Application Type	BLA Supplement
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Division / Office	DVRPA /OVRR
Committee Chair	Diana Oram
Clinical Reviewer(s)	Tina Mongeau
Project Manager	Tatiana Clarodasilva
Priority Review	Yes
Reviewer Name(s)	Laura Thompson, Ph.D.
Review Completion Date / Stamped Date	
Concurrence	Lihan Yan, Ph.D. Concurring Reviewer, Team Lead, VEB, DB, OBE
Supervisory Concurrence	Tsai-Lien Lin, Ph.D. Chief, Vaccine Evaluation Branch, DB, OBE
Applicant	PaxVax Bermuda Ltd.
Established Name	Live Oral Cholera Vaccine
(Proposed) Trade Name	VAXCHORA
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	V. cholerae strain CVD 103-HgR Vaccine
Dosage Form(s) and Route(s) of Administration	1 x 10^9 CFU/dose oral
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	Expansion of existing indication to include pediatrics (2 to <18 years of age)

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GLOSSARY

AE	adverse event
AESI	Adverse Events of Special Interest
CFU	colony forming unit
CI	confidence interval
CSR	clinical study report
GMFI	geometric mean fold-increase
GMT	geometric mean titer
IEP	immunogenicity evaluable population
IPD	important protocol deviation
LLOQ	lower limit of quantitation
LPS	lipopolysaccharide
mITT	modified Intent-To-Treat
PCO	Placebo-Crossover
SAE	serious adverse event
SMC	safety monitoring committee
SVA	serum vibriocidal antibody

1. EXECUTIVE SUMMARY

Emergent Travel Health is seeking to extend the indication of their VAXCHORA vaccine for the immunization against disease caused by V. cholerae serogroup O1 in persons 18 through 64 years of age traveling to cholera-affected areas, to persons aged 2 to 64 years of age. Due to ethical challenges in performing a cholera challenge study in children, the demonstration of efficacy in children relied on a bridging analysis using classical Inaba vibriocidal antibody seroconversion rate as the non-inferiority comparator between children aged 2 to 17 years and younger adults aged 18 to 45 years. A similar demonstration was previously done to bridge to the older adult population from 46 to 64 years.

PXV-VX-200-006 was a Phase 4 randomized, double-blind, placebo-controlled, single crossover study with two treatment groups across three age cohorts: 12 to <18 years (Cohort 1), 6 to <12 years (Cohort 2), and 2 to <6 years (Cohort 3). Cohorts were enrolled concurrently based on presentation. A total of 550 subjects were randomized 6:1 within age cohorts to VAXCHORA or Placebo. The primary immunogenicity endpoint was the vibriocidal antibody seroconversion rate at Day 11 assessed by serum vibriocidal antibody (SVA) assay. Seroconversion was defined as a 4-fold or greater increase in SVA titer over the SVA at Day 1 (baseline). The primary immunogenicity comparator group for all pediatric age cohorts was healthy adult subjects, ages 18-45 years who received a single dose of VAXCHORA while participating in the PXVX-VC-200-004 lot consistency trial.

All three age cohorts were determined to be non-inferior to the younger adult population, within a non-inferiority margin of -10%, based on the lower bound of a 96.7% confidence interval (CI) on the difference in seroconversion rates. Furthermore, for all three cohorts,

the lower bound of the 98.3% CI on seroconversion rate exceeded 70%. Therefore, both co-primary immunogenicity objectives were met. See Table 6 for detailed results. Subgroup analyses by sex, race and ethnicity did not show notable differences in immunogenicity results across subgroups. Sensitivity analyses performed on the mITT and Randomized Populations generally demonstrated robust immunogenicity of the pediatric population, aged 6 to 18 years. For children between 2 and 6 years, non-inferiority with the young adult population was not strictly shown in the Randomized Population (lower confidence bound of -11.6% < -10%). See Table 17 for details.

VAXCHORA subjects showed somewhat higher rates of abdominal pain, lack of appetite, and tiredness than Placebo subjects. Three VAXCHORA subjects reported severe treatment-related diarrhea; two reported severe fever, one with severe nausea and vomiting. See the clinical reviewer's report for complete details on safety endpoints. There were no deaths during the study.

Overall, the objectives of this study were shown to be met and support unqualified approval for the age range 6 – 17 years. Due to lower compliance in the youngest age group (2 – 6 years), results may not be as reliable; however, the prespecified endpoints were met in this group.

2. CLINICAL AND REGULATORY BACKGROUND

VAXCHORA is a live, attenuated bacterial vaccine suspension for oral administration currently indicated for active immunization against disease caused by Vibrio cholerae serogroup O1 in adults 18 through 64 years of age traveling to cholera-affected areas.

The purpose of this application is to obtain approval for the following indication: "active immunization against disease caused by V. cholerae serogroup O1 in persons 2 through 64 years of age traveling to cholera-affected areas".

2.1 Disease or Health-Related Condition(s) Studied

Cholera is an acute enteric infection caused by the bacterium V. cholerae O1 or O139 and is transmitted by the ingestion of water or food containing the organism. The illness principally occurs in countries with insufficient access to safe water and proper sanitation. Cholera is characterized in its most severe form (cholera gravis) by a sudden onset of acute electrolyte-rich watery diarrhea that can lead to severe dehydration and death. It has an extremely short incubation period (approximately 12 hours to 5 days).

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

VAXCHORA is currently approved for adults 18 to 64.

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

See prior statistical review from OBE/DB of the phase III trial PXV-VX-200-003, the lot to lot consistency trial PXV-VX-200-004, and the trial to extend indication to adults aged

46 to 64 years PXV-VX-200-005. All of these trials were submitted under BLA 125597/0.

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

Please see Clinical Reviewer's memo for this information.

2.6 Other Relevant Background Information

None

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

No data integrity issues with respect to immunogenicity and safety were found.

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

4.1 Chemistry, Manufacturing, and Controls

Please see Sherry Kurtz's (assay reviewer) memo.

4.2 Assay Validation

The key vibriocidal assay methods used to measure both classical Inaba and Ogawa and El Tor Inaba and Ogawa SVA levels in the Phase 3 trials were validated at (b) (4) (acquired by (b) (4)). The vibriocidal antibody method required revalidation as the method was not formally transferred from (b) (4) to (b) (4) . The vibriocidal antibody assessment against classical Inaba serotype of Vibrio cholerae is the only assay used in the Phase 4 trial.

The validation report comprised an assessment of the dilutability/linearity, inter-assay precision, and upper and lower limits of quantitation of the SVA assay for measuring the titers of vibriocidal antibodies against Classical Inaba at the (b) (4) (b) (4) facility. The rationale for the dilutability/linearity and intermediate precision studies was to ensure that the vibriocidal assay performs acceptably at the (b) (4) location.

The applicant has reported that all proposed validation criteria were met. Please see my statistical review for more details.

4.3 Nonclinical Pharmacology/Toxicology

N/A

4.4 Clinical Pharmacology

N/A

4.5 Clinical

Please see Tina Mongeau's (clinical reviewer) memo.

4.6 Pharmacovigilance

N/A

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

5.1 Review Strategy

I reviewed statistical aspects of efficacy, immunogenicity and safety analyses contained within the documents listed in Section 5.2, below.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- Clinical Study Report for PXV-VX-200-006 (section 5.3.5.1)
- Study Protocol v3.0: PXVX-VC-200-006 (section 5.3.5.1)
- Clinical Overview (section 2.5)

5.3 Table of Studies/Clinical Trials

Table 1 lists the clinical studies related to the proposed indication. Only the PXV-VX-200-006 study was reviewed in this memo. See prior statistical review of PXV-VX-200-003, PXV-VX-200-004, and PXV-VX-200-005 (BLA 125597/0).

Table 1: Listing of Clinical Studies

Type of Trial	Trial No[a].	Objectives of the Trial	Trial Design and Type of Control	Test Product(s); Route of Administration	Number of Subjects Randomized (Number of Subjects who Received Study Vaccine[b])	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase 1	PXVX-VC-200-002	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	4.43×10^8 CFU/dose; oral	66 55 vaccine, 11 placebo (*55 vaccine, 11 placebo*)	Healthy Subjects	Single dose

Type of Trial	Trial No[a].	Objectives of the Trial	Trial Design and Type of Control	Test Product(s); Route of Administration	Number of Subjects Randomized (Number of Subjects who Received Study Vaccine[b])	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Challenge Phase 3	PXVX-VC-200-003	Demonstrate protection from live cholera challenge	Randomized, double-blind, placebo-controlled	5×10^8 CFU/dose; oral	197 95 vaccine, 102 placebo (*95 vaccine, 102 placebo*)	Healthy Subjects	Single dose
Lot Consistency Phase 3	PXVX-VC-200-004	Demonstrate clinical lot consistency	Randomized, double-blind, placebo-controlled	1×10^9 CFU/dose; oral	3146 2795 vaccine, 351 placebo (*2789 vaccine, 350 placebo*)	Healthy Subjects	Single dose
Older Adults Phase 3	PXVX-VC-200-005	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	1×10^9 CFU/dose; oral	398 299 vaccine, 99 placebo (*296 vaccine, 99 placebo*)	Healthy Subjects	Single dose
Pediatric Phase 4	PXVX-VC-200-006	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	1×10^9 CFU/dose; oral	550 471 vaccine, 79 placebo (*468 vaccine, 75 placebo*)	Healthy Subjects	Single dose

[a] There is no trial with the suffix 001; this was assigned to a protocol which was not executed.

[b] Italics show number of subjects who actually received vaccine or placebo. A total of 3703 subjects received VAXCHORA vaccine.

Source: Table 1 of "*Tabular Listing of All Clinical Studies*" in Module 5.2

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)
N/A

5.4.2 External Consults/Collaborations (if applicable)
N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 PXVX-VC- 200-006

Title: Phase 4 Study to Assess the Safety and Immunogenicity of VAXCHORA (Cholera Vaccine, Live, Oral) in Children 2 to <18 Years of Age

6.1.1 Objectives (Primary, Secondary, etc)

Primary immunogenicity objectives:

1. Demonstrate that the seroconversion rate at Day 11 in pediatric subjects is non-inferior to the seroconversion rate at Day 11 in previously studied adult subjects between the ages of 18 and 45 years, with non-inferiority margin 10%. Seroconversion is defined as a 4-fold or greater rise over baseline Day 1 SVA titer.

