



Department of Health & Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: June 7, 2016

From: Deepa Arya, MD, MPH, MBA
Branch Chief, Analytic Epidemiology Branch (AEB)
Division of Epidemiology (DE)
Office of Biostatistics and Epidemiology (OBE)

To: Goutam Sen, PhD
Committee Chair
Office of Vaccines Research and Review (OVRR)

Through: Craig Zinderman, MD, MPH
Associate Director for Product Safety, DE, OBE

Christopher Jankosky, MD, MPH
Acting Director, DE, OBE

Subject: Pharmacovigilance Plan Memorandum

Product: VAXCHORA® (Cholera vaccine, Live attenuated, Oral,)

STN: BLA 125597 / 0000

Applicant: PaxVax Bermuda Ltd. (PaxVax)

Proposed Indication: Active immunization against disease caused by *Vibrio cholerae* serogroup O1 in adults 18 years of age or older

Submission Date: October 16, 2015

Action Due Date: June 15, 2016

Executive Summary of Pharmacovigilance Plan for VAXCHORA®

1. Introduction

- a. Background of Cholera: Cholera is an acute intestinal infection caused by Gram-negative, facultative anaerobe, bacterium *Vibrio cholera*. If left untreated, death can ensue within hours due to profuse watery diarrhea and circulatory collapse. There are over 200 serogroups of *Vibrio cholera*; however, the majority of outbreaks are caused by serogroups O1 and O139. Serogroup O1 has two major biotypes – Classical and El Tor. Each biotype is differentiated into two major serotypes - Ogawa and Inaba. Globally, most cases of cholera are caused by O1 El Tor organisms. Serogroup O139 is found only in Asia.
- b. Product Description: VAXCHORA™ is an oral, live attenuated, bacterial vaccine against disease caused by *V. cholera*. It contains CVD 103-HgR vaccine strain of *V. cholera* serogroup O1. The CVD 103-HgR vaccine strain was constructed from the *V. cholera* serogroup O1 classical Inaba strain 569B by deleting 94% of the cholera toxin A subunit gene, thereby preventing synthesis of active cholera toxin while retaining the immunogenic non-toxic B subunit of cholera toxin.
- c. Pertinent Regulatory history: No cholera vaccine has been licensed in the US. However, in 1994, CVD 103-HgR was marketed globally, although not in the US, under the trade names Orochol® and Mutacol Berna®. Also, a higher dose (x10) vaccine was marketed in cholera-endemic countries under the name Orochol E. These products have not been manufactured since 2004.

2. Pharmacovigilance Plan Review

- a. Clinical safety database: The safety database consists of four clinical trials – (PXVX-VC-200-002, PXVX-VC-200-003, PXVX-VC-200-004, PXVX-VC-200-005), which have been included in the sponsor's Integrated Summary of Safety (ISS). The ISS is summarized below.

A total of 3,797 subjects were included in the Safety Population (3,235 vaccine, 562 placebo). Reactogenicity (which was defined by the sponsor as any solicited signs or symptoms in the first 8 days after vaccination) was reported by 50.08% vaccine recipients vs. 45.75% placebo recipients ($p=0.0652$). The most common signs and symptoms of reactogenicity in both groups were tiredness and headache. A statistically significant difference between the two groups was found only for diarrhea (defined as ≥ 4 loose stools per 24 hours), which was reported in 3.62% [3.00%, 4.33%] of vaccine recipients and 1.63% [0.75%, 3.07%] of placebo recipients ($p=0.0140$). The proportion of vaccine recipients reporting any reactogenicity decreased with increasing age.

There was one death among study subjects; a suicide that occurred on Day 85 after vaccination in a vaccine recipient and was not considered related to vaccine. There were 27 Serious Adverse Events (SAEs) reported by 23 subjects, none of which were considered to be related to the vaccine or placebo.

Unsolicited Adverse events (AEs) were reported in 23.7% of vaccine recipients and 27.4% of placebo recipients (statistical comparisons not conducted due to small numbers of AEs). The only AEs reported in $\geq 2.0\%$ of vaccine or placebo recipients were headache, fatigue, and upper respiratory tract infection.

Eight vaccine recipients in the lot consistency trial were found to be pregnant following vaccination. Based on the last menstrual period, seven of these women would not have been pregnant at the time of vaccination, and one woman may have been pregnant at the time of the vaccination. Each pregnancy was followed to term and resulted in a healthy baby. No vaccine related unsolicited AEs or SAEs were noted in these eight women.

- b. Safety Concerns: The sponsor has summarized the risks as following:
 - i. Identified risks: Hypersensitivity, lack of protection against non-O1 cholera serogroups, lack of 100% protection against *V. cholera* O1, and reduction of efficacy with improper storage or when administered > 30 minutes after reconstitution.

