC]	X[PC]	X[PC]	X[PC]
Vaccination		X						X[PC]				
Acceptability/Palatability		X						X[PC]				
Memory Aid[a]		X	X				X[c]	X[PC]	X[PC]			
Solicited AEs		X					X[c]	X[PC]				
AE Evaluation		X	X	X	X	X	X	X[PC]	X[PC]	X[PC]	X[PC]	X[PC]
Serum Vibriocidal Antibody		X	X	X			X					

X = All subjects; PC = placebo crossovers; D/C = discontinuation

[a] All subjects were issued a Memory Aid at Day 1. Memory aids were reviewed at Day 11.

[b] Updated as necessary.

[c] Only if between Day 1 and Day 11 (all subjects)

Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 5, page 26 of 107.

6.1.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoint:
The seroconversion rate, defined as the percentage of subjects that achieve ≥ 4-fold rise over baseline (Day 1) Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of *V. cholerae*, at Day 11 following one dose of Vaxchora.

Secondary Immunogenicity Endpoints:
- Seroconversion of SVA against the classical Inaba biotype *V. cholerae* at Day 29 for all subjects and additionally at Days 91 and 181 for Cohort 1 subjects.
- Seroconversion of SVA against the classical Inaba biotype *V. cholerae* at Days 365, 547 and 730 for Cohort 1 subjects participating in the sub-study.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary Analysis
1. The seroconversion rate between Day 1 and Day 11 in Vaxchora recipients in each of the 3 age cohorts were compared to the seroconversion rate for Vaxchora recipients between the ages of 18 and 45 who participated in the lot consistency study PXVX-VC-200-004 by calculating the difference between the two rates and computing a 96.7% confidence interval (CI) for this difference.

   Noninferiority criterion: The lower bound of the two-sided 96.7% CI on the difference in seroconversion rates between children in each cohort and adults must be greater than -10 percentage points.

2. For each of the 3 age cohorts, the proportion of vaccinated subjects who achieved a 4-fold or greater increase in serum vibriocidal antibody titer between Day 1 and Day 11 were calculated, and a 98.3% CI on this proportion of seroconverters was computed.

   Success criterion: the lower bound of the two-sided 98.3% CI on the proportion of vaccinees who seroconvert between Day 1 and Day 11 must equal or exceed 70%.

In order to ensure that the total Type I error for the study was capped at alpha = 0.05; 2/3 of the alpha (0.033) was allotted to the primary immunogenicity objective of establishing noninferiority relative to the 004 Bridging Population, and 1/3 of the alpha (0.017) was allotted to the primary immunogenicity objective of demonstrating that the seroconversion rate was equal to or exceeded 70%.

The two primary immunogenicity objectives were evaluated independently, and within each objective, testing in the different age cohorts proceeded in a hierarchical manner beginning with the data for Cohort 1. Testing of Cohort 1 subjects versus the adult Bridging Population needed to meet the acceptance criterion prior to performing the comparison for Cohort 2. Analysis of non-inferiority in Cohort 3 was only conducted if the pre-specified acceptance criteria were met for Cohorts 1 and 2.

SVA assay results that were reported as less than 20 (the lower limit of quantification [LLOQ]) were imputed as a titer of 20 when calculating seroconversion rates and geometric means.

Sample Size Calculation

- Assuming that the true seroconversion rate among 12 to <18-year-olds was 92.4% or higher, the sample size of 143 evaluable vaccinees for that age cohort afforded 93.3% power to demonstrate that the seroconversion rate within the group was non-inferior to the 94% rate observed in the 2687 adult subjects assessed in the PaxVax lot-consistency trial, PXVX-VC-200-004. The sample size allowed for up to 5% of subjects to be inevaluable for the primary immunogenicity analyses in the two older cohorts (ages 6 to < 18). Based on the inevaluable rate observed during the study, it was estimated that approximately 30% of subjects in the youngest cohort (ages 2 to < 6) would be inevaluable, mostly due to lack of consumption of the full dose. In protocol amendment 2.0 (Version 3.0, dated November 15, 2017)[4], the protocol was revised to increase the number of subjects in Cohort 3 (in anticipation of a high rate of inevaluable subjects). Making similar assumptions about the true seroconversion rates in the other two pediatric age cohorts, and assuming that the rates in the three age cohorts are independent of one another, the overall power for demonstrating the noninferiority of all three age cohorts was $(93.3\%)^3 = 81\%$.
- Under the same assumptions as above, 143 evaluable vaccinees provided greater than 99.9% power to establish that the lower bound on the cohort-specific rate was at least 70%. Power was still greater than 99.9% when requiring the lower bound on all three cohorts to be 70% or greater.
- The overall power of meeting both primary objectives in all three age cohorts could be approximated by multiplying the power of meeting the non-inferiority objective by the power of meeting the 70% lower bound objective: 81% x 99.9% ≈ 81%. Note that the calculations above relied on the assumption that seroconversion rate in one cohort was completely independent of the rate in another. Since that assumption is conservative, it is likely that the true power of the trial was higher than 81%.
- Given a total of 510 subjects were to receive VAXCHORA, there was a 99% chance that an uncommon AE - one expected to occur in only 1% of vaccinees - would be observed at least once during the trial.

Analysis Populations

The five analysis populations delineated in this study are listed below. The primary endpoint was analyzed based on the Bridging Population (IEP for the 006 study) and repeated on the mITT population for robustness purposes. Analyses of secondary endpoints were based on the IEP only. With the exception of the safety population, analyses were performed according to the treatment group to which a subject was randomized. Analyses based on the Safety Population were performed according to the treatment group of the study vaccine received.

- The *Randomized Population* included all randomized subjects
- The *Modified Intent-to-treat Population* (mITT) included randomized, treated subject who had evaluable SVA assay results both on Days 1 and 11.
- The *Immunogenicity Evaluable Population* (IEP) included all subjects in the mITT who met the following additional criteria:
    - Received the minimum dose of vaccine correctly
    - Had SVA results at Days 1 and 11 within the required window
    - Had no exclusionary protocol deviation (i.e., important protocol deviations classified as major, that would affect immunogenicity analysis) as determined prior to unblinding. Examples of exclusionary protocol deviations are listed below.

4 Received by CBER on 12/18/2017.

- Blood draw outside of allowable window:
  - ❖ Day 1: must be prior to vaccination
  - ❖ Day 11: must be in the period from Day 8 through Day 16.
- Consumed < 80% of vaccine volume (< 80 mL for Cohorts 1 and 2 or < 40 mL for Cohort 3).
- Exclusionary deviations based on any antibiotic or non-study vaccine given within -14/+11 days of vaccination were decided on an individual antibiotic-type or vaccine-type determination.
- Wrong treatment given/no treatment given
- Enrollment more than once into the study
- Inclusion/Exclusion criteria violations:
  - ❖ Age at entry < 2 or ≥ 18 years
  - ❖ Exclusionary deviations based on prohibited medications and medical history (that could interfere with immunogenicity) were considered on a case-by-case basis
- Other miscellaneous violations discovered during the conduct of the trial which may have fundamentally affected the assessment of immunogenicity were decided on a case-by-case basis prior to unblinding.

- The *Bridging Population* included all subjects in the PXVX-VC-200-006 IEP along with subjects vaccinated with Vaxchora in the IEP from the adult Vaxchora lot consistency study PXVX-VC-200-004.
- The *Safety Population* included subjects who received any amount of study vaccine or placebo.

All safety analyses were carried out on the Safety Population.

No subjects were unblinded until their Day 181 visit. Unblinding occurred on an individual subject level at the Day 181 visit to facilitate the roll-over of Placebo subjects should they choose to receive Vaxchora.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

See Section 6.1.10.1.3.

6.1.10.1.1 Baseline Demographics

Table 6 summarized baseline demographics for randomized subjects. Among the 550 total randomized subjects, the median age was 9.0 years (ranging from 2-17 years). Overall, 52.0% of subjects were male. By race, 59.8% of randomized subjects identified as White, 31.1% as Black or African Americans,7.6% as multiple races, 0.9% as Asian, and 0.5% as American Indian or Alaskan Native. By ethnicity, 8.5% identified as Hispanic or Latino, and 91.5% identified as not Hispanic or Latino. Although the baseline demographics were generally balanced across the two treatment groups in the overall study, they differed within the age-based study cohorts by one or more demographic characteristics. The proportion of Black or African American subjects and the proportion of females in the Vaxchora group compared to the Placebo group were both higher in Cohort 2 and both lower in Cohort 3. In addition, a higher proportion of Cohort 1 subjects self-identified as White by race or Hispanic or Latino by ethnicity compared to Cohorts 2 and 3. The smaller size of the placebo groups relative to the Vaxchora groups may have

impacted the ability to maintain balance across treatment groups for all baseline demographics.