   The primary immunogenicity comparator group for all pediatric age cohorts was healthy adult subjects, ages 18-45 years who received a single dose of VAXCHORA while participating in the PXVX-VC-200-004 lot consistency trial.

2. Demonstrate that the seroconversion rate in pediatric subjects is greater than or equal to 70% with 98.3% confidence.

Secondary immunogenicity objective

Evaluate the immunogenicity of VAXCHORA in three pediatric age cohorts using the following endpoints:

- Seroconversion of SVA against the classical Inaba biotype of V. cholerae at Days 29, 91, and 181 (Days 91 and 181 in oldest cohort only) following one dose of VAXCHORA.

- Seroconversion of SVA against the classical Inaba biotype of V. cholerae at Days 365, 547 and 730 for all subjects in the oldest cohort who choose to participate in the long-term sub-study.

Exploratory immunogenicity objective

- Measure memory B cell response to VAXCHORA vaccination at each time point in Cohort 1 using Anti–O1 lipopolysaccharide (LPS) memory B cell concentration at Day 1, 91, 181 for the subjects in the active treatment group and the Placebo-Crossover (PCO) group and Days 365, 547, 730 for the subjects in the active treatment group who participate in the long term sub-study.

The submission did not include the analysis of the exploratory immunogenicity objective, which will be included in a future addendum.

Primary safety objective

Evaluate the safety and tolerability of VAXCHORA in all pediatric age cohorts.

6.1.2 Design Overview

The study was a Phase 4 randomized, double-blind, placebo-controlled, single crossover study with two treatment groups across three age cohorts: 12 to <18 years (Cohort 1), 6 to <12 years (Cohort 2), and 2 to <6 years (Cohort 3). Cohorts were enrolled concurrently based on presentation. A total of 550 subjects were randomized 6:1 within cohorts to VAXCHORA or Placebo treatment groups, across 9 out of 10 investigational sites in the United States. A single-dose vaccination was administered orally in each group on Day 1.

Neither subjects, nor clinical site personnel, including the principal investigator (except for the pharmacist/designee and dose administrator) nor the applicant knew subjects' individual treatment assignments until each subject completed their Day 181 visit. Unblinding at the Day 181 visit, on an individual subject level, was to facilitate the cross-over of Placebo subjects, should they choose to receive VAXCHORA. To maintain blinding, subjects were asked not to discuss the taste of the administered treatment with other study participants.

The study consisted of a screening period of 30 days, an observation period from Day 1 to Day 29, and a follow-up period through Day 181. Following this period, subjects who opted for the PCO group were monitored through Day 365. Additionally, subjects in Cohort 1 who opted for the long-term sub-study (see below), were monitored out to Day 730.

Long-term Sub-study

A subset of vaccinated subjects from Cohort 1 who agreed to participate longer term were followed out to 2 years to evaluate duration of protection.

Interim Monitoring

The study included a safety monitoring committee (SMC) that reviewed data on an ongoing basis to assess stopping rules and overall subject safety. The SMC convened when a stopping rule was met, and blinded safety reports were reviewed on a 6-month basis. At no time was the blind broken for a safety event.

Enrollment and vaccine dosing were to be stopped for any of the following:

- Any death or serious adverse event (SAE) experienced by a subject, regardless of causality.
- One or more subjects with a Grade 3 (severe) adverse event (AE) assessed as possibly or probably related to the study vaccine.

Throughout the duration of the study, there were 5 temporary study halts, none of which lasted more than 22 days. They were due to severe fevers and diarrhea. Four out of the five halts met study stopping rules.

There were no interim looks for immunogenicity. However, there was an interim analysis following completion of Cohorts 1 and 2 in order to facilitate a marketing application in Europe. This analysis was added to the third and final version of the protocol in November 2017.

6.1.3 Population

The study population included males and non-pregnant females between the ages of 2 and <18 years who were in good health, had no prior history of cholera infection or cholera vaccination, and had not traveled to a cholera-endemic area in the past 5 years. Concomitant or planned use of other vaccines, antibiotics, or chloroquine within 14 days prior to enrollment through 11 days after vaccination were not allowed.

6.1.4 Study Treatments or Agents Mandated by the Protocol

VAXCHORA is a live, attenuated bacterial vaccine suspension for oral administration. It was provided as a single dose of buffer and active component reconstituted in purified bottled water. (b) (4) After reconstitution, VAXCHORA contained 4 x 10^8 to 2 x 10^9 colony forming units (CFU) of live attenuated V. cholerae CVD 103-HgR. Lot Numbers of VAXCHORA were: P700.610.00-7000005 (shipped July 2017, expired June 2018) and P700.610.02-7000008 (shipped February 2018, expired December 2018).

Lot P700.610-7000005 was used for dosing in the VAXCHORA group from July 2017 to November 2017. Lot P700.610-7000008 was used afterwards for the duration of the study. Over that time period, the potency range was approximately 8.9 x 10^8 CFUs to 7.7 x 10^8 CFUs. By comparison, the VAXCHORA product used in the 004 adult study maintained a potency range of approximately 1.4 x 10^9 CFUs to 9.0 x 10^8 CFUs. According to the clinical reviewer, the potency ranges for the pediatric study and the 004 adult study were not clinically different.

The VAXCHORA vaccine was the same in content, dose, and route of administration as the VAXCHORA vaccine used in the PXVX-VC-200-004 lot consistency study in adults ages 18-45. For Cohort 3, only half of the buffer (50 mL) was used for vaccine dissolution.

The placebo consisted of normal (0.9%) saline solution and was not matched to VAXCHORA either visually or by taste. Placebo was provided as a single dose containing normal (0.9%) saline solution. Dosing varied by cohort: 100 mL for Cohorts 1 and 2 and 50 mL for Cohort 3.

VAXCHORA and placebo were administered as a single oral dose on Day 1 followed by a 30-minute observation period.

Table 2 below shows the planned cohort and study treatment assignments.

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

Cohort	Age (years)	Treatment Group	N	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	210	VAXCHORA	None
3	2 to <6	Placebo-Crossover	35	Placebo	VAXCHORA
		Total	**595**		

Source: Reproduced from Table 2 in "*PXVX-VC-200-006 Final CSR v3.0*"

6.1.6 Sites and Centers

Ten investigational sites in the United States were used. Only nine sites actually enrolled subjects.

6.1.7 Surveillance/Monitoring

Please refer to this section in the clinical reviewer's report.

6.1.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoint

The primary immunogenicity endpoint was the vibriocidal antibody seroconversion rate at Day 11 assessed by SVA assay. Seroconversion was defined as a 4-fold or greater increase in SVA titer over the SVA at Day 1 (baseline).

Immunological assessments were performed at Screening, Day 1 (baseline) and Days 11 and 29. Subjects in Cohort 1 had further measurements of SVA taken at Days 91 and 181. Cohort 1 subjects in the long-term sub-study had SVA measurements taken at Days 365, 547, and 730.

Secondary Immunogenicity Endpoint

Secondary immunogenicity endpoints were seroconversion rates of SVA against the classical Inaba biotype of V. cholerae at Days 29, 91, and 181 (Days 91 and 181 for Cohort 1 only).

Pointwise and cumulative seroconversion rates and corresponding confidence intervals were calculated for Days 29, 91, and 181. The geometric mean titers (GMTs) and 95% confidence intervals (CIs) were computed for Day 1, Day 11, Day 29, Day 91, and Day 181, Day 365, Day 547 and Day 730 along with geometric fold increases for Day 11, Day 29, Day 91, and Day 181, Day 365, Day 547 and Day 730.

Comparisons of VAXCHORA to Placebo were also performed.

Primary Safety Endpoints

- Number, frequency, and severity of solicited AEs through Day 8: abdominal pain, headache, lack of appetite, tiredness, diarrhea, nausea, vomiting and fever, by age cohort and overall. This also includes the PCO subjects between Day 181 and 188.

- Number, frequency, and severity of unsolicited AEs through Day 29, by age cohort and overall. This also includes the PCO subjects between Days 181 to 209.

- Number and frequency of SAEs through Day 181, by age cohort and overall. This includes those SAEs recorded through Day 365 (for PCO subjects) or Day 730 (for sub-study subjects).

Exploratory Endpoints

Acceptability endpoint: Acceptability was measured by the percent of subjects in each cohort who completed dosing according to protocol. This was defined as the entire volume of dose being consumed within 15 mins after reconstitution.

Palatability endpoints: Palatability of the vaccine was assessed by the subject using a 5-point Hedonic scale in Cohorts 1 and 2, and by the caregiver using a 5-point Hedonic scale in Cohort 3.

6.1.9 Statistical Considerations & Statistical Analysis Plan

In order to bridge efficacy in the younger adults aged 18-45 years who participated in the challenge trial (PXVX VC-200-003) to other age groups and populations, analyses were conducted on the data from the challenge study to assess potential immune correlates of protection. SVA GMT, fold rise, seroconversion and seroprotection levels were evaluated using the results from the 10-Day and 3-Month challenge cohorts (Report PXVX-STAT-VIB-003 submitted in section 5.3.5.1 of BLA 125597/000).

There was a statistically significant association between fold-rise in SVA titer from Day 1 to Day 11 and total post-challenge diarrheal volume (Spearman's $r=-0.72$; $p<0.001$; PXVX-STAT-HOCISE; Post Hoc Analysis 3, submitted with BLA 125597/000). The applicant explains that fold-rise neutralizes the effect of non-specific elevation in

vibriocidal titer: fold-rises in titer at Day 11 were observed frequently in vaccine recipients but rarely in placebo recipients. Furthermore, seroconversion, defined as a ≥4-fold rise in vibriocidal titer from pre-vaccination to post-vaccination levels, identified "vaccine take" such that only 2 of 62 (3%) seroconverting vaccine recipients developed moderate/severe cholera after challenge. Based on this relationship between seroconversion and protection, along with the fact that approximately 90% of vaccine recipients seroconverted, vibriocidal seroconversion (defined as a ≥4-fold rise over baseline classical Inaba SVA titer) at Day 11 was proposed as the immunogenicity endpoint to be used in an analysis to bridge between age populations. FDA ultimately concurred with this proposal.