- ii. Potential risks: Reduced effectiveness when used concomitantly with sulfonamides or other antibiotics, reduced effectiveness in immunocompromised patients or if administered with immunosuppressive therapies, and exacerbation of gastrointestinal or febrile illness.
- iii. Missing information: Use in adults aged ≥ 65 years, unproven safety and efficacy in pediatric population, and use during pregnancy.

3. Sponsor's Proposed Actions and Timelines

The sponsor has proposed routine pharmacovigilance activities for the identified and potential risks noted above, and a pregnancy registry for additional safety monitoring in pregnant women. Note that the clinical safety database only includes subject less than 65 years old. If the proposed indication for use in all adults over 18 years old is approved, then additional pharmacovigilance or clinical studies may be needed to enhance safety monitoring in the elderly.

For use in pediatric patients, the sponsor has proposed additional Phase 3 studies in children ≥ 2 to < 18 years old.

4. Post-licensure Safety Reviews:

- a. Worldwide: The sponsor-submitted Berna Biotech Ltd.'s Periodic Safety Update Report (PSUR), dated May 2, 2003, which covered the reporting period from January 1, 1998 to December 31, 2002, showed that during these five years, (b) (4) doses of Orochol were distributed world-wide. There were two spontaneous case reports of adverse drug reactions (a 35 year old male who developed Guillain Barré syndrome and a 27 year old female who developed hair loss) resulting in a reporting rate of (b) (4) case reports per (b) (4) doses distributed.
- b. US: VAXCHORA is currently not marketed or licensed in the US.

5. Integrated Risk Assessment

This reviewer has identified the following risks:

- a. **Adults aged ≥ 65 :** Based on review of submitted safety data from adults 18 through 64 years old, there are no identified safety risks that can be expected to arise or be worse among older vaccinees. However, safety data in this age group (over 65 years old) has not been submitted, and additional studies or pharmacovigilance activities beyond routine monitoring should be considered if the indication is approved as proposed.
- b. **Revaccination:** The sponsor has not studied safety outcomes in patients receiving revaccination (e.g., for repeat travel); however, the safety profile with revaccination is expected to be similar to that of the initial vaccination. The package insert notes that safety and effectiveness of revaccination with VAXCHORA have not been established. This reviewer does not recommend any mitigating activity for this potential risk.
- c. **Immunocompromised individuals:** As noted in the label, safety and effectiveness of VAXCHORA have not been established in immunocompromised persons. Also, the potential risk to immunocompromised household contacts (HHC) of vaccinees is unknown. Adverse events in immunocompromised vaccinees and HHCs will be monitored in routine surveillance.
- d. **Pregnancy:** This reviewer agrees with the sponsor's plan to establish a Pregnancy Registry.
- e. **Shedding:** In the clinical trials shedding of the vaccine strain occurred for at least 7 days post-vaccination and no household contacts (HHCs) seroconverted. There remains a potential risk of exposure to HHCs. This potential risk is addressed in the package insert and caution is advised when administering VAXCHORA to individuals with immunocompromised HHCs.

6. Recommendations

- a. Routine pharmacovigilance: This reviewer recommends routine pharmacovigilance.
- b. Pregnancy Registry (PMC): This reviewer agrees with the sponsor's plan to establish a pregnancy registry.
- c. This reviewer does not recommend postmarketing requirement (PMR) study or Risk Evaluation and Mitigation Strategy (REMS) at this time.

1. Introduction

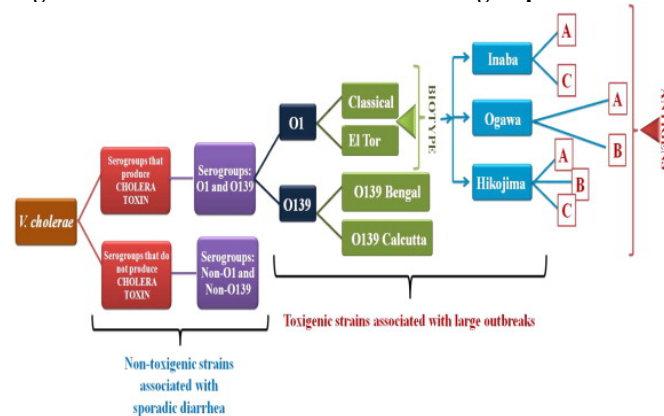
a. Background of Cholera

Cholera is an acute intestinal infection caused by Gram-negative, facultative anaerobe, bacterium *Vibrio cholera*¹, leading to profuse watery diarrhea, vomiting, circulatory collapse, and shock.² If left untreated, 25-50% of severe cholera cases can be fatal within hours of onset of symptoms.²

Based on the differences in the sugar composition of the heat-stable surface somatic “O” antigen, there are over 200 serogroups of *Vibrio cholera* known to date; however the vast majority of outbreaks are caused by two serogroups: O1 and O139.^{Error! Bookmark not defined.}

Serogroup O1 has two biotypes – Classical and El Tor. Additionally, based on antigenic factors each biotype is differentiated into two major serotypes - Ogawa and Inaba (although recently a rare third serotype, Hikojima had been identified).³ A pictorial classification of *V. cholera* can be seen in Figure 1 below.