> ***Reviewer Comment:*** *In study PXVX-VC-200-003 (the Phase 3 efficacy/challenge study) submitted to the Vaxchora BLA, imbalances were also noted in the proportion of males and females in the vaccine and placebo groups. In addition, more males and black subjects were challenged compared to females and white subjects. These differences were considered unlikely to impact the clinical results. Though they involved small numbers of subjects, the subgroup analyses of vaccine efficacy by sex and race didn't show any clear and consistent differences in vaccine effectiveness. Similarly, although some subgroups were small, there was no pattern of differences noted based on subgroup analyses of safety or immunogenicity by sex and race in study PXVX-VC-200-006.*

Table 6. Study PXVX-VC-200-006 Baseline Subject Demographics by Age and Treatment Group – Randomized Population

	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall	Total
	Ages 12 to < 18 years	Ages 12 to < 18 years	Ages 6 to < 12 years	Ages 6 to < 12 years	Ages 2 to < 6 years	Ages 2 to < 6 years	Ages 2 to < 18 years	Ages 2 to < 18 years	
Baseline Characteristics	Vaxchora (N=163) n (%)	Placebo (N=26) n (%)	Vaxchora (N=158) n (%)	Placebo (N=27) n (%)	Vaxchora (N=150) n (%)	Placebo (N=26) n (%)	Vaxchora (N=471) n (%)	Placebo (N=79) n (%)	N=550 n (%)
Age in Years									
Mean (SD)	14.4 (1.7)	14.3 (1.7)	8.6 (1.8)	8.7 (1.5)	3.5 (1.1)	3.6 (1.2)	9.0 (4.7)	8.8 (4.6)	9.0 (4.7)
Median (Min-Max)	14.0 (12-17)	15.0 (12-17)	9.0 (6-11)	9.0 (6-11)	4.0 (2-5))	3.5 (2-5	9.0 (2-17)	9.0 (2-17)	9.0 (2-17)
Sex (n, %)									
Male	88 (54.0)	14 (53.8)	77 (48.7)	17 (63.0)	81 (54.0)	9 (34.6)	246 (52.2)	40 (50.6)	286 (52.0)
Female	75 (46.0)	12 (46.2)	81 (51.3)	10 (37.0)	69 (46.0)	17 (65.4)	225 (47.8)	39 (49.4)	264 (48.0)
Race (n, %)									
American Indian or Alaskan Native	0 (0.0)	1 (3.8)	0 (0.0)	1 (3.7)	1 (0.7)	0 (0.0)	1 (0.2)	2 (2.5)	3 (0.5)
Asian	1 (0.6)	0 (0.0)	4 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.1)	0 (0.0)	5 (0.9)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	28 (17.2)	4 (15.4)	53 (33.5)	5 (18.5)	67 (44.7)	14 (53.8)	148 (31.4)	23 (29.1	171 (31.1)
White	121 (74.2)	21 (80.8)	86 (54.4)	18 (66.7)	71 (47.3)	12 (46.2)	278 (59.0)	51 (64.6)	329 (59.8)
Multiple	13 (8.0)	0 (0.0)	15 (9.5)	3 (11.1)	11 (7.3)	0 (0.0)	39 (8.3)	3 (3.8)	42 (7.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity (n, %)									
Hispanic or Latino	18 (11.0)	7 (26.9)	11 (7.0)	2 (7.4)	8 (5.3)	1 (3.8)	37 (7.9)	10 (12.7)	47 (8.5)
Not Hispanic or Latino	145 (89.0)	19 (73.1)	147 (93.0)	25 (92.6)	142 (94.7)	25 (96.2)	434 (92.1)	69 (87.3)	503 (91.5)

Min = minimum; Max = maximum; SD = standard deviation.
Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 11, page 59 of 107.

6.1.10.1.3 Subject Disposition

Table 7 summarizes the disposition of all randomized subjects by study cohort. Among a total of 550 randomized subjects, 189 were in Cohort 1, 185 were in Cohort 2, and 176 were in Cohort 3. Three subjects (two from Cohort 1 and one from Cohort 2) who received Vaxchora instead of their randomized placebo assignment were included in the Safety Population. Nine subjects enrolled twice at two different study sites (sites 9 and 13). Eight of the 9 subjects received Vaxchora twice approximately 1 to 4 months apart (2 subjects in Cohort 1, 5 subjects in Cohort 2, and 2 subjects in Cohort 3); the remaining subject in Cohort 1 received Vaxchora and placebo. The safety data associated with the duplicate subjects' first enrollment ID were included in the exposure and safety summaries; the safety data following their second treatment were included in the listings and discussed only in a narrative fashion. Please also refer to Section 6.1.12.2 for safety information pertaining to the 9 subjects who were enrolled and dosed twice in this study.

Overall, the proportions of subjects with at least one important protocol deviation were similar across study groups in each cohort. The most common important protocol deviations included visit out of window and incomplete or missed dose [Data not shown, Table 8 of CSR, p53]. Important protocol deviations classified as major (i.e., that would affect immunogenicity analyses) resulted in exclusion from the IEP analysis population.

Table 8 below summarizes the analysis populations, including a list of important protocol deviations classified as major and resulting in exclusion of subjects from the IEP population. The most common important protocol deviation resulting in exclusion from the IEP was receiving a prohibited medication or vaccine in cohort 1 and consuming less than 80% of the dose (80 mL for Cohort 1 and 2 and 40 mL for Cohort 3) in cohorts 2 and 3. See Table 9 for information regarding compliance with dosing.

> ***Reviewer Comment:*** *CBER was first notified about duplicate enrollments in study PXVX-VC-200-006 by email on 4/16/19 and in amendment 86 (received 5/15/19). PaxVax initiated an investigation upon being provided with a list of subjects with exact matches on birth date and sex. This problem was identified when a programmer for the study ran an exploratory analysis in order to identify "professional" subjects. Site monitoring visits were performed on March 21, 2019 and April 10-11, 2019, during which the duplicate enrollments were confirmed unbeknownst to the PIs who were within 10 miles of one another. A total of 13 pediatric subjects in the study enrolled or attempted to enroll at both clinical study sites located in the Kansas City/Lenexa (site #9 and site #13). Four of the 12 subjects were screen fails at one site. Nine subjects were enrolled at both sites. There was no evidence of investigator misconduct. All study procedures were followed, and there was no indication of failure in the screening and enrollment process. Enrollment at more than 1 site should have been prevented by the study exclusion criteria. The motivation for the duplicate enrollment is reportedly unknown. The Sponsor implemented corrective action to prevent future occurrence of this nature. No significant effect on study integrity was anticipated.*

Table 7. Study PXVX-VC-200-006 Summary of Subject Disposition by Study Cohorts

Cohort	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall	Total
Ages (Years)	**12 to < 18**	**12 to < 8**	**6 to < 12**	**6 to < 12**	**2 to < 6**	**2 to < 6**	**2 to < 18**	**2 to < 18**	
Study Group	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	
Subjects Randomized	163	26	158	27	150	26	471	79	550
Received complete dose	162 (99.4)	24 (92.3)	142 (89.9)	24 (88.9)	115 (76.7)	19 (73.1)	419 (89.00)	71 (89.9)	495 (90.0)
Received incomplete dose	1 (0.6)	2 (7.7)[1]	16 (10.1)	3 (11.1)	35 (23.3)	7 (26.9)	52 (11.0)	12 (15.2)	56 (10.2)
Randomized but not treated	0 (0.0)	0 (0.0)	2 (1.3)	1 (3.7)	4 (2.7)	0 (0.0)	6 (1.4)	1 (1.3)	7 (1.3)
Consumed at least 80%	0 (0.0)	0 (0.0)	4 (2.5)	0 (0.0)	5 (3.3)	3 (11.5)	9 (1.9)	3 (3.8)	4 (0.7)
Consumed < 80%	1 (0.6)	0 (0.0)	10 (6.3)	1 (3.7)	26 (17.3)[3]	4 (15.4)	37 (7.9)	5 (6.3)	42 (7.6)
Dispensing error	0 (0.0)	2 (7.7)[1]	0 (0.0)	1 (3.7)[2]	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.8)	3 (0.5)
Study Visit Completion									
Day 1	163 (100.0)	26 (100.0)	158 (100.0)	27 (100.0)	150 (100.0)	26 (100.0)	471 (100.0)	79 (100.0)	550 (100.0)
Day 11	162 (99.4)	26 (100.0)	155 (98.1)	26 (96.3)	144 (96.0)	25 (96.2)	461 (97.9)	77 (97.5)	538 (97.8)
Day 29	161 (98.8)	26 (100.0)	154 (97.5)	26 (96.3)	141 (94.0)	25 (96.2)	456 (96.8)	77 (97.5)	533 (96.9)
Day 91	160 (98.2)	26 (100.0)	153 (96.8)	26 (96.3)	139 (92.7)	25 (96.2)	452 (96.0)	77 (97.5)	529 (96.2)
Day 181	157 (96.3)	24 (92.3)	146 (92.4)	24 (88.9)	130 (86.7)	25 (96.2)	433 (91.9)	73 (92.4)	506 (92.0)
Reason for Withdrawal Prior to D181									
Withdrawal of consent	4 (2.5)	1 (3.8)	4 (2.5)	1 (3.7)	4 (2.7)	0 (0.0)	12 (2.5)	2 (2.5)	14 (2.5)
Lost to follow-up	2 (1.2)	1 (3.8)	6 (3.8)	1 (3.7)	13 (8.7)	1 (3.8)	21 (4.5)	3 (3.8)	24 (4.4)
Other	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Non-compliance with protocol	0 (0.0)	0 (0.0)	1 (0.6)	1 (3.7)	3 (2.0)	0 (0.0)	4 (0.8)	1 (1.3)	5 (0.9)
Placebo Crossover (PC) Visit Completion									
Day 191	13 (100.0)	N/A	11 (100.0)	N/A	7 (100.0)	N/A	31 (100.0)	N/A	31 (100.0)
Day 209	13 (100.0)	N/A	11 (100.0)	N/A	6 (85.7)	N/A	30 (96.8)	N/A	30 (96.8)
Day 271	13 (100.0)	N/A	11 (100.0)	N/A	6 (85.7)	N/A	30 (96.8)	N/A	30 (96.8)
Day 365	13 (100.0)	N/A	11 (100.0)	N/A	5 (71.4)	N/A	29 (93.5)	N/A	29 (93.5)
Reason for not Completing PC									
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	2 (6.5)	0 (0.0)	2 (6.5)
Optional Long-term Substudy Completion	N=73	-	-	-	-	-	-	-	-
Day 365	71 (97.3)	-	-	-	-	-	-	-	-
Day 547	68 (93.2)	-	-	-	-	-	-	-	-
Day 730	62 (84.9)	-	-	-	-	-	-	-	-
Reason for not completing substudy									
Lost to Follow-up	9 (12.3)	-	-	-	-	-	-	-	-
Other reasons	1 (1.4)	-	-	-	-	-	-	-	-
Withdrawal of Consent	1 (1.4)	-	-	-	-	-	-	-	-

[1] Two subjects were randomized to the placebo group but were vaccinated with Vaxchora. [2] One subject was randomized to the placebo group but was vaccinated with Vaxchora.
[3] Includes one subject whose reduction in vaccine solution from 100 mL to 50 mL was performed after adding the active vaccine packet to the buffer solution rather than before.
Source: Module 5.3.5.1, PXVX-VC-200-006 Study Report v3.0, Figures 2-4 and Tables 14.1.3.1, 14.1.3.2, 14.1.3.3 and 14.1.6 in vc200006final_tablesversion1_20200306-bookmarked.pdf.