Sequence of Analyses

The seroconversion rate between Day 1 and Day 11 for vaccinees in each of the three age cohorts was compared to the seroconversion rate for vaccinees 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) using Newcombe's hybrid method. The lower bound of the two-sided 96.7% CI on the difference in seroconversion rates between children and adults must be greater than -10% to conclude non-inferiority in seroconversion rate for children aged 2 to <18 to adults aged 18 to 45.

For each of the three age cohorts, the proportion of vaccinated subjects who experienced a 4-fold or greater increase in serum vibriocidal titer between Day 1 and Day 11 was calculated, along with a 98.3% CI. The lower bound of the two-sided 98.3% CI (Wilson method) on the proportion of vaccinees who seroconverted between Day 1 and Day 11 must equal or exceed 70% to meet immunogenicity success.

Multiplicity Adjustments

The primary objective was assessed using an alpha-spending strategy to account for multiplicity. In order to ensure that the total type I error rate for the study was capped at alpha = 0.05, 2/3 of the alpha was allotted to the primary objective of establishing non-inferiority relative to adults, and 1/3 of the alpha was allotted to the objective of demonstrating that the seroconversion rate equaled or exceeded 70%. The two objectives were evaluated independently, and within each objective, testing in the different age cohorts proceeded sequentially beginning with the data for the 12 to <18 age cohort, as follows:

Non-inferiority: Non-inferiority between vaccinees in the 12-18 age cohort and adults in the 18 - 45 age cohort was tested first. A test of non-inferiority in the 6 to <12 age cohort was to be performed only if the lower bound of the two-sided 96.7% CI on the difference between the seroconversion rates for children in the 12 to <18 age cohort and adults equaled or exceeded the pre-specified acceptance criterion. Non-inferiority in the 2 to <6 age cohort was to be tested only if the pre-specified acceptance criteria were met for the

12 to <18 age and 6 to <12 age cohorts. This strategy maintained the overall type I error rate for the primary objective of non-inferiority at alpha = 0.033.

Seroconversion Rate: A test of the seroconversion rate among vaccinees in the 12 to <18 age cohort was conducted first. A test of the seroconversion rate in the 6 to <12 age cohort was to be performed only if the lower bound of the two-sided 98.3% CI on the seroconversion rate in the 12 to <18 age cohort met the pre-specified acceptance criterion. A test of the seroconversion rate in 2 to <6 age cohort was to be performed only if the acceptance criteria were met for both the 12 to <18 age and 6 to <12 age cohorts. This strategy maintained the overall type I error for the primary objective concerning the magnitude of the seroconversion rate at alpha = 0.017.

Reviewer comment
If both endpoints had to be met, it is not clear why they had to split the significance level. A significance level is split between two co-primary endpoints when only one of the endpoints has to be met for study success.

Sample Size Determination

The true seroconversion rate among 12 to <18-year olds was assumed to be 92.4%. A sample size of 143 evaluable vaccinees for this age cohort gave 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 PXVX-VC-200-004. The overall power for demonstrating the non-inferiority of all three age cohorts was then $(93.3\%)^3$ = 81%, by extrapolating the assumed rate of 92.4% to the remaining cohorts.

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 was 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%.

Given a total of 510 subjects were planned 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.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Randomized Population
The Randomized Population included all subjects who were randomized into the study. Analyses based on the Randomized Population were performed according to the treatment group to which a subject was randomized.

Modified Intent-to-Treat Population
The modified Intent-To-Treat (mITT) Population included all subjects in the randomized population who had both Day 1 and Day 11 SVA assay results, and who were only enrolled once. Analyses based on the mITT Population were performed according to the treatment group to which a subject was randomized.

Immunogenicity Evaluable Population
The Immunogenicity Evaluable Population (IEP) included all subjects in the mITT Population who:

- Received the minimum dose of vaccine correctly (80 mL for Cohorts 1 and 2 or 40 mL for Cohort 3)
- Had serum vibriocidal assay (SVA) results at the Day 1 and the Day 11 visit within required window
- Had no additional exclusionary protocol deviation (PD). An exclusionary deviation is defined as a PD that could potentially have a significant impact on the immunogenicity result of the subject. These were identified prior to unblinding. They include the following:

    1. Any antibiotic or non-study vaccine given within -14/+11 days of vaccination.
    2. Wrong treatment given/no treatment given
    3. Enrollment more than once into the study
    4. Prohibited medications

Analyses for the primary immunogenicity objectives are based on the IEP, as well as the mITT Population. Analyses for the secondary immunogenicity objective were carried out on the IEP.

Bridging Population
The Bridging Population comprises all subjects in the PXVX-VC-200-006 IEP along with all subjects vaccinated with PXVX0200 in the IEP from the adult VAXCHORA lot consistency trial PXVX-VC-200-004.

Safety Population
The Safety Population included subjects who received any amount of study vaccine or placebo. Analyses based on the Safety Population were performed according to the treatment group of the study vaccine received.

The numbers of subjects included in the Randomized Population, the mITT Population, and the IEP, by treatment group and cohort is shown in Table 3, below.

Table 3: Analysis Populations by Age Cohort and Treatment Group

Analysis Populations n (%)	Cohort 1 (ages 12 – < 18)	Cohort 1 (ages 12 –< 18)	Cohort 2 (ages 6 – < 12)	Cohort 2 (ages 6 – < 12)	Cohort 3 (ages 2 - <6)	Cohort 3 (ages 2 - <6)	Overall	Overall
	VAXCHORA	**Placebo**	**VAXCHORA**	**Placebo**	**VAXCHORA**	**Placebo**	**VAXCHORA**	**Placebo**
Randomized Population	163	26	158	27	150	26	471	79
Safety Population	165 (101.2%)	24 (92.3%)	157 (99.4%)	25 (92.6%)	146 (97.3%)	26 (100%)	468 (99.4%)	75 (94.9%)
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%)
Immunogenicity Evaluable Population	157 (96.3%)	23 (88.5%)	139 (88.0%)	24 (88.9%)	103 (68.7%)	20 (76.9%)	399 (84.7%)	67 (84.8%)

Source: Adapted from Table 9 in *PXVX-VC-200-006 Final CSR v3.0*

- There were nine subjects who were randomized and had duplicate enrollment in error (two from Cohort 1, four from Cohort 2, and three from Cohort 3). These subjects were excluded from all immunogenicity populations.

- Seven subjects were randomized but not vaccinated. Three of these subjects were in Cohort 2 and 4 were in Cohort 3. All of them have been excluded from all analysis populations, except for the Randomized Population.

- In Cohort 1, three subjects were excluded from the mITT Population for discontinuing the study prior to Day 11 or duplicate enrollment. Nine subjects were excluded from the IEP due to the following: prohibited medication or vaccine (n = 3), received incorrect randomized treatment (n = 2), duplicate enrollment (n = 2), consumed less than 80% of dose (n = 1), corticosteroid use (n = 1), or discontinuation from the study prior to Day 11 (n = 1).

- In Cohort 2, nine subjects were excluded from the mITT Population for the following reasons: duplicate enrollment (n = 4), being randomized but not treated (n = 3), discontinuing the study prior to Day 11 (n = 1), or not having a Day 11 SVA sample (n = 1). Twenty-two subjects were excluded from the IEP due to the following: consumed less than 80% of dose (n = 11), duplicate enrollment (n = 4), randomized but not treated (n = 3), discontinued study prior to Day 11 (n = 1), prohibited medication or vaccine (n = 1), received incorrect randomized treatment (n = 1), or no Day 11 SVA sample (n = 1).

- In Cohort 3, 23 subjects were excluded from the mITT Population for the following reasons: discontinuing the study prior to Day 11 (n = 10), not having a

Day 11 SVA sample (n = 5), being randomized but not treated (n = 4), duplicate enrollment (n = 3), or not having a Day 1 SVA sample (n = 3). Fifty-three subjects were excluded from the IEP due to the following: consumed less than 80% of dose (n = 30), discontinued study prior to Day 11 (n = 8), no Day 11 SVA sample (n = 5), randomized but not treated (n = 4), duplicate enrollment (n = 3), not having a Day 1 SVA sample (n = 3), prohibited medication or vaccine (n = 3), or due to a dose preparation documentation error (n = 1).

Reviewer comment

Table 10 on p. 57 of the CSR tabulates reasons for exclusions by cohort and treatment group. Notable differences between treatment groups occur in exclusions from the mITT population and from the IEP in Cohort 3. For example, 14% (n=21) of VAXCHORA subjects were excluded from mITT population, whereas only 7.7% (n=2) of Placebo subjects were excluded. Similarly, 31.3% (n=47) of VAXCHORA subjects were excluded from the IEP, whereas only 23.1% (n=6) of Placebo subjects were excluded. However, similar differences were not found in cohorts 1 and 2. In fact, in Cohort 1, 11.5% (n=3) of Placebo subjects were excluded from the IEP, whereas only 3.7% (n=6) of VAXCHORA subjects were excluded. It is possible that due to the apparent unpleasant taste of VAXCHORA to very young children in Cohort 3, there were more exclusions. In section 6.1.10.1.3 on Subject Disposition, I mention that Cohort 3 experienced relatively more protocol deviations than other cohorts.

6.1.10.1.1 Demographics

Subject demographic data (i.e., age, sex, weight, height, body mass index, race, and ethnicity) were summarized by cohort, treatment group and overall. Of the 550 randomized subjects, 52.0% of subjects were male and 48.0% were female. 59.8% of the enrolled subjects were White, 31.1% were Black or African American, 0.9% were Asian, 0.5% were American Indian or Alaska Native, and 7.6% identified as multiple races. The median age was 9.0 (range 2 to 17) years, with each age group represented (see Table 4).