Figure 1. Classification of *Vibrio cholera* serogroups³



To date, seven cholera pandemics have been recorded and classified by year of commencement, namely 1817, 1829, 1852, 1861, 1881, 1899, and 1961. The first six pandemics were caused by classical biotype of O1 *V. cholera*, and the seventh was caused by the El Tor biotype, which gradually replaced classical strains.^{3,3} In 1992, a new, non-O1 strain appeared in Asia, which was named O139 Bengal.^{Error! Bookmark not defined.} Serogroup O139 is found only in Asia.²

In the US, the occurrence of cholera is very low (0-5 cases per year) and is usually due to ingestion of contaminated food or international travel.² Cholera is endemic in about 50 countries and has the potential to emerge as epidemics. Globally, most cases of cholera are caused by O1 El Tor organisms. In recent years, an El Tor variant with characteristics of both classical and El Tor biotypes has emerged in Asia and spread to Africa and the Caribbean. This strain has been responsible for epidemic in Hispaniola and may cause more severe episodes of cholera and higher death rates.⁴

The major virulence factor in *V. cholera* is cholera toxin (CT), which consists of two subunits: toxic subunit A (CTA) and non-toxic subunit B (CTB), which binds to mammalian cells with high affinity.⁵

1 Cecchini, Francesca, et al "Vibrio cholerae detection: Traditional assays, novel diagnostic techniques and biosensors " *TrAC Trends in Analytical Chemistry* (2016)

2 Centers for Disease Control and Prevention (CDC) Cholera – Vibrio cholera infection <http://www.cdc.gov/cholera/index.html> Accessed on April 26, 2016

3 Banerjee, Rachana, et al "Dynamics in genome evolution of Vibrio cholerae " *Infection, Genetics and Evolution* 23 (2014): 32-41

4 CDC <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/cholera> Accessed on April 28, 2016

5 Baldauf KJ, Royal JM, Hamorsky KT, Matoba N Cholera Toxin B: One Subunit with Many Pharmaceutical Applications Krakauer T, ed *Toxins* 2015;7(3):974-996 doi:10.3390/toxins7030974

Serum vibriocidal antibodies constitute the best correlate of protection against cholera, with high antibody titers correlating with low cholera case rates in field-trial populations.^{6,7}

b. Product description

VAXCHORA™ is an oral, live attenuated, bacterial vaccine against disease caused by *V. cholera* serogroup O1. It contains the CVD 103-HgR vaccine strain of *V. cholera* serogroup O1.⁸

The CVD 103-HgR vaccine strain was constructed from the *V. cholera* serogroup O1 classical Inaba strain 569B by deleting 94% of the cholera toxin A subunit gene (*ctxA* gene), thereby preventing synthesis of active cholera toxin (CT). The attenuated strain retains the *ctxB* gene and remains able to synthesize the immunogenic non-toxic B subunit of CT.⁸ Additionally, a mercury resistance gene (*mer*) has been inserted, which inactivates hemolysin A toxin and provides a marker to differentiate the vaccine strain from wild type *V. cholera* O1.

c. Pertinent regulatory history

i. Prior licensure in the US or other nations

No cholera vaccine is currently marketed or licensed in the US.

The attenuated recombinant *V. cholera* serogroup O1 strain CVD 103-HgR was developed at the Center for Vaccine Development at the University of Maryland, Baltimore (CVD UMB). In 1987, vials of the original CVD 103-HgR progenitor strain were transferred from CVD UMB to the Swiss Serum and Vaccine Institute (SSVI) and were used to produce the Master Seed Lot for Orochol® (commercial name used globally except in North America), or Mutacol Berna® (commercial name in North America except the US). This product was marketed mainly in Switzerland, Canada, New Zealand, and Australia. Additionally, a higher dose (x10) vaccine was marketed in cholera-endemic countries under the trade name Orochol E. SSVI became Berna Biotech (Bern, Switzerland), and (b) (4) production of Orochol ceased in 2004.⁹ In 2006, Berna Biotech was purchased by Crucell NV (Leiden, the Netherlands). Crucell made a business decision to discontinue marketing Orochol and returned the license for CVD 103-HgR to CVD UMB. In 2009, PaxVax acquired a worldwide, exclusive license to the strain CVD 103-HgR from CVD UMB.^{Error!} PaxVax submitted an IND for VAXCHORA in October 2012.¹⁰