Table 8. Study PXVX-VC-200-006 Analysis Populations by Age Cohort and Treatment Group

	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall	Total
	Ages 12 to < 18 years	Ages 12 to < 18 years	Ages 6 to < 12 years	Ages 6 to < 12 years	Ages 2 to < 6 years	Ages 2 to < 6 years	Ages 2 to < 18 years	Ages 2 to < 18 years	
	Vaxchora n (%)	Placebo n (%)	Vaxchora n (%)	Placebo n (%)	Vaxchora n (%)	Placebo n (%)	Vaxchora n (%)	Placebo n (%)	
Randomized Population	163	26	158	27	150	26	471	79	550
Safety Population (SP)	165 (101.2)[1]	24 (92.3)	157 (99.4)[1]	25 (92.6)	146 (97.3)	26 (100)	468 (99.4)	75 (94.9)	543 (98.7)
Subjects excluded from SP	0 (0.0)	0 (0.0)	2 (1.3)	1 (3.7)	4 (2.7)	0 (0.0)	6 (1.3)	1 (1.3)	7 (1.3)
Randomized, Not Treated	0 (0.0)	0 (0.0)	2 (1.3)	1 (3.7)	4 (2.7)	0 (0.0)	6 (1.3)	1 (1.3)	7 (1.3)[2]
mITT Population	160 (98.2)	26 (100.0)	150 (94.9)	26 (96.3)	129 (86.0)	24 (92.3)	439 (93.2)	76 (96.2)	515 (93.6)
Subjects excluded from mITT	3 (1.8)	0 (0.0)	8 (5.1)	1 (3.7)	21 (14.0)	2 (7.7)	32 (6.8)	3 (3.8)	35 (6.4)
Duplicate Enrollment	2 (1.2)	0 (0.0)	4 (2.5)	0 (0.0)	3 (2.0)	0 (0.0)	9 (1.9)	0 (0.0)	9 (1.6)
Randomized, Not Treated	0 (0.0)	0 (0.0)	2 (1.3)	1 (3.7)	4 (2.7)	0 (0.0)	6 (1.3)	1 (1.3)	7 (1.3)[1]
Discontinued prior to Day 11	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	9 (6.0)	1 (3.8)	11 (2.3)	1 (1.3)	12 (2.2)
No Day 1 SVA Sample	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	1 (3.8)	2 (0.4)	1 (1.3)	3 (0.5)
No Day 11 SVA Sample	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	4 (2.7)	1 (3.8)	5 (1.1)	1 (1.3)	6 (1.1)
Immunogenicity Evaluable Pop (IEP)	157 (96.3)	23 (88.5)	139 (88.0)	24 (88.9)	103 (68.7)	20 (76.9)	399 (84.7)	67 (84.8)	466 (84.7)
Subjects excluded from IEP	6 (3.7)	3 (11.5)	19 (12.0)	3 (11.1)	47 (31.3)	6 (23.1)	72 (15.3)	12 (15.2)	84 (15.3)
Consumed < 80% of Dose	1 (0.6)	0 (0.0)	10 (6.3)	1 (3.7)	26 (17.3)[3]	4 (15.4)	37 (7.9)	5 (6.3)	42 (7.6)
Duplicate Enrollment	2 (1.2)	0 (0.0)	4 (2.5)	0 (0.0)	3 (2.0)	0 (0.0)	9 (1.9)	0 (0.0)	9 (1.6)
Prohibited Concomitant Med/Vaccine	2 (1.2)	1 (3.8)	0 (0.0)	1 (0.6)	0 (0.0)	3 (2.0)	0 6 (1.3)	1 (1.3)	7 (1.3)
Randomized, Not Treated	0 (0.0)	0 (0.0)	2 (1.3)	1 (3.7)	4 (2.7)	0 (0.0)	6 (1.3)	1 (1.3)	7 (1.3)
Received Incorrect Treatment	0 (0.0)	2 (7.7)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.8)	3 (0.5)
Discontinued Study Prior to Day 11	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	7 (4.7)	1 (3.8)	9 (1.9)	1 (1.3)	10 (1.8)
Corticosteroid Use	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
No Day 1 SVA Sample	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	1 (3.8)	2 (0.4)	1 (1.3)	3 (0.5)
No Day 11 SVA Sample	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	4 (2.7)	1 (3.8)	5 (1.1)	1 (1.3)	6 (1.1)
Dose Preparation Documentation Error	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)[3]	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)

Note: Percentages are based on the number of randomized subjects in each treatment arm. Subjects may have more than one reason for exclusion. SVA: serum vibriocidal antibody

[1] Three subjects (two from Cohort 1 and one from Cohort 2) received Vaxchora instead of their randomized placebo assignments and were included in the Vaxchora Safety Population.

[2] One Cohort 2 subject was randomized to Vaxchora in error (eligibility criteria not met), and 6 subjects (2 in Cohort 2 and 4 in Cohort 3) were randomized but not vaccinated (refused to consume the assigned treatment).

[3] Includes one subject who received a full dose of vaccine, but proper reconstitution process couldn't be confirmed resulting in possibly 50% of the dose.

Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Tables 9+10 (p56-57) and Table 14.1.8.2 (p151-155) in vc2000006final_tablesversion1_20200306-bookmarked.pdf.

Table 9. Study PXVX-VC-200-006 Vaccine Administration and Consumption

Cohort	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall	Total
Age (in years)	**12 to < 18**	**12 to < 18**	**6 to < 12**	**6 to < 12**	**2 to < 6**	**2 to < 6**	**2 to < 18**	**2 to < 18**	
Treatment Group	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	
Randomized	163	26	158	27	150	26	471	79	550
Vaccinated on Day 1									
Yes	163	26[1]	156 (98.7)	26 (96.3)[2]	146 (97.3)	26 (100.0)	465 (98.7)	78 (98.7)	543 (98.7)
No	0	0	2 (1.3)	1 (3.7)	4 (2.7)	0 (0.0)	6 (1.3)	1 (1.3)	7 (1.3)
Complete Dose Consumed (100%)									
Yes	162 (99.4)	26 (100.0)	142 (91.0)	25 (96.2)[2]	115 (78.8)	19 (73.1)	419 (90.1)	70 (89.7)	489 (90.1)
No	1 (0.6)	0 (0.0)	14 (9.0)[1]	1 (3.8)	31 (21.2)[2,3]	7 (26.9)	46 (9.9)	8 (10.3)	54 (9.9)
Dose volume consumed									
0	0	0	0	0	5 (16.7)	1 (14.3)	5 (11.1)	1 (12.5)	6 (11.3)
10	0	0	4 (28.6)	0	9 (30.0)	1 (14.3)	13 (28.9)	1 (12.5)	14 (26.4)
20	0	0	1 (7.1)	1 (100.0)	5 (16.7)	2 (28.6)	6 (13.3)	3 (37.5)	9 (17.0)
30	0	0	1 (7.1)	0	6 (20.0)	0	7 (15.6)	0	7 (13.2)
40	1	0	3 (21.4)	0	5 (16.7)	1 (14.3)	9 (20.0)	1 (12.5)	10 (18.9)
50	0	0	0	0	0	2 (28.6)	0	2 (25.0)	2 (3.8)
60	0	0	1 (7.1)	0	NA	NA	1 (2.2)	0	1 (1.9)
70	0	0	0	0	NA	NA	0	0	0
80	0	0	3 (21.4)	0	NA	NA	3 (6.7)	0	3 (5.7)
90	0	0	1 (7.1)	0	NA	NA	1 (2.2)	0	1 (1.9)

NA: not applicable.

Note: A single dose of Vaxchora is 100 mL for persons 6 years through64 years of age or 50 mL for children less than 6 years of age.

[1] This includes 2 subjects randomized to placebo group but who were actually injected with Vaxchora in error.

[2] This includes 1 subject randomized to the placebo group but who was actually injected with Vaxchora in error.

[3] Includes one subject who received a full dose of vaccine, but proper reconstitution process couldn't be confirmed resulting in possibly 50% of the dose.

Source: STN 125597/123.0. Module 5.3.5.1, Table 14.1.6 in vc200006final_tablesversion1_20200306-bookmarked.pdf.