Table 4: Subject Demographics by Age Cohort and Treatment Group - Randomized Population

Baseline Characteristics	**Cohort 1 (ages 12 - <18)**	**Cohort 1 (ages 12 - <18)**	**Cohort 2 (ages 6 - <12)**	**Cohort 2 (ages 6 - <12)**	**Cohort 3 (ages 2 - <6)**	**Cohort 3 (ages 2 - <6)**
	VAXCHORA (N=163)	**Placebo (N=26)**	**VAXCHORA (N=158)**	**Placebo (N=27)**	**VAXCHORA (N=150)**	**Placebo (N=26)**
Age 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)
Age 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)
Male	88 (54.0%)	14 (53.8%)	77 (48.7%)	17 (63.0%)	81 (54.0%)	9 (34.6%)
Female	75 (46.0%)	12 (46.2%)	81 (51.3%)	10 (37.0%)	69 (46.0%)	17 (65.4%)
American Indian or Alaskan Native	0	1 (3.8%)	0	1 (3.7%)	1 (0.7%)	0
Asian	1 (0.6%)	0	4 (2 5%)	0	0	0

Baseline Characteristics	**Cohort 1 (ages 12 - <18)**	**Cohort 1 (ages 12 - <18)**	**Cohort 2 (ages 6 - <12)**	**Cohort 2 (ages 6 - <12)**	**Cohort 3 (ages 2 - <6)**	**Cohort 3 (ages 2 - <6)**
	VAXCHORA (N=163)	**Placebo (N=26)**	**VAXCHORA (N=158)**	**Placebo (N=27)**	**VAXCHORA (N=150)**	**Placebo (N=26)**
Native Hawaiian or Other Pacific	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%)
White	121 (74.2%)	21 (80.8%)	86 (54.4%)	18 (66.7%)	71 (47.3%)	12 (46.2%)
Multiple races	13 (8.0%)	0	15 (9 5%)	3 (11.1%)	11 (7.3%)	0
Other race	0	0	0	0	0	0
Ethnicity Hispanic or Latino	18 (11.0%)	7 (26.9%)	11 (7.0%)	2 (7.4%)	8 (5.3%)	1 (3.8%)
Ethnicity Not Hispanic or Latino	145 (89.0%)	19 (73.1%)	147 (93.0%)	25 (92.6%)	142 (94.7%)	25 (96.2%)
	Overall (ages 2 - <18) VAXCHORA (N=471)	**Overall (ages 2 - <18) Placebo (N=79)**	**Total (N=550)**			
Mean (SD)	9.0 (4.7)	8.8 (4.6)	9.0 (4.7)			
Median (Min-Max)	9.0 (2-17)	9.0 (2-17)	9.0 (2-17)			
Male	246 (52.2%)	40 (50.6%)	286 (52.0%)			
Female	225 (47.8%)	39 (49.4%)	264 (48.0%)			
American Indian or Alaskan Native	1 (0.2%)	2 (2.5%)	3 (0.5%)			
Asian	5 (1.1%)	0	5 (0.9%)			
Native Hawaiian or Other Pacific Islander	0	0	0			
Black or African American	148 (31.4%)	23 (29.1%)	171 (31.1%)			
White	278 (59.0%)	51 (64.6%)	329 (59.8%)			
Multiple	39 (8.3%)	3 (3.8%)	42 (7.6%)			
Other	0	0	0			

Source: *Adapted from Table 11 in PXVX-VC-200-006 Final CSR v3.0*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Please see this section in the clinical reviewer's memo.

6.1.10.1.3 Subject Disposition

Of the 574 potential subjects screened, 550 were randomized. In Cohort 1, 189 subjects were randomized: 26 subjects in the Placebo group and 163 in the VAXCHORA group. 181 (95.8%) subjects completed the main study through the Day 181 visit (157

VAXCHORA, 24 placebo). The reasons for withdrawal prior to Day 181 were: withdrawal of consent (n = 5) and lost to follow-up (n = 3). Of the 157 subjects who completed the main study, 73 subjects opted for the long-term sub-study. Of these 73 subjects, 71 (97.3%) completed Day 365, 68 (93.2%) completed Day 547 and 62 (84.9%) completed through the Day 730 visit. The reasons for withdrawal prior to Day 730 were: lost to follow-up (n=9), other (n=1), and withdrawal of consent (n=1). Of the 24 placebo subjects who completed the main study, 13 subjects opted for the PCO. All of these subjects completed the PCO study to Day 365.

In Cohort 2, 185 subjects were randomized: 27 subjects in the Placebo group and 158 in the VAXCHORA group. 170 (91.9%) subjects completed the main study through the Day 181 visit (146 VAXCHORA, 24 placebo). The reasons for withdrawal prior to Day 181 were: lost to follow-up (n = 7), withdrawal of consent (n = 5), non-compliance with protocol (n = 2), and other (n = 1). Of the 24 placebo subjects who completed the main study, 11 opted for the PCO study. All of these subjects completed the PCO study through Day 365.

In Cohort 3, 176 subjects were randomized: 26 subjects in the Placebo group and 150 in the VAXCHORA group. 155 (88.1%) subjects completed the main study through the Day 181 visit (130 VAXCHORA, 25 placebo). The reasons for withdrawal prior to Day 181 were: lost to follow-up (n = 14), withdrawal of consent (n = 4), and non-compliance with protocol (n = 3). Of the 25 placebo subjects who completed the main study, 7 opted for the PCO study. 5 (71.4%) of these subjects completed the PCO study through Day 365 (2 subjects were lost to follow-up).

Protocol Deviations

The percentage of subjects with any important protocol deviation (IPD) in the study was 31.6% (174/550). The most common IPD across treatment groups was a visit out of window, followed by incomplete or missed dose, and protocol-required assessment not done. 84 subjects (15.3%) had IPDs resulting in exclusion from the IEP. The most common IPD resulting in exclusion was consuming less than 80% (80 mL for Cohort 1 and 2, and 40 mL for Cohort 3) of the dose (42/550 subjects, 7.6%). This percentage was weighted toward Cohort 3 with 30/176 (17.0%), followed by Cohort 2 with 11/185 (5.9%), and Cohort 1 with 1/189 (0.5%). See Table 5, below.

Table 5: Important Protocol Deviations by Treatment Group and Cohort

Deviation	**Cohort 1 VAXCHORA (N=163)**	**Placebo (N=26)**	**Total (N=189)**	**Cohort 2 VAXCHORA (N=158)**	**Placebo (N=27)**	**Total (N=185)**
No. subjects with at least one IPD	32 (19.6%)	6 (23.1%)	38 (20.1%)	49 (31.0%)	9 (33 3%)	58 (31.4%)
Visit out of window	22 (13.5%)	3 (11.5%)	25 (13.2%)	22 (13.9%)	5 (18 5%)	27 (14.6%)
Protocol required assessment not done	3 (1.8%)	0	3 (1.6%)	3 (1.9%)	1 (3.7%)	4 (2.2%)

Deviation	**Cohort 1 VAXCHORA (N=163)**	**Placebo (N=26)**	**Total (N=189)**	**Cohort 2 VAXCHORA (N=158)**	**Placebo (N=27)**	**Total (N=185)**
Received excluded concomitant treatment	2 (1 2%)	1 (3.8%)	3 (1.6%)	1 (0.6%)	0	1 (0.5%)
Dispensing error	0	2 (7.7%)	2 (1.1%)	0	1 (3.7%)	1 (0.5%)
Other	5 (3.1%)	0	5 (2.6%)	6 (3.8%)	0	6 (3.2%)
Incomplete/Missed dose	1 (0.6%)	0	1 (0.5%)	15 (9.5%)	2 (7.4%)	17 (9.2%)
Informed consent deviation	1 (0.6%)	0	1 (0.5%)	0	0	0
Required assessment out of window	0	0	0	4 (2.5%)	0	4 (2.2%)
Inclusion/Exclusion criteria not met	0	0	0	1 (0.6%)	0	1 (0.5%)
No. subjects with at least one IPD	66 (44.0%)	12 (46.2%)	78 (44.3%)	147 (31.2%)	27 (34.2%)	174 (31.6%)
Visit out of window	27 (18.0%)	2 (7.7%)	29 (16.5%)	71 (15.1%)	10 (12.7%)	81 (14.7%)
Protocol required assessment not done	13 (8.7%)	1 (3.8%)	14 (8.0%)	19 (4.0%)	2 (2 5%)	21 (3.8%)
Received excluded concomitant treatment	3 (2.0%)	0	3 (1.7%)	6 (1.3%)	1 (1 3%)	7 (1.3%)
Dispensing error	0	0	0	0	3 (3.8%)	3 (0.5%)
Other	6 (4.0%)	1 (3.8%)	7 (4.0%)	17 (3.6%)	1 (1 3%)	18 (3.3%)
Incomplete/Missed dose	34 (22.7%)	8 (30.8%)	42 (23.9%)	50 (10.6%)	10 (12.7%)	60 (10.9%)
Informed consent deviation	1 (0.7%)	0	1 (0.6%)	2 (0.4%)	0	2 (0.4%)
Required assessment out of window	2 (1.3%)	0	2 (1.1%)	6 (1.3%)	0	6 (1.1%)
Inclusion/Exclusion criteria not met	1 (0.7%)	0	1 (0.6%)	2 (0.4%)	0	2 (0.4%)

Source*:* Adapted from *Table 8 in PXVX-VC-200-006 Final CSR v3.0*

In Cohort 3, 44.3% of subjects had at least one IPD (compared to 20.1% in Cohort 1 and 31.4% in Cohort 2). The most common IPDs were: incomplete or missed dose (n = 42), visit out of window (n = 29), and protocol required assessment not done (n = 14).

Treatment compliance

In Cohort 1, 99.4% of VAXCHORA recipients and 100% of Placebo received the complete dose for the main study. In Cohort 2, 91.0% of VAXCHORA recipients and 96.2% of Placebo recipients received the complete dose. In Cohort 3, 79.5% of VAXCHORA recipients and 73.1% of Placebo recipients received the complete dose.