1. Summary of indications and usage

Indication: Proposed indication for VAXCHORA is for active immunization against disease caused by *V. cholera* serogroup O1 in adults 18 years of age and older traveling to cholera-affected areas.¹¹

The sponsor plans to study the safety and efficacy of VAXCHORA in the pediatric population (2 to < 18 years) in a pediatric study (Protocol PXVX-VC-200-006). The sponsor intends to submit the protocol in December 2016 and initiate the study in June 2017.¹²

6 Chen WH, Greenberg RN, Pasetti MF, et al Safety and Immunogenicity of Single-Dose Live Oral Cholera Vaccine Strain CVD 103-HgR, Prepared from New Master and Working Cell Banks Burns DL, ed *Clinical and Vaccine Immunology: CVI* 2014;21(1):66-73 doi:10.1128/CVI.00601-13

7 Mosley WH, Ahmad S, Benenson AS, Ahmed A The relationship of vibriocidal antibody titre to susceptibility to cholera in family contacts of cholera patients *Bulletin of the World Health Organization* 1968;38(5):777-785

8 eCTD 125597, SN 0000, 2.5 Clinical Overview

9 eCTD 125597, SN 0021, 1.11.3 Clinical Information Amendment, Berna Biotech Ltd's Periodic Safety Update Report 5 (PSUR) dated May 2, 2003 for the reporting period January 1, 1998 to December 31, 2002

10 Letter to the sponsor, dated December 20, 2012, Reference : IND 15010

11 eCTD 125597, SN 0000, 2.2 Introduction

12. 1.16 Pharmacovigilance Plan, submitted on

Usage: The sponsor has proposed that VAXCHORA should be administered as a single dose oral vaccine, a minimum of 10 days prior to potential exposure to cholera. VAXCHORA is formulated as a powder to be reconstituted with bottled water for oral administration. The carton, which should be stored frozen at 5°F to -13°F (-15°C to -25°C), contains a single-dose foil bacteria sachet and a single-dose foil buffer sachet. The bacteria sachet contains live attenuated *V. cholera* CVD 103-HgR (along with sucrose, sodium chloride, casein, ascorbic acid, and dried lactose) in a powder form. The buffer sachet contains sodium bicarbonate, ascorbic acid, and dried lactose, also in a powder form. The buffer sachet should first be emptied into 100 mL of bottled purified water in a clean cup and stirred. Then the bacteria sachet should be emptied into the cup and stirred. The vaccine must be consumed within 15 minutes of reconstitution. Vaccinees should not eat or drink for 60 minutes before and 60 minutes after oral ingestion of the vaccine.¹³

2. Major postmarketing safety findings

VAXCHORA has never been marketed anywhere in the world; however, Orochol and Mutachol Berna (same vaccine strain as VAXCHORA) were licensed in Switzerland in 1994; the production was stopped in 2004.⁹ The sponsor has provided a PSUR dated May 2, 2003, which was submitted by Berna Biotech Ltd. According to this report, from January 1994 until March 2004, [REDACTED] doses of Orochol were distributed. Data on the number of doses that were actually administered are unknown. During these 10 years, 4 spontaneous reports were received by Berna Biotech Ltd. - one serious labeled, one serious unlabeled, and two non-serious reports - with a total of 5 AEs. The sponsor concluded that a low reporting rate confirms good tolerability of Orochol in the period from 1994 to 2002.

ii. CBER Complete Response letters

This is an original BLA for VAXCHORA, which has never been issued a Complete Response letter. However, in February 1997 a PLA was submitted by SSVI to the FDA for Mutachol Berna. This vaccine contained the same vaccine strain as VAXCHORA. In May 1998, FDA issued a Complete Response (CR) letter, citing issues related to study design, sample size, and manufacturing.¹⁴

d. Objectives/Scope of the review

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should VAXCHORA be licensed.