6.1.11 Analyses of Effectiveness

6.1.11.1 Analyses of Primary Endpoint(s)

Both co-primary objectives were met for each of the three study cohorts (Table 10). The lower limit of the 2-sided 96.7% confidence interval (CI) on the difference in seroconversion rates between Vaxchora recipients in each cohort of study PXVX-VC-200-006 and adult Vaxchora recipients in study PXVX-VC-200-004 was > -10% (the pre-specified immunobridging success criterion). In addition, the lower limit of the 98.3% CI on the seroconversion rate in pediatric subjects in study PXVX-VC-200-006 was > 70%. Although not pre-specified, an additional analysis conducted on the overall study population also met the pre-specified success criteria for both co-primary endpoints.

Table 10. Immunobridging of Classical Inaba *V. cholerae* Vaccine Strain Vibriocidal Antibody Seroconversion Rates at 10 Days Post-Vaccination in Vaxchora recipients 2 through 17 Years of Age (PVXV-VC-200-006) Compared to Vaxchora Recipients 18 through 45 Years of Age (PXVX-VC-200-004) [Bridging Analysis Population]

	Study 004 Vaxchora recipients 18-45 years	**Study 006 Cohort 1 Vaxchora recipients 12 to < 18 years**	**Study 006 Cohort 2 Vaxchora recipients 6 to < 12 years**	**Study 006 Cohort 3 Vaxchora recipients 2 to < 6 years**	**Study 006 Overall Vaxchora recipients 2 to <18 years**
Day 11 Visit					
N analyzable	2687	157	139	103	399
N (%) Seroconverted [98.3% CI]	2513 (93.5) [92.3, 94.6]	156 (99.4) [95.4, 99.9]	136 (97.8) [92.5, 99.4]	101 (98.1) [91.5, 99.6]	393 (98.5) [96.2, 99.4]
Difference (Study 006 minus Study 004)	-	5.8%	4.3%	4.5%	5.0%
96.7% CI on % Difference	-	[2.4, 7.1]	[-0.3, 6.2]	[-1.1, 6.4]	[2.8, 6.4]

CI: confidence interval
A subject is considered to have seroconverted if they achieve an antibody titer by the Day 11 visit that is at least 4-fold higher than their Day 1 titer.
Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 12, p 62.

The primary analysis was conducted using the bridging analysis population, consisting of the study PXVX-VC-200-006 IEP population. Analyses based on the study PXVX-VC-200-006 mITT population yielded similar results and did not impact study outcomes.

6.1.11.2 Analyses of Secondary Endpoints

Secondary study endpoints, which were descriptive in nature, included the proportion of subjects achieving a ≥ 4-fold of SVA against the classical Inaba biotype *V. cholerae* at Day 29 for all cohorts, at Days 91 and 181 for cohort 1, and at Days 365, 547 and 730 among vaccinees participating in the Cohort 1 sub-study. Table 11 present results of these secondary endpoint analyses for the Vaxchora treatment group.

On Day 29, 100.0%, 94.9% and 93.9% of subjects in Cohorts 1, 2, and 3, respectively, achieved a 4-fold or higher increase in antibody titers compared to baseline (day 1). There appeared to be a decrease in the proportion by age cohorts that was not seen in Day 11 seroconversion rates noted in Section 6.1.11.2. In Cohort 1 subjects who opted

to participate in the long-term follow-up sub-study, 64.5% achieved ≥ 4-fold increase in vibriocidal antibody titers by Day 730 compared to Day 1.

Table 11. Study PXVX-VC-200-006 Subjects Achieving ≥ 4-fold Increase in Vibriocidal Antibody Titer (From Day 1 Baseline) Against Classical Inaba *V. cholerae* By Age-Based Cohort.

	Study 006 Cohort 1 Vaxchora recipients 12 to < 18 years	**Study 006 Cohort 2 Vaxchora recipients 6 to < 12 years**	**Study 006 Cohort 3 Vaxchora recipients 2 to < 6 years**	**Study 006 Overall Vaxchora recipients 2 to <18 years**
Day 29 Visit				
N analyzable	156	138	98	392
N (%) 4-fold increase [95.0% CI]	156 (100.0) [97.6, 100.0]	131 (94.9) [89.9, 97.5]	92 (93.9) [87.3, 97.2]	379 (96.7) [94.4, 98.1]
Day 91 Visit				
N analyzable	153	NA	NA	NA
N (%) 4-fold increase [95.0% CI]	131 (85.6) [79.2, 90.3]	NA	NA	NA
Day 181 Visit				
N analyzable	151	NA	NA	NA
N (%) 4-fold increase [95.0% CI]	111 (73.5) [66.0, 79.9]	NA	NA	NA
Day 365 Visit				
N analyzable	70	NA	NA	NA
N (%) 4-fold increase [95.0% CI]	48 (68.6) [57.0, 78.2]	NA	NA	NA
Day 547 Visit				
N analyzable	67	NA	NA	NA
N (%) 4-fold increase [95.0% CI]	49 (73.1) [61.5, 82.3]	NA	NA	NA
Day 730 Visit				
N analyzable	62	NA	NA	NA
N (%) 4-fold increase [95.0% CI]	40 (64.5) [52.1, 75.3]	NA	NA	NA

CI: confidence interval. NA: not available (there were no blood draws beyond day 29 in Cohorts 2 and 3).
Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 13, p 64-65.

> ***Reviewer Comment:*** *Subjects in Cohorts 2 and 3 had blood drawn only on Days 1, 11 and 29. Seroconversion rates were not available beyond Day 29 for cohorts 2 and 3.*

Serum vibriocidal antibody titers were also summarized by GMTs (see Table 12). GMTs peaked at Day 11 in Vaxchora recipients in each cohort (8735, 8305 and 4852 in Cohorts 1, 2 and 3, respectively); they remained moderately elevated at Day 29 in Vaxchora recipients with values of 2749, 1952, and 1014 in Cohort 1, 2, and 3, respectively. GMTs on Days 1, 11 and appear to be lower with decreasing age cohorts.

Table 12. Study PXVX-VC-200-006 Geometric Mean Titers (GMTs) Against Classical Inaba *V. cholerae* by Age Group Cohort – Immunogenicity Evaluable Population

	Study 006 Cohort 1 Vaxchora recipients 12 to < 18 years	Study 006 Cohort 2 Vaxchora recipients 6 to < 12 years	Study 006 Cohort 3 Vaxchora recipients 2 to < 6 years	Study 006 Overall Vaxchora recipients 2 to <18 years
Day 1 Visit				
N analyzable	157	139	103	399
GMT (95.0% CI)	32.1 (28.1, 36.6)	31.5 (27.7, 35.8)	26.7 (23.8, 30.0)	30.4 (28.2, 32.8)
Day 11 Visit				
N analyzable	157	139	103	399
GMT (95.0% CI)	8735 (7053, 10819)	8305 (6516, 10586)	4852 (3445, 6832)	7347 (6353, 8560)
Day 29 Visit				
N analyzable	156	138	98	392
GMT (95.0% CI)	2749 (2311, 3270)	1952 (1554, 2452)	1014 (741, 1387)	1899 (1657, 2176)
Day 91 Visit				
N analyzable	153	NA	NA	NA
GMT (95.0% CI)	319 (263, 386)	NA	NA	NA
Day 181 Visit				
N analyzable	151	NA	NA	NA
GMT (95.0% CI)	186 (154, 225)	NA	NA	NA
Day 365 Visit				
N analyzable	70	NA	NA	NA
GMT (95.0% CI)	158 (122, 206)	NA	NA	NA
Day 547 Visit				
N analyzable	67	NA	NA	NA
GMT (95.0% CI)	176 (134, 230)	NA	NA	NA
Day 730 Visit				
N analyzable	62	NA	NA	NA
GMT (95.0% CI)	134 (102, 176)	NA	NA	NA

CI: confidence interval. NA: not available (there were no immunogenicity blood draws beyond day 29 in Cohorts 2 and 3).
Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 15, p 70-73.

6.1.11.3 Subpopulation Analyses

In post-hoc subgroup analyses by sex and race using the IEP population, there were no clinically significant differences in seroconversion rates by Day 11 [Data not shown, STN 125597/123.6, module 1.11.3, clinical information amendment response to FDA IR5]. Seroconversion rates appeared higher among female (100%) compared to male (95.5%-98.9%) Vaxchora recipients and higher among White (98.7%-100%) compared to Black

or African American (95.7%-97.9%) Vaxchora recipients; however, seroconversion rates among males and Black or African American Vaxchora recipients were notably high across each study cohort and overall. Among cohort 3 subjects self-categorized as "other" for race, seroconversion rates were lower (88.9%) compared to White subjects (100%). By ethnicity, there were no clear or consistent differences in seroconversion rates between Hispanic or Latino subjects and Non-Hispanic or Latino subjects across the three study cohorts.

6.1.11.4 Dropouts and/or Discontinuations

Missing values were not imputed for subjects who had missing blood draws.

6.1.11.5 Exploratory and Post Hoc Analyses

Acceptability

A high proportion of subjects in cohort 1 consumed a complete dose (100%) according to the protocol (entire volume within 15 minutes). In Cohort 2, 91% of Vaxchora recipients and 96.2% of placebo recipients consumed a complete dose. In Cohort 3, a lower proportion of subjects consumed a complete dose (79.5% in the Vaxchora group and 73.1% in the placebo group) [Table 13].