Issues with palatability possibly contributed to subjects who did not consume a complete dose of their respective randomized treatment, especially in Cohort 2 subjects. In Cohorts 1, 2, and 3, respectively, 6.9%, 22.0% and 20.3% of study subjects reported treatment palatability as "Super Bad", 30.2%, 19.8% and 16.3% of study subjects reported treatment palatability as "Bad", 39.2%, 25.8% and 12.8% of study subjects reported treatment palatability as "Maybe Good or Maybe Bad", 18.5%, 15.4% and 21.5% of study subjects reported treatment palatability as "Good", and only 5.3%, 17.0% and 29.1% of study subjects reported treatment palatability as "Super Good". The palatability assessments did not differ much between the vaccine groups within each cohort. (b) (4)

Reviewer comment

Cohort 3, the youngest cohort, had relatively more protocol deviations and non-compliance than the older cohorts, and this resulted in a much higher proportion of missing data. The protocol deviations could be due to the younger age of Cohort 3, compared to Cohorts 1 and 2. However, to have greater comfort that missing data are not due to worsening results, FDA requested that the applicant perform some sensitivity analyses to assess whether missing data could have reasonably impacted conclusions for this cohort. In particular, we requested that they provide the primary analyses using the mITT and Randomized populations, which included subjects who had protocol deviations. In sub-section 6.1.11.1, I present the results from these populations.

Thirty subjects randomized into Cohort 3 consumed less than 80% of the dose (26 VAXCHORA, 4 placebo). FDA requested that the applicant provide an analysis that relates dose amount to seroconversion in the mITT or Randomized population to see whether it affects the non-inferiority comparisons (especially in Cohort 3). Section 6.1.11.5 provides such a sensitivity analysis.

6.1.11 Efficacy Analyses

The primary endpoint was analyzed based on the Bridging Population (IEP for the 006 study) and repeated on the mITT Population for robustness purposes. The secondary endpoints were based on only the IEP. SVA assay results that were reported as less than 20 (the lower limit of quantitation - LLOQ) were imputed as a titer of 20 when calculating seroconversion rates and geometric means.

Reviewer comment*: The applicant initially proposed to impute ½ LLOQ for values that were less than the LLOQ. However, during the briefing meeting for the original BLA, CBER recommended imputing the LLOQ.*

The Day 11 seroconversion rate for vaccinees in each of the cohorts was compared to the seroconversion rate for vaccinees between the ages of 18 and 45 who participated in the lot consistency study, PXVX-VC-200-004 (the "004 Bridging Population"), by

calculating the difference between the two rates and computing a 96.7% CI for this difference based on the Newcombe hybrid score method.

For each age cohort, a two-sided 98.3% CI of the Day 11 seroconversion rate was computed using the Wilson method. Fisher's exact test was used to test equality of seroconversion across treatment groups.

For each co-primary objective, testing was conducted hierarchically by cohort, as described in section 6.18.

6.1.11.1 Analyses of Primary Endpoint(s)

The Day 11 seroconversion rates of subjects in the IEP dataset who received VAXCHORA were compared to those of the PXVX-VC-200-004 adult Bridging Population, as shown in Table 6 below.

Table 6: Comparison of Seroconversion Rates at Day 11 Visit by Age Group Compared to the Adult Bridging Population

	Study 004 VAXCHORA (N=2688)	**006 Cohort 1 (ages 12 - <18) VAXCHORA (N=157)**	**006 Cohort 2 (ages 6 - <12) VAXCHORA (N=139)**	**006 Cohort 3 (ages 2 - <6) VAXCHORA (N=103)**	**Overall 006 (ages 2 -<18) VAXCHORA (N=399)**
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 (006 Cohort minus 004 Adults) [96.7% CI]	-	5.8% [2.4%, 7.1%]	4.3% [-0.3%, 6.2%]	4.5% [-1.1%, 6.4%]	5.0% [2.8%, 6.4%]

* $p < 0.05$ from Fisher's Exact test of equality of seroconversion between the 004 Adults and 006 Cohort
** $p < 0.01$ from Fisher's Exact test of equality of seroconversion between the 004 Adults and 006 Cohort
*** $p < 0.0001$ from Fisher's Exact test of equality of seroconversion between the 004 Adults and 006 Cohort

Source*: Adapted from Table 12 in PXVX-VC-200-006 Final CSR v3.0*

At Day 11, Cohort 1 was non-inferior to the adult Bridging Population with the lower limit of the difference between the groups for the 96.7% CI greater than -10% (difference = +5.8%; 96.7% CI: [2.4%, 7.1%]). This was also a statistically significant increase in the number of subjects who seroconverted compared to the adult population. For the second co-primary objective, Cohort 1 had 99.4% (98.3% CI: [95.4%, 99.9%]) of subjects seroconverting by the Day 11 visit, with lower limit of the 98.3% CI exceeding 70%. This rate was also significantly higher than the Placebo seroconversion rate of 0%.

Cohort 2 was non-inferior to the adult Bridging Population with the lower limit of the difference between the groups for the 96.7% CI greater than -10% (difference = +4.3%; 96.7% CI: [- 0.3%, 6.2%]). For the second co-primary objective, Cohort 2 had 97.8% (98.3% CI: [92.5%, 99.4%]) of subjects seroconverting by the Day 11 visit, with lower limit of the 98.3% CI exceeding 70%. This rate was also significantly higher than the Placebo seroconversion rate of 4.2%.

Cohort 3 was non-inferior to the adult Bridging Population with the lower limit of the difference between the groups for the 96.7% CI greater than -10% (difference = +4.5%; 96.7% CI: [- 1.1%, 6.4%]). For the second co-primary objective, Cohort 3 had 98.1% (98.3% CI: [91.5%, 99.6%]) of subjects seroconverting by the Day 11 visit, with lower limit of the 98.3% CI exceeding 70%. This rate was also significantly higher than the Placebo seroconversion rate of 0%.

The overall seroconversion rate was 98.5% (n = 393/399) among the pediatric VAXCHORA recipients (98.3% CI: [96.2%, 99.4%]) and was found to be significantly higher than the adult VAXCHORA recipients with seroconversion rate 93.5%. The overall difference between the IEP and the adult Bridging Population was 5.0%.

Reviewer comment*:*

The comparator group for the primary immunogenicity analyses was the adult subjects from the lot consistency trial PXVX-VC-200-004 who received the vaccine. Normally, the confidence intervals used to perform non-inferiority tests assume concurrently randomized groups. When the groups come from different studies, there could be bias or additional study-to-study variability that is not accounted for in the non-inferiority test. Accounting for additional variability or bias could increase the confidence interval width. I examined robustness of results by varying the proportion of subjects who seroconverted, as well as sample size, from the PXVX-VC-200-004 study.

I conducted a sensitivity analysis to see how high the seroconversion rate could be for adults in order to push the lower confidence bound on the difference between rates to below -10%. I assumed that the seroconversion rate in each pediatric cohort is fixed, then increased the rate in the adult group to investigate bias (lowering the rate in the adult group would increase in the lower confidence bound instead of decreasing it). For the sample size in the adult group, I used the current sample size of 2687, as well as a sample size of 150 that might be assumed had the adults been enrolled concurrently with the pediatric cohorts (whose sample sizes ranged from 103 to 157 subjects).

Regardless of adult sample size, even when the seroconversion rate was 100%, the lower confidence bound on the difference of rates (computed in the same way as was done by the applicant, using the Newcombe hybrid method) never went below -10%. The lowest bound occurred when comparing Cohort 3 with adults, which gave a lower bound of -8.2%.

Therefore, it does not appear that the use of a non-concurrent adult comparator group resulted in bias that would change the conclusion of the comparison of seroconversion rates.

6.1.11.2 Analyses of Secondary Endpoints

The seroconversion rate, cumulative seroconversion rate, and 95% CIs at Day 29, Day 91, Day 181, Day 365, Day 547 and Day 730 were estimated for each treatment group for

each cohort (as applicable) and across all cohorts. The 95% CIs were calculated using the Wilson method.

The cumulative seroconversion rate was defined as the cumulative number of subjects who met the seroconversion criterion at or prior to that visit. The denominator for the rate at each time point was the number of subjects in the treatment group who had a baseline assay result and at least one post-vaccination assay result. A baseline value was defined as the last available value collected prior to the vaccination.

The GMT and mean fold-increase in titer over baseline were presented at each visit, along with 95% CIs. The SVA and fold-increase results were log10-transformed and then exponentiated to convert to the non-transformed scale. A t-test was used to compare the log10-transformed fold increase between VAXCHORA and Placebo subjects.

The Day 29 seroconversion rate among Cohort 1 VAXCHORA subjects was 100% (95% CI: [97.6%, 100%]), which was significantly higher than the rate among Placebo recipients for the same time point (0%, 95% CI: [0.0%, 14.3%]). Similarly, the Day 29 cumulative seroconversion rate for Cohort 1 VAXCHORA subjects was 100% (95% CI: [97.6%, 100%]). The cumulative rate among Placebo recipients for the same time point was 0% (95% CI: [2.3%, 25.8%]) which was significantly lower than the rate observed for the VAXCHORA group ($p< 0.0001$).

The Day 91 seroconversion rate among Cohort 1 VAXCHORA subjects was 85.6% (95% CI: [79.2%, 90.3%]), which was significantly higher than the rate among Placebo recipients for the same time point (0%; (95% CI: [0.0%, 14.3%])). Similarly, the Day 181 seroconversion rate for Cohort 1 VAXCHORA subjects was 73.5% (95% CI: [66.0%, 79.9%]). The seroconversion rate among Placebo recipients remained 0% which was significantly lower than the rate for the VAXCHORA group ($p< 0.0001$). The seroconversion rate for Days 365, 547 and 730 were 68.6% (95% CI: [57.0%, 78.2%]), 73.1% (95% CI: [61.5%, 82.3%]) and 64.5% (95% CI: [52.1%, 75.3%]), respectively. The cumulative seroconversion rates remained 100% for VAXCHORA subjects, out to Day 730, and 0% for Placebo out to Day 181.