2. Materials reviewed

a. Routine items:

i. Pharmacovigilance Plan (PVP)

“Pharmacovigilance Plan – Cholera vaccine, Live, Oral (VAXCHORA/PXVX0200) dated October 9, 2015.

ii. Pertinent sections of the licensing application selected by the reviewer

1. Cover letter of October 16, 2015

2. Annotated Draft Labeling Text

¹³ 1 14 1 2 Annotated Draft Labeling Text

¹⁴ Transcript of VRBPAC meeting held on May 27, 1998

3. Clinical Review
4. Structure (PXVX0200, PaxVax, Inc.)
5. General Properties (PXVX0200, PaxVax, Inc.)
6. Integrated Summary of Safety (ISS) of Sep 25, 2015
7. PXVX-VC-200-002: A Phase I randomized, double-blind, placebo controlled trial to evaluate the safety and immunogenicity of the vaccine.
8. PXVX-VC-200-003: A Phase III randomized, double-blind, placebo-controlled trial to evaluate the efficacy, reactogenicity, and safety of the vaccine following challenge with *V. cholera* at 10 days or 3 months post-vaccination in healthy adults 18 to 45 years of age.
9. PXVX-VC-200-005: A Phase III randomized, double-blind, placebo-controlled trial to demonstrate equivalence in immune response to the vaccine in older adults (46 to 64 years of age) and younger adults.
10. Pregnancy registry Protocol Synopsis

iii. Medical Literature and other materials

1. Safety and Immunogenicity of Single-dose Live Oral Cholera Vaccine Strain CVD 103-HgR, Prepared from New Master and Working Cell Banks. Chen *et al.* 2014.¹⁵
This is the pivotal study submitted as PXVX-VC-200-002 by the sponsor. The study is discussed in detail in section 3a(i).
2. A single dose of live oral cholera vaccine CVD 103-HgR is safe and immunogenic in HIV-infected and HIV-noninfected adults in Mali. Perry *et al.* 1998.¹⁶
This is a randomized, placebo-controlled, double-blind, cross-over clinical trial in 38 HIV-positive (without clinical acquired immunodeficiency syndroms (AIDS)) and 387 HIV-seronegative adults in Mali. Adverse reactions (fever, diarrhea, and vomiting) were observed with similar frequency among vaccine and placebo recipients. The vaccine strain was not isolated from the stool cultures of any subject. In this trial, CVD 103-HgR was found to be safe in HIV-infected Malian adults.
3. Safety, Immunogenicity, and Transmissibility of Single-dose Live Oral Cholera Vaccine Strain CVD 103-HgR in 24-59-Month-Old Indonesian Children. Simanjuntak *et al.* 1993.¹⁷
This is a placebo-controlled, double-blind study among 24- to 59-month-old children in Jakarta. Incidence of diarrhea, vomiting, abdominal cramps, and fever were similar in both groups. Excretion of vaccine strain was seen in 2.5% of the vaccinees from whom stool cultures were obtained. Vaccine strain was recovered from the stool culture of 0.6% of the unvaccinated family contacts.
4. Cholera vaccine information on World health Organization (WHO) public website¹⁸
The website provides information on Live attenuated CVD 103 HgR with the brand name Orochol. Only rare gastrointestinal side-effects were noted.
5. Update on Cholera Vaccines, Strategic Advisory Group of Experts on Immunization, 28 October, 2009.
No major safety concerns were noted with Orochol.

b. Other items

15 Chen, Wilbur H , et al "Safety and immunogenicity of single-dose live oral cholera vaccine strain CVD 103-HgR, prepared from new master and working cell banks " *Clinical and Vaccine Immunology* 21 1 (2014): 66-73

16 Perry, R T , et al "A single dose of live oral cholera vaccine CVD 103-HgR is safe and immunogenic in HIV-infected and HIV-noninfected adults in Mali " *Bulletin of the World Health Organization* 76 1 (1998): 63

17 Simanjuntak, Cyrus H , et al "Safety, Immunogenicity, and Transmissibility of Single-Dose Live Oral Cholera Vaccine Strain CVD 103-HgR in 24-to 59-Month-Old Indonesian Children " *Journal of infectious diseases* 168 5 (1993): 1169-1176

18 WHO website http://www.who.int/cholera/tsunami_cholera_vaccine/en/index3.html accessed on June 3, 2016

- i. Vaccine and Related Biological Products Advisory Committee (VRBPAC) from 1993
 - ii. Vaccine and Related Biological Products Advisory Committee (VRBPAC) from 1998
 - iii. An Orochol monograph (publication sponsored by an educational grant from CSL vaccines) was obtained from National Library of Australia was submitted by the sponsor. This monograph summarizes the post-marketing Experience since 1994.
 - iv. PSUR dated May 2, 2003, which was submitted by Berna Biotech Ltd.
 - v. Information available at the WHO public website.
 - vi. Update on Cholera Vaccines, Strategic Advisory Group of Experts on Immunization, 28 October, 2009.
- c. Input from CBER Clinical Reviewers