Palatability

(b) (4)

Table 13. Study PXVX-VC-200-006 Dose Acceptability (Complete Dose Consumption According to Protocol)

Cohort	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall	Total
Age (in years)	**12 to < 18**	**12 to < 18**	**6 to < 12**	**6 to < 12**	**2 to < 6**	**2 to < 6**	**2 to < 18**	**2 to < 18**	
Treatment Group	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	
Randomized	163	26	158	27	150	26	471	79	550
Vaccinated on Day 1									
Yes	163	26	156 (98.7)	26 (96.3)	146 (97.3)	26 (100.0)	465 (98.7)	78 (98.7)	543 (98.7)
No	0	0	2 (1.3)	1 (3.7)	4 (2.7)	0 (0.0)	6 (1.3)	1 (1.3)	7 (1.3)
Complete Dose (100%) Consumed									
Yes	162 (99.4)	26 (100.0)	142 (91.0)	25 (96.2)	116 (79.5)	19 (73.1)	420 (90.3)	70 (89.7)	490 (90.2)
No	1 (0.6)	0 (0.0)	14 (9.0)[1]	1 (3.8)	30 (20.5)[2]	7 (26.9)	45 (9.7)	8 (10.3)	53 (9.8)

Note: Acceptability is defined as all dose was consumed within 15 minutes of reconstitution.
Source: Module 5.3.5.1. Table 14.1.6 (p111-138) in vc200006final_tableversion1_20200306-bookmarked.pdf

Table 14. Study PXVX-VC-200-006 Palatability Ratings Overall and By the Status of (b) (4) Vaccine

Cohort	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall	Total
Age (in years)	**12 to < 18**	**12 to < 18**	**6 to < 12**	**6 to < 12**	**2 to < 6**	**2 to < 6**	**2 to < 18**	**2 to < 18**	
Treatment Group	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	**Vaxchora n (%)**	**Placebo n (%)**	
Randomized (N)	163	26	158	27	150	26	471	79	
Vaccinated on Day 1	163 (100.0)	26 (100.0)	156 (98.7)	26 (96.3)	146 (97.3)	26 (100.0)	465 (98.7)	78 (98.7)	543 (98.7)
Palatability Among Vaccinated[3]									
Super Bad	12 (7.4)	1 (3.8)	34 (21.8)	6 (23.1)	31 (21.2)	4 (15.4)	77 (16.6)	11 (14.1)	88 (16.2)
Bad	50 (30.7)	7 (26.9)	30 (19.2)	6 (23.1)	24 (16.4)	4 (15.4)	104 (22.4)	17 (21.8)	121 (22.3)
Maybe Good or Maybe Bad	64 (39.3)	10 (38.5)	37 (23.7)	10 (38.5)	19 (13.0)	3 (11.5)	120 (25.8)	23 (29.5)	143 (26.3)
Good	29 (17.8)	6 (23.1)	27 (17.3)	1 (3.8)	28 (19.2)	9 (34.6)	84 (18.1)	16 (20.5)	100 (18.4)
Super Good	8 (4.9)	2 (7.7)	28 (17.9)	3 (11.5)	44 (30.1)	6 (23.1)	80 (17.2)	11 (14.1)	91 (16.8)

(b) (4)

[1] Palatability scores went from Super Bad to Super Good and recorded as values of 1-5, respectively. Percentages for palatability ratings within (b) (4) use or acceptability determination are based on the number of subjects included in the respective no/yes category. [2] Denominator includes all subjects vaccinated on day 1.
Note: Palatability ratings in Cohort 2 Vaxchora recipients were “super bad” and “bad” among 80% and 0% of subjects with incomplete dosing vs 15.6% and 21.3% of subjects with complete dosing, respectively. Palatability ratings in Cohort 3 Vaxchora recipients were “super bad” and “bad” among 41.9% and 29.0% of subjects with incomplete dosing vs 15.7% and 13.0% of subjects with complete dosing, respectively.
Source: STN 125597/123.0, Module 5.3.5.1. Table 14.1.6 (p111-138) in vc200006final_tableversion1_20200306-bookmarked.pdf

Seroconversion Rates Among Subjects Excluded From Primary Analyses Due to Incomplete Dosing (<80%)

Only subjects who consumed ≥ 80% of the full dose were included in the primary analysis (per-protocol population). In post-hoc analyses requested by CBER, the Applicant provided an analysis of the rate of seroconversion among subjects who consumed < 80% of the full dose using the mITT population (Table 15). Subjects were categorized as those who received < 50% of the dose (< 50 mL for cohorts 1 and 2, < 25 mL for cohort 3), between 50 to < 80% (50 to < 80 mL for cohorts 1 and 2, 25 to < 40 mL for cohort 3). Each of the 7 subjects who consumed at least 50% of the full dose seroconverted. Among subjects who consumed < 50% of the dose, seroconversion rates ranged from 66.7% to 100%.

> ***Reviewer Comment:*** *Study PXVX-VC-200-006 did not include a pre-specified evaluation of the effectiveness of an incomplete dose of Vaxchora (< 80% of the dose). The post-hoc analyses shown in Table 15 suggest that a high proportion of subjects who consume between 50% and 80% of the full Vaxchora dose would be expected to seroconvert by Day 11 post-vaccination. Meanwhile, the data suggest that a substantially lower proportion of subjects who consume < 50% of the full Vaxchora dose would be expected to seroconvert by Day 11 post-vaccination. However, the data were not considered sufficient to support the optimal management of incomplete dosing to the Vaxchora prescribing information. Because of the post-hoc nature of these analyses and the small numbers of subjects who consumed between 50%-80% of the dose or < 50% of the dose, no conclusions could be made regarding the effectiveness of Vaxchora when < 80% of the dose is consumed. In addition, the safety or effectiveness of a replacement dose was not evaluated in study PXVX-VC-200-006.*

Table 15. Study PXVX-VC-200-006 Vibriocidal Seroconversion Against Classical Inaba *V. cholerae* at Day 11, Stratified by Dose Consumed, Among Vaxchora-treated mITT Subjects Consuming < 80% of Expected Dose.

	< 50% of Dose n/N (%)	**50 to < 80% of Dose n/N (%)**	**Total < 80% of Dose n/N (%)**
Cohort 1	1/1 (100)	0/0	1/1 (100.0)
Cohort 2	6/9 (66.7)	1/1 (100.0)	7/10 (70.0)
Cohort 3	11/16 (68.8)	6/6 (100.0)	17/23 (73.9)
Overall	18/26 (69.2)	7/7 (100.0)	25/33 (75.8)

[a] A subject was considered to have seroconverted if they achieve a titer at Day 11 at least 4-fold higher than their Day 1 titer.

[b] N is the number of subjects with an analyzable sample available at the indicated visit.

Source: STN 125597/123.6, module 1.11.3, Table 1 in Clinical Information Amendment Response to FDA IR5 and module 5.3.5.1, supplementary Table 14.2.1.3.2-1 of vc200006final_tableversion1_20200306-bookmarked.pdf.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses were descriptive. Please see Section 6.1.7 for details regarding safety surveillance/monitoring, Section 6.1.8 for a listing of safety endpoints, and Section 6.1.9 for details regarding the safety analysis population.

6.1.12.2 Overview of Adverse Events

Rates of any AEs (solicited through day 8 and unsolicited AEs through Day 29) and rates of unsolicited AEs through Day 29 (Table 16) were similar across treatment groups within each study cohort. There was no clear trend when comparing the rates of any AEs graded as severe or worse between treatment groups.

There were no deaths and no discontinuations due to an AE. Four SAEs were reported among four Vaxchora recipients in Cohort 1 and one SAE reported in 1 placebo recipient in Cohort 1; these were all determined to be unrelated to study treatment. Please refer to Section 6.1.12.4 for more details.

Overall, the most common solicited reactions occurring through Day 8 (Table 17) included tiredness, headache, and abdominal pain. There appeared to be a trend across the study cohorts toward lower rates of solicited adverse reactions (following Vaxchora and following placebo) with decreasing age. Within each cohort, rates of solicited reactions between the two treatment groups generally appeared similar with the exception of abdominal pain (all 3 cohorts) and lack of appetite (cohorts 1 and 3), which were reported in a higher proportion of Vaxchora recipients compared to placebo recipients. Overall, severe or worse solicited reactions were reported by 2.1% and 2.7% of Vaxchora and placebo recipients respectively; within the individual cohorts, rates ranged from 0% to 4.2% of subjects, with no clear trend when comparing the two treatment groups. Among Vaxchora recipients, the median number of days that any solicited reaction was reported was 3.0 days (ranging 1 – 8 days) in Cohort 1, 2 days (ranging 1-8 days) in Cohort 2, and 2 days (ranging 1-8) in Cohort 3 [data not shown, module 5.3.5.1 Table 14.3.3.1, p383-418 in vc200006final_tableversion1_20200306-bookmarked.pdf].

> ***Reviewer Comment:*** *The trend of lower rates of solicited adverse reactions (following Vaxchora and following placebo) with decreasing age may be explained by differences in the ability to communicate feeling ill based on age. There may also be some differences in tolerability by age due to differences in gastrointestinal maturity; the lower serum vibriocidal geometric mean titers achieved in Cohort 3 subjects compared to older subjects in Cohorts 1 and 2 suggest this may be a potential explanation as well.*

Rates of unsolicited AEs through Day 29 (Table 18) between the two study groups were generally similar within each cohort; there were no trends observed across the cohorts. The most common unsolicited AE was loose stools (defined as > 4 loose stools). Most unsolicited AEs were mild or moderate. There were 12 severe (grade 3) events, none of which were considered treatment-related (fatigue, pyrexia, viral pharyngitis, decreased appetite, headache, lower limb fracture (SAE), acute asthma with pneumonia, hyperglycemia and influenza (SAE), intentional acetaminophen overdose (SAE), and neck swelling (SAE). Four of these events occurred in Vaxchora subject (b) (6) (severe fatigue, pyrexia, decreased appetite, and headache). Four occurred in Placebo subject (b) (6) (acute asthma, pneumonia, hyperglycemia, and influenza). None of the grade 3 AEs were considered treatment-related by the investigator or sponsor. There were no grade 4 unsolicited events reported.