The Day 29 seroconversion rate among Cohort 2 VAXCHORA subjects was 94.9% (95% CI: [89.9%, 97.5%]), which was significantly higher than the rate among Placebo recipients for the same time point (4.3%; (95% CI: [0.8%, 21.0%])). Similarly, the Day 29 cumulative seroconversion rate for Cohort 2 VAXCHORA subjects was 97.8% (95% CI: [93.8%, 99.3%]). The cumulative rate among Placebo recipients for the same time point was 8.3% (95% CI: [2.3%, 25.8%]) which was significantly lower than the rate observed for the VAXCHORA group ($p< 0.0001$).

The Day 29 seroconversion rate among Cohort 3 VAXCHORA subjects was 93.9% (95% CI: [87.3%, 97.2%]), which was significantly higher than the rate among Placebo recipients for the same time point (0%; (95% CI: [0.0%, 17.6%])). Similarly, the Day 29 cumulative seroconversion rate for Cohort 3 VAXCHORA subjects was 98.1% (95% CI: [93.2%, 99.5%]). The cumulative rate among Placebo recipients for the same time point

was 0% (95% CI: [0.0%, 16.1%]) which was significantly lower than the rate observed for the VAXCHORA group (p< 0.0001). See Table 7 through Table 10 below.

Table 7: Seroconversion Rate by Treatment Group and Cohort

	Cohort 1 VAXCHORA (N=157)	**Placebo (N=23)**	**Cohort 2 VAXCHORA (N=139)**	**Placebo (N=24)**	**Cohort 3 VAXCHORA (N=103)**	**Placebo (N=20)**
Day 11 Visit N analyzable	157	23	139	24	103	20
N (%) Seroconverted (95% CI)	156 (99.4%)*** [96 5%, 99.9%]	0 [0.0%, 14.3%]	136 (97.8%)*** [93.8%, 99.3%]	1 (4.2%) [0.7%, 20.2%]	101 (98.1%)*** [93.2%, 99.5%]	0 [0.0%, 16.1%]
Day 29 Visit N analyzable	156	23	138	23	98	18
N (%) Seroconverted (95% CI)	156 (100%)*** [97.6%, 100%]	0 [0.0%, 14.3%]	131 (94.9%)*** [89.9%, 97.5%]	1 (4.3%) [0.8%, 21.0%]	92 (93.9%)*** [87.3%, 97.2%]	0 [0.0%, 17.6%]
	Overall VAXCHORA (N=399)	**Overall Placebo (N=67)**				
Day 11 N analyzable	399	67				
N (%) Seroconverted (95% CI)	393 (98.5%)*** [96.8%, 99.3%]	1 (1.5%) [0.3%, 8.0%]				
Day 29 N analyzable	392	64				
N (%) Seroconverted (95% CI)	379 (96.7%)*** [94.4%, 98.1%]	1 (1.6%) [0.3%, 8.3%]				

*** p < 0.0001 from Fisher's Exact test of equality of seroconversion between the VAXCHORA and Placebo

Source: Adapted from Table 13 in *PXVX-VC-200-006 Final CSR v3.0*

Table 8: Long-Term Sub-study Seroconversion Rate by Treatment Group (Cohort 1)

	Cohort 1 VAXCHORA (N=157)	**Placebo (N=23)**
Day 91 Visit N analyzable	153	23
N (%) Seroconverted (95% CI)	131 (85.6%)*** [79.2%, 90.3%]	0 [0.0%, 14.3%]
Day 181 Visit N analyzable	151	21
N (%) Seroconverted (95% CI)	111 (73.5%)*** [66.0%, 79.9%]	0 [0.0%, 15.5%]
Day 365 Visit N analyzable	70	-
N (%) Seroconverted (95% CI)	48 (68.6%) [57.0%, 78.2%]	-
Day 547 Visit N analyzable	67	-

	Cohort 1 VAXCHORA (N=157)	**Placebo (N=23)**
N (%) Seroconverted	49 (73 1%)	-
Day 739 Visit N analyzable	62	-
N (%) Seroconverted (95% CI)	40 (64.5%) [52.1%, 75.3%]	-

Source: Adapted from Table 13 in *PXVX-VC-200-006 Final CSR v3.0*

Table 9: Cumulative Seroconversion Rate by Treatment Group and Cohort

	Cohort 1 VAXCHORA (N=157)	**Placebo (N=23)**	**Cohort 2 VAXCHORA (N=139)**	**Placebo (N=24)**	**Cohort 3 VAXCHORA (N=103)**	**Placebo (N=20)**
Day 11 Visit N analyzable	157	23	139	24	103	20
N (%) Seroconverted (95% CI)	156 (99.4%)*** [96.5%, 99.9%]	0 [0%, 14.3%]	136 (97.8%)*** [93.8%, 99.3%]	1 (4.2%) [0.7%, 20.2%]	101 (98.1%) [93.2%, 99.5%]	0 [0.0%, 16.1%]
Day 29 Visit N analyzable	157	23	139	24	103	20
N (%) Seroconverted (95% CI)	157 (100%)*** [97.6%, 100%]	0 [0%, 14.3%]	136 (97.8%)*** [93.8%, 99.3%]	2 (8.3%) [2.3%, 25.8%]	101 (98.1%) [93.2%, 99.5%]	0 [0.0%, 16.1%]
	Overall VAXCHORA (N=399)	**Overall Placebo (N=67)**				
Day 11 N analyzable	399	67				
N (%) Seroconverted (95% CI)	393 (98.5%)*** [96.8%, 99.3%]	1 (1.5%) [0.3%, 8.0%]				
Day 29 N analyzable	399	67				
N (%) Seroconverted (95% CI)	394 (98.7%)*** [97.1%, 99.5%]	2 (3.0%) [0.8%, 10 2%]				

*** p < 0.0001 from Fisher's Exact test of equality of seroconversion between the VAXCHORA and Placebo

Source: Adapted from Table 14 in *PXVX-VC-200-006 Final CSR v3.0*

Table 10: Long-Term Sub-study Cumulative Seroconversion Rate by Treatment Group (Cohort 1 Only)

	Cohort 1 VAXCHORA (N=157)	**Placebo (N=23)**
Day 91 Visit N analyzable	157	23
N (%) Seroconverted (95% CI)	157 (100%)*** [97.6%, 100%]	0 [0%, 14.3%]
Day 181 Visit N analyzable	157	23

	Cohort 1 VAXCHORA (N=157)	**Placebo (N=23)**
N (%) Seroconverted (95% CI)	157 (100%)*** [97.6%, 100%]	0 [0%, 14.3%]
Day 365 Visit N analyzable	72	-
N (%) Seroconverted (95% CI)	72 (100%) [94.9%, 100%]	-
Day 547 Visit N analyzable	72	-
N (%) Seroconverted (95% CI)	72 (100%) [94.9%, 100%]	-
Day 730 Visit N analyzable	72	-
N (%) Seroconverted (95% CI)	72 (100%) [94.9%, 100%]	-

Source: Adapted from Table 14 in *PXVX-VC-200-006 Final CSR v3.0 "Cumulative Seroconversion Rate by Treatment Group and Cohort"*

The GMT of vibriocidal antibodies by visit are presented in Table 11 and Table 12 by cohort and treatment group.

Table 11: Geometric Mean Titers Against Classical Inaba *V. cholerae*, All Time Points by Age Group and Cohort – Immunogenicity Evaluable Population

	Cohort 1 VAXCHORA (N=157)	**Placebo (N=23)**	**Cohort 2 VAXCHORA (N=139)**	**Placebo (N=24)**	**Cohort 3 VAXCHORA (N=103)**	**Placebo (N=20)**
Day 1 N analyzable	157	23	139	24	103	20
GMT (95% CI)	32.1 [28.1, 36.6]	43.8 [27.5, 69.6]	31.5 [27.7, 35.8]	35.6 [24.3, 52.3]	26.7 [23.8, 30.0]	26.4 [19.1, 36.4]
Day 11 Visit N analyzable	157	23	139	24	103	20
GMT (95% CI)	8735.2 *** [7053 1, 10818.5]	41.2 [26.1, 65.1]	8305.0 *** [6515.6, 10585 9]	40.0 [22.7, 70.4]	4851.6 *** [3445 2, 6832.3]	28.3 [20.4, 39.1]
Day 29 Visit N analyzable	156	23	138	23	98	18
GMT (95% CI)	2748.6 *** [2310.8, 3269.5]	42.5 [27.1, 66.7]	1951.8 *** [1554.0, 2451.5]	40.0 [22.1, 72.3]	1013 5 [740.7, 1386.8]	27.2 [20.8, 35.7]
Day 91 Visit N analyzable	153	23				
GMT (95% CI)	318.6 *** [263.0, 385.8]	42.5 [28.7, 62.9]				
Day 181 Visit N analyzable	151	21				
GMT (95% CI)	186.2 *** [154.3, 224.6]	38.7 [25.8, 58.0]				

	Overall VAXCHORA (N=399)	**Placebo (N=67)**				
Day 1 N analyzable	399	67				
GMT (95% CI)	30.4 [28.2, 32.8]	35.0 [27.9, 43.8]				
Day 11 N analyzable	399	67				
GMT (95% CI)	7347.1 *** [6352.6, 8559.8]	36.4 [28.0, 47.4]				
Day 29 N analyzable	392	64				
GMT (95% CI)	1898.7 *** [1657.0, 2175.7]	36.7 [28.1, 48.0]				

*** p < 0.0001; p-values are based on t-statistics assuming normal distribution of the log titer.

Source*:* Adapted from Table 15 *Geometric Mean Titers Against Classical Inaba V. cholerae, All Time Points by Age Group and Cohort – Immunogenicity Evaluable Population in PXVX-VC-200-006 Final CSR v3.0*

Table 12: Long-Term Sub-study GMT by Treatment Group (Cohort 1 Only)

	Cohort 1 VAXCHORA (N=157)	**Placebo (N=23)**
Day 1 Visit N analyzable	72	-
GMT (95% CI)	32.4 [26.2, 40.0]	-
Day 11 Visit N analyzable	72	-
GMT (95% CI)	9035.4 [6745.3, 12103.0]	-
Day 29 Visit N analyzable	72	
GMT (95% CI)	2791.7 [2176.4, 3580.9]	-
Day 91 Visit N analyzable	72	-
GMT (95% CI)	391.7 [293.9, 522.1]	-
Day 181 Visit N analyzable	71	-
GMT (95% CI)	223.0 [166.5, 298.6]	-
Day 365 Visit N analyzable	70	-
GMT (95% CI)	158.4 [121.6, 206.4]	-

*** p < 0.0001; p-values are based on t-statistics assuming normal distribution of the log titer.

Source*:* Adapted from Table 15 *Geometric Mean Titers Against Classical Inaba V. cholerae, All Time Points by Age Group and Cohort – Immunogenicity Evaluable Population in PXVX-VC-200-006 Final CSR v3.0*

For comparisons of geometric mean fold-increase (GMFI) of vibriocidal antibodies from baseline by cohort and by treatment group, please see the clinical reviewer's memo.