The Clinical reviewer has the following concerns, all of which are addressed in the package insert:

 - i. Lack of data in immunocompromised patients: The package insert states that the safety and effectiveness of VAXCHORA have not been established in immunocompromised persons.
 - ii. Fecal shedding: The duration of fecal shedding is not known. Also, there is potential of transmission of the vaccine strain to HHCs. Package insert advises caution when administering VAXCHORA to persons with immunocompromised HHCs.
 - iii. Lack of data on concomitant administration of VAXCHORA with other travel vaccines or medications: The package insert notes that no data are available on concomitant administration of VAXCHORA with other vaccines or medications.
 - iv. Revaccination: The package insert notes that the safety and effectiveness of revaccination with VAXCHORA have not been established.

3. Pharmacovigilance Plan Review

a. Clinical Safety Database

The safety database consists of data on four trials - PXVX-VC-200-002, PXVX-VC-200-003, PXVX-VC-200-004, and PXVX-VC-200-005. These four trials and Integrated Summary of Safety (ISS) are discussed below.

The research name for CVD 103-HgR vaccine as manufactured by PaxVax is PXVX0200.

In all clinical trials and ISS, the sponsor has defined “reactogenicity” as any solicited sign or symptom recorded on a memory aid that covered the day of vaccination and the 7-day period following vaccination (Days 1-8) and was considered at least possibly related to vaccine by the investigator.

i. Trial PXVX-VC-200-002

This is a phase 1 randomized, double-blind placebo controlled study to evaluate safety and immunogenicity. The study was conducted from 7 May 2012 to 7 January 2013 at two sites in the US.

The trial was conducted in 66 healthy volunteers aged 18 to 50 years. Of these, 55 were vaccine recipients and 11 were placebo recipients. In addition 28 household contacts (HHCs) were enrolled, of whom 24 were associated with a vaccine recipient and 4 were associated with a placebo recipient. Vaccine shedding and transmission were assessed with fresh stool samples or rectal swabs before vaccination and post-vaccination.

Reactogenicity

Reactogenicity was reported by 40.0% (95% CI 27.0-54.1) of vaccinees and 45.5% (95% CI 16.6-76.6) of placebo recipients. Reactogenicity signs and symptoms ordered by frequency are shown in Table 1 below.

Table 1. Reactogenicity Signs and Symptoms Ordered by Frequency of Occurrence – Any Severity for Vaccine and Placebo Recipients

	PXVX0200 (N=55) n (% , 95% CI)	Placebo (N=11) n (% , 95% CI)	P value [1]
Any sign or symptom	22 (40%, 27.0% - 54.1%)	5 (45.5%, 16.7 - 76.6%)	0.749
Abdominal Pain	10 (18.2%, 9.1% - 30.9%)	3 (27.3%, 6.0% - 61.0%)	0.678
Diarrhea	8 (14.5%, 6.5% - 26.7%)	0 (0.0%, 0.0% - 28.5%)	0.334
Headache	8 (14.5%, 6.5% - 26.7%)	2 (18.2%, 2.3% - 51.8%)	0.668
Tiredness	6 (10.9%, 4.1% - 22.2%)	0 (0.0%, 0.0% - 28.5%)	0.579
Nausea/Vomiting	4 (7.3%, 2.0% - 17.6%)	1 (9.1%, 0.2% - 41.3%)	>0.999
Lack of Appetite	3 (5.5%, 1.1% - 15.1%)	1 (9.1%, 0.2% - 41.3%)	0.527
Fever [2]	1 (1.8%, 0.0% - 9.7%)	1 (9.1%, 0.2% - 41.3%)	0.308

[1] P value is from Fisher's exact test comparing the PXVX0200 and placebo

[2] Fever is defined as a temperature greater than 100.4 degrees Fahrenheit

The most common signs and symptoms of reactogenicity were abdominal pain, diarrhea, and headache. There were no statistically significant differences between the treatment and placebo groups in the frequency of symptoms. Most reactogenicity was mild. Diarrhea (defined as > 2 stools per 24 hours) was reported in 8 vaccinees and none of the placebo recipients. Of these 8 vaccinees, 7 reported mild diarrhea and 1 reported moderate diarrhea (≥ 4 loose stools within 24 hours). Only one case of severe reactogenicity in the form of fever (temperature > 102.4° F) in a placebo recipient was recorded.

Adverse Events

Unsolicited AEs were reported by 17 (30.9%) of the 55 vaccine recipients and 4 (36.4%) of the 11 placebo recipients. Adverse events ordered by frequency are shown in Table 2 below.