Loose stools were the most frequently reported vaccine-related unsolicited AE among both Vaxchora and Placebo recipients. Other related unsolicited AEs reported by

Vaxchora recipients included: fatigue, decreased appetite, abdominal pain, flatulence, headache, abdominal distension, cough, dermatitis diaper, diarrhea, dyspepsia, eructation, feeling cold, insomnia, irritability, myalgia, pyrexia, rash generalized, rectal tenesmus, upper respiratory tract infection, viral infection, and vomiting.

Table 16. Study PXVX-VC-200-006 Summary of Adverse Events (AEs) by Cohort and Treatment Group

	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall
Category [n (%)]	Vaxchora N=165	Placebo N=24	Vaxchora N=157	Placebo N=25	Vaxchora N=146	Placebo N=26	Vaxchora N=468	Placebo N=75
Any solicited (through Day 8) or unsolicited (through Day 29) AE	116 (70.3)	16 (66.7)	93 (59.2)	15 (60.0)	74 (50.7)	12 (46.2)	283 (60.5)	43 (57.3)
Severe or worse	4 (2.4)	1 (4.2)	5 (3.2)	0 (0.0)	1 (0.7)	1 (3.8%)	10 (2.1)	2 (2.7)
Any solicited AE thru Day 8	113 (68.5)	16 (66.7)	86 (54.8)	13 (52.0)	59 (40.4)	9 (34.6)	258 (55.1)	38 (50.7)
Severe or worse	4 (2.4)	1 (4.2)	5 (3.2)	0 (0.0)	1 (0.7)	1 (3.8)	10 (2.1)	2 (2.7)
Any unsolicited AE thru Day 29	46 (27.9)	7 (29.2)	28 (17.8)	8 (32.0)	38 (26.0)	6 (23.1)	112 (23.9)	21 (28.0)
Severe or worse	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4%)	0 (0.0)
Any serious AE (SAE)	4 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	4 (0.9)	1 (1.3)
Any treatment-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 17, pages 82-83 and STN 125597/123.12, CSR_v3.0_aAddendum_2020OCT20, Table 18, p15.

Table 17. Study PXVX-VC-200-006 Solicited Adverse Reactions by Study Group, Cohort and Severity- Safety Population

	Cohort 1	**Cohort 1**	**Cohort 2**	**Cohort 2**	**Cohort 3**	**Cohort 3**	**Overall**	**Overall**
	Ages 12 to < 18 years	**Ages 12 to < 18 years**	**Ages 6 to < 12 years**	**Ages 6 to < 12 years**	**Ages 2 to < 6 years**	**Ages 2 to < 6 years**	**Ages 2 to < 18 years**	**Ages 2 to < 18 years**
	Vaxchora N=165 n (%)	**Placebo N=24 n (%)**	**Vaxchora N=157 n (%)**	**Placebo N=25 n (%)**	**Vaxchora N=146 n (%)**	**Placebo N=26 n (%)**	**Vaxchora N=468 n (%)**	**Placebo N=75 n (%)**
Any Solicited Reaction	113 (68.5)	16 (66.7)	86 (54.8)	13 (52.0)	59 (40.4)	9 (34.6)	258 (55.1)	38 (50.7)
Mild	78 (47.3)	13 (54.2)	58 (36.9)	7 (28.0)	35 (24.0)	5 (19.2)	171 (36.5)	25 (33.3)
Moderate	31 (18.8)	2 (8.3)	23 (14.6)	6 (24.0)	23 (15.8)	3 (11.5)	77 (16.5)	11 (14.7)
Severe	3 (1.8)	1 (4.2)	5 (3.2)	0 (0)	0 (00)	1 (3.8)	8 (1.7)	2 (2.7)
Potentially Life-Threatening	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	2 (0.4)	0 (0)
Tiredness[a]	67 (40.6)	9 (37.5)	55 (35.0)	8 (32.0)	45 (30.8)	6 (23.1)	167 (35.7)	23 (30.7)
Mild	52 (31.5)	8 (33.3)	35 (22.3)	5 (20.0)	28 (19.2)	4 (15.4)	115 (24.6)	17 (22.7)
Moderate	14 (8.5)	0 (0)	19 (12.1)	3 (12.0)	17 (11.6)	2 (7.7)	50 (10.7)	5 (6.7)
Severe	0 (0)	1 (4.2)	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.2)	1 (1.3)
Potentially Life-Threatening	1 (0.6)[e]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Headache[a]	74 (44.8)	11 (45.8)	41 (26.1)	6 (24.0)	13 (8.9)	2 (7.7)	128 (27.4)	19 (25.3)
Mild	57 (34.5)	11 (45.8)	30 (19.1)	5 (20.0)	10 (6.8)	1 (3.8)	97 (20.7)	17 (22.7)
Moderate	16 (9.7)	0 (0)	9 (5.7)	1 (4.0)	3 (2.1)	1 (3.8)	28 (6.0)	2 (2.7)
Severe	1 (0.6)	0 (0)	2 (1.3)	0 (0)	0 (0)	0 (0)	3 (0.6)	0 (0)

	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall
	Ages 12 to < 18 years	Ages 12 to < 18 years	Ages 6 to < 12 years	Ages 6 to < 12 years	Ages 2 to < 6 years	Ages 2 to < 6 years	Ages 2 to < 18 years	Ages 2 to < 18 years
	Vaxchora N=165 n (%)	Placebo N=24 n (%)	Vaxchora N=157 n (%)	Placebo N=25 n (%)	Vaxchora N=146 n (%)	Placebo N=26 n (%)	Vaxchora N=468 n (%)	Placebo N=75 n (%)
Abdominal Pain[a]	62 (37.6)	4 (16.7)	43 (27.4)	6 (24.0)	25 (17.1)	4 (15.4)	130 (27.8)	14 (18.7)
Mild	47 (28.5)	3 (12.5)	37 (23.6)	4 (16.0)	21 (14.4)	4 (15.4)	105 (22.4)	11 (14.7)
Moderate	14 (8.5)	1 (4.2)	6 (3.8)	2 (8.0)	4 (2.7)	0 (0)	24 (5.1)	3 (4.0)
Severe	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Lack of Appetite[a]	48 (29.1)	3 (12.5)	24 (15.3)	5 (20.0)	28 (19.2)	3 (11.5)	100 (21.4)	11 (14.7)
Mild	39 (23.6)	3 (12.5)	20 (12.7)	4 (16.0)	18 (12.3)	2 (7.7)	77 (16.5)	9 (12.0)
Moderate	9 (5.5)	0 (0)	3 (1.9)	1 (4.0)	10 (6.8)	1 (3.8)	22 (4.7)	2 (2.7)
Severe	0 (0)	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Nausea[a]	37 (22.4)	6 (25.0%)	22 (14.0)	4 (16.0)	10 (6.8)	4 (15.4)	69 (14.7)	14 (18.7)
Mild	28 (17.0)	5 (20.8)	19 (12.1)	2 (8.0)	9 (6.2)	4 (15.4)	56 (12.0)	11 (14.7)
Moderate	8 (4.8)	1 (4.2)	3 (1.9)	2 (8.0)	1 (0.7)	0 (0)	12 (2.6)	3 (4.0)
Severe	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Vomiting[b]	9 (5.5)	0 (0)	7 (4.5)	0 (0)	2 (1.4)	3 (11.5)[g]	18 (3.8)	3 (4.0)
Mild	6 (3.6)	0 (0)	4 (2.5)	0 (0)	2 (1.4)	2 (7.7)	12 (2.6)	2 (2.7)
Moderate	2 (1.2)	0 (0)	3 (1.9)	0 (0)	0 (0)	1 (3.8)	5 (1.1)	1 (1.3)
Severe	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Fever[c]	2 (1.2)	0 (0)	5 (3.2)	1 (4.0)	3 (2.1)	1 (3.8)	10 (2.1)	2 (2.7)
Mild	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	2 (0.4)	0 (0)
Moderate	0 (0)	0 (0)	1 (0.6)	1 (4.0)	1 (0.7)	0 (0)	2 (0.4)	1 (1.3)
Severe	1 (0.6)	0 (0)	4 (2.5)	0 (0)	0 (0.0)	1 (3.8)	5 (1.1)	1 (1.3)
Potentially Life-Threatening	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)[f]	0 (0)	1 (0.2)	0 (0)
Diarrhea[d]	6 (3.6)	1 (4.2)	0 (0)	0 (0)	1 (0.7)	0 (0.0)	7 (1.5)	1 (1.3)
Mild	3 (1.8)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0.0)	4 (0.9)	0 (0.0)
Moderate	0 (0)	1 (4.2)	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0.0)	1 (1.3)
Severe	3 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.6)	0 (0)

[a] The severity grading for tiredness, headache, abdominal pain, lack of appetite and nausea consisted of the following: Mild (Grade 1): mild, no interference with activity; Moderate (Grade 2): Some interference with activity; severe (Grade 3): significant, prevents daily activity; Potentially Life-Threatening (Grade 4): emergency room (ER) visit or hospitalization.

[b] Mild vomiting (Grade 1): 1-2 episodes/24 hours; Moderate vomiting (Grade 2): > 2 episodes/24 hours; Severe vomiting (Grade 3): requires IV hydration; Potentially life-threatening vomiting (grade 4): ER visit or hospitalization.