6.1.11.3 Subpopulation Analyses

Seroconversion rates by sex, race, and ethnicity, per cohort, are provided in Table 13 through Table 15 for VAXCHORA subjects in the IEP set. There do not appear to be notable subgroup differences.

Table 13: Vibriocidal Seroconversion Against Classical Inaba *V. cholerae* at Day 11, Stratified by Sex

	Male	**Female**
Cohort 1	86/87 (98.9%)	70/70 (100%)
Cohort 2	63/66 (95.5%)	73/73 (100%)
Cohort 3	56/58 (96.6%)	45/45 (100%)
All Age Groups	205/211 (97.2%)	188/188 (100%)

Source: 1.11.3 *Clinical Information Amendment response to FDA on August 14, 2020*

Table 14: Vibriocidal Seroconversion Against Classical Inaba *V. cholerae* at Day 11, Stratified by Race

	White	**Black or African American**	**Other**
Cohort 1	115/115 (100%)	27/28 (96.4%)	14/14 (100%)
Cohort 2	76/77 (98.7%)	45/47 (95.7%)	15/15 (100%)
Cohort 3	46/46 (100%)	47/48 (97.9%)	8/9 (88.9%)
All Age Groups	237/238 (99.6%)	119/123 (96.7%)	37/38 (97.4%)

Source: 1.11.3 *Clinical Information Amendment response to FDA on August 14, 2020*

Table 15: Vibriocidal Seroconversion Against Classical Inaba *V. cholerae* at Day 11, Stratified by Ethnicity

	Hispanic or Latino	**Non-Hispanic or Latino**
Cohort 1	16/16 (100%)	140/141 (99.3%)
Cohort 2	8/9 (88.9%)	128/130 (98.5%)
Cohort 3	5/5 (100%)	96/98 (98.0%)
All Age Groups	29/30 (96.7%)	364/369 (98.6%)

Source: 1.11.3 *Clinical Information Amendment response to FDA on August 14, 2020*

Given that nearly 100% of pediatric subjects seroconverted, no statistical analyses were performed to study potential differential impact of VAXCHORA at different clinical sites.

6.1.11.4 Dropouts and/or Discontinuations

Subjects were excluded from the IEP due to major PDs. All samples analyzed were included in the analysis to the extent that samples produced valid titers and the subjects met the IEP or mITT dataset requirements. Missing values were not imputed for subjects who had missing blood draws and any data missing due to missed blood draws were regarded as non-informative.

In the IEP analysis, 95%, 88% and 70% of the subjects in Cohorts 1, 2 and 3, respectively, were included. Table 16 and Table 17, below, contain primary immunogenicity results for the mITT and Randomized Populations, respectively.

6.1.11.5 Exploratory and Post Hoc Analyses

Sensitivity Analyses

A logistic regression for seroconversion was also performed, with age group, baseline titer, and gender as predictors in the model. Significance of the comparison between the Bridging Population groups (children versus adults) was assessed via the type III test of the age group effect at Day 11. The estimate of the adjusted difference between the groups and its CI were obtained from the model. The results based on the logistic regression model were similar to the seroconversion rates from the primary analysis. Sex was not a significant factor for any cohort, nor overall. The coefficient on baseline titer was statistically significant for all cohorts, but the magnitude of the coefficient was very small, around -0.0005 in each analysis.

The applicant provided a robustness analysis based on the mITT Population to determine the degree to which PDs may have affected the results. Below I present tables of primary immunogenicity results using the mITT and Randomized Populations that follow the structure of Table 6.

Table 16 provides results using the mITT population (identified using the MITTFL=YES flag in the adimmuno data set). Although the lower confidence limit for Cohort 3 decreases to -5.0%, the non-inferiority bound of -10% is still met. Also, the lower confidence limits on the seroconversion rates exceed 70% in all cohorts.

Table 16: Comparison of Seroconversion Rates at Day 11 Visit by Age Group Compared to the Adult Bridging Population (mITT population)

	Study 004 VAXCHORA (N=2688)	**006 Cohort 1 (ages 12 - <18) VAXCHORA (N=160)**	**006 Cohort 2 (ages 6 - <12) VAXCHORA (N=150)**	**006 Cohort 3 (ages 2 - <6) VAXCHORA (N=129)**	**Overall 006 (ages 2 -<18) VAXCHORA (N=439)**
N analyzable	2687	160	150	129	439
N (%) Seroconverted	2513 (93.5%)	159 (99.4%)	144 (96.0%)	122 (94 5%)	425 (96.8%)
[98.3% CI]	[92.3%, 94.6%]	[95.8%, 99 9%]	[90.4%, 98.8%]	[87.8%, 98.2%]	[94.2%, 98.5%]
Difference (006 Cohort minus 004 Adults) [96.7% CI]	-	5.9% [2.5%, 7.1%]	2.5% [-2.6%, 5.0%]	1.1% [-5.0%, 4.2%]	3.3% [0.8%, 5.0%]

Source: *Reviewer created table*

Table 17 provides results using the Randomized Population (with available data for Day 1 and Day 11). This analysis set is identical to the mITT population with the exception that the immunogenicity data from after the first vaccination for the nine subjects who enrolled twice into the study are now included. Using the Randomized Population, the lower confidence limit comparing Cohort 3 to Study 004 remains above the bound of -10%, and the lower confidence limit for the seroconversion rate remains above 70%. A worst-case scenario that assumes all subjects excluded from the Randomized Population did not seroconvert gives a 98.3% CI of [74.9%, 89.3%] for the seroconversion rate, and a 96.7% CI of [-17.7%, -4.6%].

Table 17: Comparison of Seroconversion Rates at Day 11 Visit by Age Group Compared to the Adult Bridging Population (Randomized population)

	Study 004 VAXCHORA (N=2688)	**006 Cohort 1 (ages 12 - <18) VAXCHORA (N=163)**	**006 Cohort 2 (ages 6 - <12) VAXCHORA (N=158)**	**006 Cohort 3 (ages 2 - <6) VAXCHORA (N=150)**	**Overall 006 (ages 2 -<18) VAXCHORA (N=471)**
N analyzable	2687	162	154	132	448
N (%) Seroconverted [98.3% CI]	2513 (93.5%) [92.3%, 94.6%]	161 (99.4%) [95.5%, 99 9%]	148 (96.1%) [90.5%, 98 5%]	125 (94.7%) [87.9%, 97.8%]	434 (96 9%) [94.2%, 98.3%]
Difference (006 Cohort minus 004 A dults) [96.7% CI]	-	5.9% [2.5%, 7.1%]	2.6% [-2.4%, 5.0%]	1.2% [-4.7%, 4.2%]	3.4% [0.9%, 5.1%]

Source: Table 1 in *1.11.3 Clinical Information Amendment*

Table 18 displays the rate of seroconversion among subjects in the mITT Population who consumed < 80% of the expected dose. The subjects have been categorized as those who received < 50% of the dose (< 50 mL for Cohorts 1 and 2, < 25 mL for Cohort 3) and between 50% to < 80% (50 to < 80 mL for Cohorts 1 and 2, 25 to < 40 mL for Cohort 3).

Table 18: Vibriocidal Seroconversion Against Classical Inaba *V. cholerae* at Day 11, Stratified by Dose Consumed; Vaxchora-treated mITT Subjects Consuming < 80% of Expected Dose

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

Source: Table 1 in *1.11.3 Clinical Information Amendment response to FDA on August 14, 2020*

Reviewer's comments:

Seroconversion rates for subjects who consumed less than 50% of the VAXCHORA dose are not non-inferior to the adult rate in the lot to lot consistency study, as the observed rate difference is less than -10%. However, as 100% of subjects who took between 50% and 80% of the dose seroconverted, consumption of at least 50% of the dose may still be non-inferior to the adult rate. A 96.7% confidence bound on the difference between each cohort that consumed at least 50% and the adult rate may meet the non-inferiority criterion, but the confidence interval will be a post-hoc calculation, making any inference potentially problematic.

Exploratory Analysis of Acceptability

Acceptability was measured by the percent of subjects in each cohort and treatment group who completed dosing according to protocol. This is defined as the entire dose being consumed within 15 mins after reconstitution. Acceptability was summarized for the Randomized Population. See description in clinical reviewer's memo.

Exploratory Analysis of Palatability

Palatability of vaccine was assessed by the subject using a 5-point Hedonic scale in Cohorts 1 and 2. Palatability for the subjects in Cohort 3 was assessed by the caregivers. Subject responses to the 5-point Hedonic scale are summarized descriptively by cohort and treatment group for the Randomized Population. See description in clinical reviewer's memo.

6.1.12 Safety Analyses

Safety was reviewed on an ongoing basis by the investigator and the Medical Monitor. AEs were assessed for relatedness to vaccination by the investigator. A Safety Monitoring Committee (SMC), composed of two independent physicians and one independent statistician, conducted safety oversight.

The primary safety objective was assessed through the evaluation of solicited AEs through Day 8 (Days 181 – 188 in PCO group), unsolicited AEs through Day 29 (Days 181 – 209 in PCO group), and the incidence of SAEs through Day 730. The percent of subjects who experienced a solicited AE was tallied by treatment group, broken out by the maximum severity reported and by relationship to treatment. The number of days that a subject experienced any solicited AE and each solicited AE were summarized using descriptive statistics and a frequency distribution.

Solicited AEs included: abdominal pain, headache, lack of appetite, tiredness, diarrhea, nausea, vomiting, and fever and were documented using a memory aid.