Table 2. Adverse Events by System Organ Class Ordered by Frequency of Occurrence for Vaccine and Placebo Recipients

SYSTEM ORGAN CLASS	PXVX0200 (N=55) n(% , 95% CI)	PLACEBO (N=11) n(% , 95% CI)
ANY EVENT	17 (30.9%, 19.1%-44.8%)	4 (36.4%, 10.9%-69.2%)
Infections and infestations	8 (14.5%, 6.5%-26.7%)	2 (18.2%, 2.3%-51.8%)
Gastrointestinal disorders	3 (5.5%, 1.1%-15.1%)	1 (9.1%, 0.2%-41.3%)
Musculoskeletal and connective tissue disorders	3 (5.5%, 1.1%-15.1%)	0 (0.0%, 0.0%-28.5%)
General disorders and administration site conditions	2 (3.6%, 0.4%-12.5%)	0 (0.0%, 0%-28.5%)
Respiratory, thoracic and mediastinal disorders	2 (3.6%, 0.4%-12.5%)	1 (9.1%, 0.2%-41.3%)
Skin and subcutaneous tissue disorders	2 (3.6%, 0.4%-12.5%)	0 (0.0%, 0%-28.5%)
Injury, poisoning and procedural complications	1 (1.8%, 0.1%-9.7%)	0 (0.0%, 0%-28.5%)
Nervous system disorders	1 (1.8%, 0.1%-9.7%)	0 (0.0%, 0%-28.5%)

Note: Within each System Organ Class, vaccine or placebo recipients experiencing more than one event are counted only once

Most AEs were mild or moderate; however, 3 severe AEs were reported: a two-day headache that occurred 22 days post vaccination in a vaccine recipient, a case of streptococcus pharyngitis in a placebo recipient, and a 10-day bout of diarrhea in a vaccine recipient that began 28 days after vaccination and was accompanied by pharyngitis and pyrexia of moderate degree. The site physicians did not consider these AEs related to the vaccine. Only one AE in each group was assessed as

possibly related to the vaccine: Mild abdominal discomfort starting on Day 3 and lasting for two days in a vaccine recipient, and mild abdominal distention starting on Day 1 and resolving on Day 2 in a placebo recipient. AEs were also reported by 3 of the 24 HHCs of vaccine recipients and by none of the 4 HHCs of placebo recipients. All events were mild and none were considered related to the vaccine by site physicians.

Serious Adverse Events

No SAEs were reported among vaccine or placebo recipients. One SAE was reported in a HHC of a vaccine recipient- a 29 year old male who was diagnosed with prostatitis 62 days and pericarditis 67 days post-vaccination. There was no evidence of exposure to vaccine in the form of shedding or seroconversion and the event was not considered to be related to the vaccine.

Fecal Shedding

Fecal shedding of the vaccine strain occurred in a total of 11.3% [95% CI 4.3%, 23.0%] vaccine recipients on any day through 7 days post-vaccination. Shedding increased in frequency over the week following vaccination and reached a peak on Day 7 when it was detected in 7.5% [95% CI 2.1%, 18.2%] vaccine recipients. The duration of shedding is unknown.

Household Contacts

None of the 24 HHCs of the vaccine recipients had *V. cholera* detected in either stool samples or rectal swabs collected 7 days post-vaccination. No significant rise in vibriocidal antibody was detected in any HHC.

Deaths

No subjects died during the study.

ii. **Trial PXVX-VC-200-003**

This is a Phase 3 randomized, double-blind, placebo-controlled trial to evaluate efficacy, reactogenicity, and safety of a single dose of PXVX0200 CVD 103-HgR following challenge with *V. cholera* O1 El Tor Inaba 10 days or 3 months after vaccination. This study was conducted from 13 September 2013 to 28 July 2014 at three sites in the US.

This study included 95 vaccine recipients and 102 placebo recipients; all were men and non-pregnant women aged 18 to 45 years enrolled. The challenge inoculum was 1×10^5 CFU of wild type *V. cholera* O1 El Tor Inaba strain N16961.

Reactogenicity post-vaccination

Reactogenicity signs and symptoms were reported by 49.5% of vaccine recipients and 50.0% of placebo recipients. The most common signs and symptoms of reactogenicity among vaccine and placebo recipients were tiredness, headache, and abdominal pain. There were no statistically significant differences between vaccine and placebo groups in the frequency of symptoms. Diarrhea (defined as ≥ 4 loose stools per 24 hours) was reported in 1.1% of vaccine recipients and 3.0% of placebo recipients ($p=0.6221$). Most reactogenicity was mild.