[c] Fever was defined as ≥ 100.4°F or ≥ 38.0°C. Mild fever: ≥ 38.0°C to 38.4°C. Moderate fever: ≥ 38.5°C to 38.9°C. Severe fever: ≥ 39.0°C to 40.0°C. Potentially life-threatening fever: ≥ 40.0°C.
[d] Mild diarrhea (Grade 1): 4 loose stools/24 hours; Moderate diarrhea (Grade 2): 5 loose stools/24 hours; Severe diarrhea (Grade 3): ≥ 6 stools/24 hours; Potentially life-threatening diarrhea (Grade 4): ER visit or hospitalization.
[e] This case was categorized as a grade 4 event because the subject had an emergency room visit due to the adverse event. The investigator assessed this to be related to an underlying viral pharyngitis (unrelated to study treatment).
[f] This event was categorized as a grade 4 event, because the fever measurement was > 40.0°C. The investigator assessed this event to be non-life threatening, non-serious, and related to an underlying viral infection (unrelated to study treatment).
[g] The increased rate of vomiting may represent the physiologic effects of oral administration of normal saline (0.9%) solution in younger children (a solution of higher osmolarity than their usual diet).
Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 18, pages 85-86.

Table 18. Study PXVX-VC-200-006 Unsolicited Adverse Events (≥ 1.5% Overall Frequency) by Preferred Terms Through Day 29 - Safety Population

	Cohort 1	Cohort 1	Cohort 2	Cohort 2	Cohort 3	Cohort 3	Overall	Overall
	Ages 12 to < 18 years	Ages 12 to < 18 years	Ages 6 to < 12 years	Ages 6 to < 12 years	Ages 2 to < 6 years	Ages 2 to < 6 years	Ages 2 to < 18 years	Ages 2 to < 18 years
Preferred term	Vaxchora N=165 n (%)	Placebo N=24 n (%)	Vaxchora N=157 n (%)	Placebo N=25 n (%)	Vaxchora N=146 n (%)	Placebo N=26 n (%)	Vaxchora N=468 n (%)	Placebo N=75 n (%)
Any unsolicited adverse event	46 (27.9)	7 (29.2)	28 (17.8)	8 (32.0)	38 (26.0)	6 (23.1)	112 (23.9)	21 (28.0)
Loose stools	23 (13.9)	5 (20.8)	18 (11.5)	0 (0)	8 (5.5)	2 (7.7)	49 (10.5)	7 (9.3)
Upper respiratory tract infection	7 (4.2)	0 (0)	2 (1.3)	0 (0)	6 (4.1)	3 (11.5)	15 (3.2)	3 (4.0)
Headache	4 (2.4)	0 (0)	2 (1.3)	0 (0)	1 (0.7)	0 (0)	7 (1.5)	0 (0)
Fatigue	4 (2.4)	0 (0)	1 (0.6)	0 (0)	5 (3.4)	0 (0)	10 (2.1)	0 (0)
Decreased appetite	3 (1.8)	0 (0)	1 (0.6)	0 (0)	3 (2.1)	0 (0)	7 (1.5)	0 (0)

Note: Due to the modification of the toxicity grades for Diarrhea requiring ≥ 4 loose stools, a modified preferred term of 'Loose stools' is used for unsolicited adverse events that do not meet the Diarrhea definition.
Source: Module 5.3.5.1, PXVX-VC-200-006 Final Clinical Study Report v3.0, Table 19, page 89 and Table 14.4.6 in vc2000006final_tablesversion1_20200306-bookmarked.pdf.

Safety Among 9 Subjects Who Were Enrolled and Dosed Twice
A total of 9 subjects (two subjects in Cohort 1, four subjects in Cohort 2 and three subjects in Cohort 3) were enrolled twice and dosed twice. Eight of the 9 subjects received Vaxchora twice approximately 1 to 4 months apart (one Cohort 1 subject received Vaxchora followed by Placebo).

Cohort 1 duplicate enrollments (n=2):
- Subject [redacted] reported abdominal pain, headache, lack of appetite, and tiredness through Day 8 after the first dose of Vaxchora, with prolonged mild abdominal pain and lack of appetite through Day 15, and then abdominal pain through Day 4 and tiredness through Day 8 after the second dose of Vaxchora. Additional unrelated AEs were low back pain, left ankle laceration and tiredness.
- Subject [redacted] who received Vaxchora as the first dose then placebo as the second dose reported abdominal pain, nausea, and tiredness through Day 3 after the Vaxchora dose, and then abdominal pain through Day 1 after the placebo dose.

Cohort 2 duplicate enrollments (n=4):
- Subject [redacted] reported headache and tiredness though Day 1 after the first dose of Vaxchora, and headache through Day 2 after the second dose of Vaxchora.
- Subject [redacted] reported headache through Day 1 after the first dose of Vaxchora, and no solicited AEs after the second dose of Vaxchora.
- Subjects [redacted] reported no solicited or unsolicited AEs after either Vaxchora dose.

Cohort 3 duplicate enrollments (n=3):
- Subject [redacted] reported no solicited AEs after the first dose of Vaxchora. Following the second dose of Vaxchora, the subject reported mild tiredness on Day 1, mild nausea on Day 2 and mild tiredness and lack of appetite on Day 3.
- Subject [redacted] reported no solicited or unsolicited AEs after either dose of Vaxchora.
- Subject [redacted] reported no solicited AEs after either dose of Vaxchora. From Day 118 to Day 124, following the second dose, the subject reported bronchitis.

> ***Reviewer Comment:*** No safety concern was identified based on the review of the safety data collected from the 8 study subjects who received two consecutive doses of Vaxchora. Although these data are reassuring, they are insufficient to support the safety of repeat vaccination among children 2 through 17 years of age.

Open Label Safety Among Placebo Crossover Subjects
After unblinding of study subjects on study day 181, placebo recipients were offered Vaxchora in an open-label manner (placebo-crossover). Vaxchora was administered to a total of 31 placebo-crossover subjects (13, 11 and 7 subjects in Cohorts 1, 2 and 3, respectively). Rates of solicited reactions through day 8 post-vaccination were generally consistent with the findings from the primary safety analyses [Data not shown, Table 14.3.5 of module 5.3.5.1, vc2000006final_tablesversion1_20200306-bookmarked.pdf]. Overall, 15 subjects (48.4%) reported any solicited event. Rates in order of frequency were as follows: tiredness (32.3%), headache (25.8%), abdominal pain (16.1%), nausea

(16.1%), lack of appetite (12.9%), diarrhea (6.5%), vomiting (3.2%) and fever (0%). All reactions were graded as mild or moderate in severity.

Unsolicited adverse event data through day 29 post-vaccination at day 181 was also consistent with the results from the primary analysis [Data not shown, Table 14.4.10, module 5.3.5.1, vc2000006final_tablesversion1_20200306-bookmarked.pdf].

Subgroup analyses by Race and Sex
There was no clear pattern of difference in reported rates of adverse events through day 29 (unsolicited and solicited) between VAXCHORA and placebo recipients among male and female subjects. Of note, overall, rates of adverse events through day 29 were 20-30% higher among girls 12 to < 18 years of age than all other males and females by age groups.

There was no clear pattern of difference in reported rates of AE through day 29 between Vaxchora and placebo recipients by race (categorized as White, Black or African American and Other).

6.1.12.3 Deaths

No subjects died during this study.

6.1.12.4 Nonfatal Serious Adverse Events

No treatment-related SAEs were reported during this study. SAEs were reported among 4 Vaxchora recipients in Cohort 1 and one SAE was reported in 1 placebo recipient in Cohort 1; these SAEs were determined to be unrelated to study treatment. The reported SAEs included the following:

1. Fracture of right tibia and fibula after a 16- year old male Vaxchora recipient jumped off a porch 53 days post-vaccination
2. New onset seizure disorder on Days 442 and 497 post-vaccination (brain scan revealed a pineal cyst); hospitalization for possible recurrence or worsening of epilepsy vs syncope on Day 497 (15-year old female)
3. Intentional overdose of acetaminophen and diphenhydramine on Day 543 in a 14-year-old Vaxchora recipient
4. Neck swelling secondary to pharyngitis (suspected reactive lymphadenitis secondary to pharyngitis) on Day 675 post-vaccination with Vaxchora (15-year old female)
5. Acute asthma exacerbation accompanied by pneumonia in 2-year old female 76 days after vaccination with Placebo

6.1.12.5 Adverse Events of Special Interest

There were no pre-specified adverse events of special interest.

6.1.12.6 Clinical Test Results

Not applicable.

6.1.12.7 Dropouts and/or Discontinuations

There were no adverse events that led to withdrawal from the study.

6.1.13 Study Summary and Conclusions

The effectiveness of Vaxchora was demonstrated in persons 2 through 17 years of age by immunobridging to the established efficacy of Vaxchora observed in the adult population (STN 125597/0). The lower limit of the 2-sided 96.7% confidence interval (CI) on the difference in seroconversion rates between Vaxchora recipients in each cohort of study PXVX-VC-200-006 and adult Vaxchora recipients in study PXVX-VC-200-004 was greater than -10% (the pre-specified immune-bridging success criterion). In addition, the seroconversion rate in pediatric Vaxchora recipients 2 through 17 years of age who participated in study PXVX-VC-200-006 was demonstrated to be > 70% with 98.3% confidence.

Overall, the safety profile of Vaxchora in this age group was consistent with the safety profile as described in the Vaxchora Prescribing Information and no safety concerns were identified.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Maternal cholera disease is associated with adverse pregnancy outcomes including fetal death.

V. cholerae strain CVD 103-HgR, the active component of Vaxchora, is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the bacteria.

The vaccine strain may be shed in the stool of the vaccinated mother for at least 7 days, with a potential for transmission of the vaccine strain from mother to infant during vaginal delivery.

9.1.2 Use During Lactation

Vaxchora is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to Vaxchora.