Study enrollment was stopped five times for severe solicited reactogenicity signs/ symptoms, four considered possibly related to study product by the investigator, one severe fever considered unrelated, and for one unrelated SAE. In each case, SMC review was done and the study restarted without modification.

In Cohort 1, 165 subjects received any amount of VAXCHORA and 24 subjects received any amount of placebo. In Cohort 2, 157 subjects received any amount of VAXCHORA and 25 subjects received any amount of placebo. In Cohort 3, 146 subjects received any amount of VAXCHORA and 26 subjects received any amount of placebo. In total, 468 VAXCHORA recipients and 75 Placebo recipients were included in the safety analysis.

6.1.12.1 Methods

A Fisher's exact test was used to compare the frequency of solicited and treatment-related AEs between VAXCHORA and Placebo during Days 1 through 8 of at least severe (Grade 3) severity or higher.

Day of onset of the solicited AE was summarized by age group and treatment group. The median and its 95% CI was estimated by Kaplan-Meier analysis. The log-rank test was used to compare day of onset between VAXCHORA and Placebo. This summary was repeated for treatment-related solicited AEs.

A Wilcoxon rank sum test compared VAXCHORA and Placebo on the number of days a subject experienced each solicited AE and each treatment-related solicited AE.

6.1.12.3 Deaths

There were no deaths or discontinuations due to AEs in any cohort or treatment group.

6.1.12.4 Nonfatal Serious Adverse Events

Frequencies of AEs were generally higher in both treatment groups in Cohort 1, followed by Cohort 2, and then Cohort 3, consistent with age-associated reporting bias. Differences in age may have contributed to subjects' ability to communicate feeling ill.

<u>Any severe or worse AEs (through Day 8)</u>
Cohort 1: 2.4% VAXCHORA; 4.2% Placebo
Cohort 2: 3.2% VAXCHORA; 0% Placebo
Cohort 3: 1.4% VAXCHORA; 3.8% Placebo
Overall: 2.4% VAXCHORA; 2.7% Placebo

<u>Any solicited AEs (through Day 8)</u>
Cohort 1: 68.5% VAXCHORA, 66.7% Placebo
Cohort 2: 54.8% VAXCHORA, 52.0% Placebo
Cohort 3: 40.4% VAXCHORA, 34.6% Placebo
Overall: 55.1% VAXCHORA, 50.7% Placebo

Among solicited AEs, the most frequent across all cohorts were tiredness (35.7% VAXCHORA; 30.7% Placebo), headache (27.4% VAXCHORA; 25.3% Placebo), and abdominal pain (27.8% VAXCHORA; 18.7% Placebo).

While no p-value for Fisher's Exact Test was lower than 0.05, some notable differences between groups include higher rates of abdominal pain and lack of appetite for VAXCHORA subjects versus Placebo in Cohort 1, and to a lesser extent in Cohort 3 (see Table 19). Placebo subjects tended to report solicited AEs earlier than did VAXCHORA subjects.

Table 19: Solicited Adverse Events

	Abdominal Pain VAXCHORA	Abdominal Pain Placebo	Lack of Appetite VAXCHORA	Lack of Appetite Placebo
Cohort 1	62/165 (37.6%)	4/24 (16.7%) (p = 0.065)	48/165 (29.1%)	3/24 (12.5%) (p = 0.137)
Cohort 2	43/157 (27.4%)	6/25 (24.0%) (p = 0.813)	24/157 (15.3%)	5/25 (20%) (p = 0.559)
Cohort 3	25/146 (17.1%)	4/26 (15.4%) (p = 1.00)	28/146 (19.2%)	3/26 (11.5%) (p = 0.421)
Overall	130/468 (27.8%)	14/75 (18.7%) (p = 0.121)	100/468 (21.4%)	11/75 (14.7%) (p = 0.218)

Source*:* Table 14.3.1.1 in *PXVX-VC-200-006 Final CSR v3.0*

Any treatment-related solicited AEs (through Day 8)
Cohort 1: 57.6% VAXCHORA, 55.0% Placebo
Cohort 2: 36.9% VAXCHORA, 36.0% Placebo
Cohort 3: 30.1% VAXCHORA, 30.8% Placebo
Overall: 42.1% VAXCHORA, 38.7% Placebo

Any treatment-related severe or worse solicited AEs (through Day 29)
Cohort 1: 1.8% VAXCHORA; 0% Placebo
Cohort 2: 0.6% VAXCHORA; 0% Placebo
Cohort 3: 0.7% VAXCHORA; 3.8% Placebo
Overall: 1.1% VAXCHORA; 1.3% Placebo

Of the treatment-related severe solicited AEs, 3 VAXCHORA subjects reported severe diarrhea; 3 subjects (2 VAXCHORA, 1 Placebo) reported severe fever; 1 VAXCHORA subject also reported severe nausea and vomiting, and 1 VAXCHORA subject also reported severe abdominal pain.

As with any solicited AEs, differences in treatment-related solicited AEs between groups include higher rates of abdominal pain and lack of appetite for VAXCHORA subjects versus Placebo (see Table 20). There was also an indication of increased treatment-related tiredness in Cohort 3 subjects who took VAXCHORA (22.6% versus 11.5%, p = 0.296).

Table 20: Treatment-related Solicited Adverse Events

	Abdominal Pain VAXCHORA	Abdominal Pain Placebo	Lack of Appetite VAXCHORA	Lack of Appetite Placebo
Cohort 1	48/165 (29.1%)	3/24 (12.5%) (p = 0.137)	41/165 (24.8%)	2/24 (8.3%) (p = 0.114)
Cohort 2	31/157 (19.7%)	4/25 (16.0%) (p = 0.790)	17/157 (10.8%)	4/25 (16%) (p = 0.489)
Cohort 3	18/146 (12.3%)	2/26 (7.7%) (p = 0.742)	20/146 (13.7%)	1/26 (3.8%) (p = 0.206)

	Abdominal Pain VAXCHORA	Abdominal Pain Placebo	Lack of Appetite VAXCHORA	Lack of Appetite Placebo
Overall	97/468 (20.7%)	9/75 (12.0%) (p = 0.085)	78/468 (16.7%)	7/75 (9.3%) (p = 0.124)

Source: Table 14.3.1.3 in *PXVX-VC-200-006 Final CSR v3.0*

The minimum number of symptom days reported by VAXCHORA recipients who reported any solicited AEs during the 8-day reporting period was 1 day for all cohorts. The median for Cohort 1 was 3 days, for Cohorts 2 and 3 was 2 days, and the maximum was 8 days for all cohorts. The minimum number of symptom days for Placebo recipients was 1 day, the median was 2.5 days, and the maximum was 8 days for the same time period.

The median number of days of any solicited AE was longer for VAXCHORA subjects (3 days) versus Placebo subjects (2.5 days) for Cohort 1 (p = 0.71), but the same for Cohort 2 (2 days), and shorter for Cohort 3 (2 days versus 3 days, p = 0.93).

Any unsolicited AEs (through Day 29)
Cohort 1: 27.9% VAXCHORA, 29.2% Placebo
Cohort 2: 17.8% VAXCHORA, 32.0% Placebo
Cohort 3: 26.0% VAXCHORA, 23.1% Placebo
Overall 23.9% VAXCHORA, 28.0% Placebo

Any treatment-related unsolicited AEs (through Day 8)
Cohort 1: 18.2% VAXCHORA, 20.8% Placebo
Cohort 2: 11.5% VAXCHORA, 0.0% Placebo
Cohort 3: 9.6% VAXCHORA, 7.7% Placebo
Overall 13.2% VAXCHORA, 9.3% Placebo

Loose stools were the most frequently reported treatment-related unsolicited AE among both VAXCHORA and Placebo recipients.

There were no reports of any treatment-related severe or worse unsolicited AEs.

The minimum number of symptom days of an unsolicited AE reported by all treatment groups was 1 day; the median for Cohorts 1, 2 and 3 was 1 day; and the maximum for all three cohorts was 8 days. The applicant stated that there were no trends in unsolicited AE symptom days between treatment groups.

6.1.12.5 Adverse Events of Special Interest (AESI)
N/A

6.1.12.6 Clinical Test Results
N/A

6.1.12.7 Dropouts and/or Discontinuations

There were nine subjects (two from Cohort 1, four from Cohort 2 and three from Cohort 3) who were enrolled at two sites and received two treatments. One subject received VAXCHORA followed by placebo; all other subjects received two doses of VAXCHORA. The safety data associated with each subject's first enrollment ID are included in the exposure and safety summaries; the data following their second treatment are included in the listings and discussed only in a narrative fashion. These nine subjects have been included in the VAXCHORA Safety Population summaries.

There were no treatment-related SAEs or discontinuations due to AEs in either cohort or treatment group.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A

8. INTEGRATED OVERVIEW OF SAFETY

N/A

9. ADDITIONAL STATISTICAL ISSUES

None

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data
N/A

9.1.2 Use During Lactation
N/A

9.1.3 Pediatric Use and PREA Considerations

See Clinical Reviewer's memo

9.1.4 Immunocompromised Patients
N/A

9.1.5 Geriatric Use
N/A

9.2 Aspect(s) of the Statistical Evaluation Not Previously Covered

None

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The applicant appears to have met the statistical criteria for the objectives of this study. The seroconversion rates in each pediatric cohort were shown to be non-inferior (within 10%) to the seroconversion rate in younger adults from the previous lot to lot consistency study, with 96.7% confidence. Also, the seroconversion rates were shown to be greater than 70% with 98.3% confidence.

Two potential concerns with the immunogenicity analyses have been addressed through sensitivity analyses. These concerns were 1) potential bias from using a comparator group from a different study and 2) relatively high amount of missing data in the youngest pediatric cohort. Both my and the applicant's sensitivity analyses demonstrate general robustness to bias and missing data. In addition, analyses across subgroups do not appear to show statistically significant differences in seroconversion rates.

10.2 Conclusions and Recommendations

Overall, the objectives of this study were shown to be met, and support unqualified approval for the age range 6 – 17 years. Due to lower compliance in the youngest age group (2 – 6 years), results may not be as reliable; however, the prespecified endpoints were met in this group.