9.1.3 Pediatric Use and PREA Considerations

In the June 10, 2016 Vaxchora approval letter, in accordance with PREA, the FDA waived the requirement to conduct a study in individuals 0 to 2 years of age traveling to cholera-affected areas, because Vaxchora is not likely to be used by a substantial number of children in this age group and does not represent a meaningful therapeutic benefit over existing measures recommended by the Centers for Disease Control (CDC) for the prevention of cholera in this age group.

The safety and immunogenicity data from study PXVX-VC-200-006 included in this submission fulfill the PREA requirement to evaluate the safety and immunogenicity of Vaxchora in children aged 2 through 17 years of age.

9.1.4 Immunocompromised Patients

The safety and effectiveness of Vaxchora have not been established in immunocompromised individuals. The immunologic response to Vaxchora may be diminished in immunocompromised individuals.

Shedding of Vaxchora strain CVD103-HgR was detected overall in 9.6% (95% CI 3.2, 21.0) of vaccine recipients on any day through 7 days post-vaccination in a Phase 1 study in healthy adults 18 through 50 years of age (see Section 6.4 of clinical review of STN 125597/0). The highest proportion of subjects shedding was on day 7 [5.8% (95% CI 1.2, 15.9)]. The duration of shedding of the vaccine strain is unknown, as day 7 was the latest time point evaluated. Due to the potential for transmission of the vaccine strain to non-vaccinated close contacts (i.e., household contacts), caution is advised when considering whether to administer Vaxchora to individuals with immunocompromised close contacts.

9.1.5 Geriatric Use

The safety and effectiveness of Vaxchora have not been established in adults 65 years of age or older.

10. CONCLUSIONS

The safety and immunogenicity data from study PXVX-VC-200-006 support the use of Vaxchora in children 2 years through 17 years of age and fulfills the post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA), as specified in the June 10, 2016 approval letter for the Vaxchora BLA. Vaxchora prescribing information was appropriately updated to extend approved Usage to children 2 through 17 years of age.

The routine pharmacovigilance plan proposed by the Applicant is adequate.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 19 summarizes risk-benefit considerations with Vaxchora in persons 2 years through 17 years of age.

Table 19: Risk Benefit Considerations of Vaccination with Vaxchora in Persons 2 through 17 Years of Age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severe cholera is characterized by acute diarrhea which leads rapidly (within 4 to 18 hours) to moderate or profound dehydration. Complications from cholera arise from the loss of fluid volume and electrolytes, resulting in hypovolemia, metabolic acidosis, and potassium deficiency. Secondary complications may include renal failure. • In general, children with cholera have the same signs and symptoms as adults. However, children may also experience extreme drowsiness, convulsions, hypoglycemia, and clinical effects of hypokalemia (cardiac arrythmias, muscle spasms). • If left untreated, cholera may lead to severe dehydration, hypovolemic shock and death within hours. Case fatality rates observed globally range from < 1% to 13.6%. • There is an estimated burden of 1.4 to 4.3 million cases of cholera and 28,000 to 142,000 deaths per year worldwide due to cholera. The highest cholera incidence rate and case fatality rate globally is in children less than 5 years of age. In endemic areas, the prevalence of cholera is highest in children and decreases age. • Although > 200 *V. cholerae* serogroups cause a cholera-like illness, only toxigenic strains of serogroups O1 and O139 that produce cholera-toxin have caused widespread epidemics and are reportable to the WHO as cholera. • *V. cholerae* O1 is the predominant cause of cholera globally, and most *V. cholerae* O1 cases are caused by O1 El Tor organisms.	• Cholera is a rapidly progressive, serious, life-threatening illness. The risk of morbidity and mortality is high if cholera is not treated in a timely manner. • Potential exposure to *V. cholerae* represents a risk to U.S. pediatric travelers visiting cholera-affected areas.
Unmet Medical Need	• There is currently no cholera vaccine licensed for use pediatric age groups in the United States. • Primary prevention currently consists of five recommendations made by the CDC. These include: 1) drinking and using safe water, 2) washing hands often with soap and water, 3) using latrines or burying feces, 4) cooking food well (especially seafood), keeping it covered, eating it hot, and peeling fruits and vegetables, and 5) bathing and washing diapers and clothes 30 meters (98 feet) away from drinking water sources. • Although rates of cholera are low among travelers from the United States, travelers at highest risk are those who are visiting remote areas where access to safe food and water and access to medical care is likely to be limited. Risk is also higher among persons with underlying medical conditions that predispose them to increased morbidity due to mild or worse diarrhea.	• In U.S. pediatric travelers, particularly those at increased risk of exposure or at increased risk of morbidity if infected with *V. cholerae*, there is an unmet medical need for effective prevention of cholera.
Clinical Benefit	• In one clinical study (PXVX-VC-200-006) the effectiveness of Vaxchora for the pediatric population 2 through 17 years of age was demonstrated following comparison of the immune response to *V. cholerae* in children and adolescents to the immune response in adults following Vaxchora (immunobridging). The primary endpoint was seroconversion, defined as ≥ 4-fold rise in serum vibriocidal antibody titer against classical Inaba *V. cholerae*, at 10 days post-vaccination). This study bridged seroconversion rates in 2 through 17-year-old persons to the corresponding seroconversion rates in a historical comparator consisting of 18 through 45-year-old adults in study PXVX-VC-200-004. The specific immune mechanism responsible for conferring protection against cholera following receipt of Vaxchora has not been determined. However, data from the challenge study (PXVX-VC-200-003) showed that vibriocidal antibody seroconversion (defined as a 4-fold rise in vibriocidal antibody titer against classical Inaba *V. cholerae* at 10 days post-vaccination) is associated with protection against moderate to severe diarrhea.	• Effectiveness of a single dose of Vaxchora in persons 2 through 17 years of age was established by immunogenicity bridging to the population in whom efficacy was demonstrated (18 to 45-year-old adults). • The effectiveness of Vaxchora in persons who live in cholera-affected areas has not been established. • The effectiveness of Vaxchora in persons who have pre-existing immunity due to cholera infection or receipt of a cholera vaccine has not been established.

Risk	• The safety of Vaxchora was evaluated in 468 Vaxchora recipients and 75 placebo recipients 2 through 17 years of age in a single randomized, double-blind study PXVX-VC-200-006. • The most frequent adverse reactions reported in this age group following vaccination with Vaxchora were tiredness, headache, abdominal pain, lack of appetite, and nausea. Most reactions were mild or moderate in severity. • No other safety signals were apparent in the studied population. • No hypersensitivity reactions were noted during the Vaxchora pre-licensure clinical studies; however, hypersensitivity reactions are theoretically possible. • Shedding of the vaccine strain was detected overall in stool samples of 9.6% (95% CI 3.2, 21.0) of vaccine recipients. During the 7 days post-vaccination, the proportion of subjects shedding was highest on day 7 post-vaccination. The duration of shedding is unknown, because 7 days post-vaccination was the latest time point evaluated. • The vaccine strain was not detected in stool samples or rectal swabs collected on day 7 post-vaccination in a study of 24 household contacts of vaccinees.	• The safety profile of Vaxchora in persons 2 through 17 years of age is acceptable.
Risk Management	• See “Clinical Benefit” and “Risk” sections above. • The cumulative number of exposed pediatric subjects in study PXVX-VC-200-006 was sufficient to provide enough power to detect common (≥ 1/100) and uncommon (≥1/1000) adverse reactions; however, the power to detect rare (≥ 1/10,000) and very rare (< 1/10,000) was limited.	• If Vaxchora is approved for persons 2 through 17 years of age, routine measures, such as providing information about pediatric use in the Vaxchora prescribing information and the current pharmacovigilance plan, would be adequate to manage the risks. • The 5-year post-licensure U.S. based pregnancy registry monitoring safety in women exposed to VAXCHORA during pregnancy or within 28 days preceding conception is ongoing.

11.2 Risk-Benefit Summary and Assessment

Data submitted to this BLA supplement establish a likelihood of benefit of vaccination with Vaxchora with respect to the prevention of disease caused by *V. cholerae* serogroup O1 in persons 2 through 17 years of age traveling to cholera-affected areas. The risks of vaccination with Vaxchora in this population have been found to be minimal. Therefore, the overall risk-benefit profile of this product for persons 2 through 17 years of age who are traveling to cholera-affected areas is determined to be favorable.

The greatest benefit is expected among a subpopulation of pediatric U.S. travelers who are at increased risk of exposure or at increased risk of morbidity if infected with serogroup O1 *V. cholerae*. The benefit is unknown in persons living in cholera-affected areas and in persons with pre-existing immunity (due to previous exposure to V. cholerae or receipt of a cholera vaccine) traveling to cholera-affected areas.

11.3 Discussion of Regulatory Options

Please see below section 11.4.

11.4 Recommendations on Regulatory Actions

This reviewer recommends approval of this BLA supplement to extend approved Usage of Vaxchora to children 2 years through 17 years of age and to update the U.S. prescribing information to include the safety and immunogenicity results from study PXVX-VC-200-006.

11.5 Labeling Review and Recommendations

CBER communicated with the applicant to achieve consistency with CBER's current guidance on the intent and format of prescribing information. The final prescribing information was reviewed by the clinical team and found to be acceptable.

11.6 Recommendations on Postmarketing Actions

The Applicant agrees to carefully monitor for any unanticipated risks in surveillance systems and postmarketing adverse reaction reports (i.e., routine pharmacovigilance).

The ongoing pregnancy registry, which is monitoring pregnancy outcomes in women exposed to Vaxchora during pregnancy, is anticipated to be completed on September 1, 2021 and a final report of the outcomes is planned to be submitted to FDA on or before September 2, 2022.