Table 3. Post-Vaccination Reactogenicity Signs and Symptoms by Highest Reported Severity – Safety Population

Symptoms	PXVX0200 N=95	Placebo N=102	P-value ^a
No. of Subjects Assessed	93	100	
Any Reactogenicity ^b	46 (49.5%)	50 (50.0%)	1.0000

Tiredness	32 (34.4%)	33 (33.0%)	0.8795
Mild	22 (23.7%)	17 (17.0%)	
Moderate	8 (8.6%)	13 (13.0%)	
Severe	2 (2.2%)	3 (3.0%)	
Potentially Life-Threatening	0	0	
Headache	23 (24.7%)	31 (31.0%)	0.3415
Mild	15 (16.1%)	16 (16.0%)	
Moderate	8 (8.6%)	12 (12.0%)	
Severe	0	3 (3.0%)	
Potentially Life-Threatening	0	0	
Abdominal Pain	20 (21.5%)	20 (20.0%)	0.8598
Mild	12 (12.9%)	11 (11.0%)	
Moderate	8 (8.6%)	8 (8.0%)	
Severe	0	1 (1.0%)	
Potentially Life-Threatening	0	0	
Lack of Appetite	17 (18.3%)	23 (23.0%)	0.4790
Mild	10 (10.8%)	17 (17.0%)	
Moderate	6 (6.5%)	3 (3.0%)	
Severe	1 (1.1%)	3 (3.0%)	
Potentially Life-Threatening	0	0	
Nausea/Vomiting	14 (15.1%)	21 (21.0%)	0.3508
Mild	10 (10.8%)	13 (13.0%)	
Moderate	4 (4.3%)	6 (6.0%)	
Severe	0	2 (2.0%)	
Potentially Life-Threatening	0	0	
Fever	2 (2.2%)	1 (1.0%)	0.6097
Mild	1 (1.1%)	1 (1.0%)	
Moderate	1 (1.1%)	0	
Severe	0	0	
Potentially Life-Threatening	0	0	
Diarrhea	1 (1.1%)	3 (3.0%)	0.6221
Mild	0	1 (1.0%)	
Moderate	1 (1.1%)	1 (1.0%)	
Severe	0	1 (1.0%)	
Potentially Life-Threatening	0	0	

Note: Severity was from the toxicity grading scale: 1=Mild; 2=Moderate; 3=Severe; 4=Potentially Life threatening

Note: For each reactogenicity sign or symptom, subjects were counted at most once at the highest reported severity

Note: The number of subjects assessed was the number of subjects who completed a diary card following the vaccination

Note: Percentages were calculated using the number of subjects assessed in the given treatment arm as the denominator

a P-value was calculated using a Fisher's exact test comparing the frequency of the corresponding reactogenicity sign or symptom between vaccine and placebo recipients

b Subjects were included if any severity (mild, moderate, severe, life-threatening) had been specified for any symptom and any time following the vaccination

When reactogenicity was at least of moderate severity, no pattern of temporality or association with vaccine recipients compared with placebo recipients was noted. Subgroup analysis by blood type (O and non-O), sex (female and male), and race (black and white) did not reveal trends in reactogenicity between subgroups.

Reactogenicity post-challenge

Reactogenicity post-challenge was solicited for both 10-Day and 3-Month challenge groups. Reactogenicity signs and symptoms were reported by 65.7 % of vaccine recipients in the 10-Day Challenge group and by 51.5% of the vaccine recipients in the 3-Month Challenge group compared with the 87.9% of combined placebo group post-challenge. The most common signs and symptoms of reactogenicity among vaccine and placebo recipients were malaise, abdominal cramps, headache, and nausea/vomiting. There were statistically significant differences in the frequencies of symptoms between the vaccine and placebo groups, with lower frequencies for the vaccine groups for the categories of any reactogenicity, malaise, abdominal cramps, nausea/vomiting, and fever in both 10-Day and 3-Month Challenge group and for headache in the 3-Month Challenge group.

Adverse events

Adverse events, excluding those following challenge, were reported by 17.9% of vaccine recipients and 16.7% of placebo recipients and were mostly mild in severity. Unsolicited AEs after vaccine administration collected through the 28 days following the study product are summarized by descending order of incidence in Table 4.

Table 4. Post-vaccination Adverse Events through Day 29 by Preferred Term in Descending Order of Incidence – Safety Population

Preferred Term^a	PXVX0200 N=95	Placebo N=102
Number of subjects with at Least One AE	17 (17.9%)	17 (16.7%)
Upper respiratory tract infection	3 (3.2%)	2 (2.0%)
Flatulence	2 (2.1%)	1 (1.0%)
Diarrhoea	2 (2.1%)	0
Fatigue	1 (1.1%)	4 (3.9%)
Musculoskeletal pain	1 (1.1%)	2 (2.0%)
Decreased appetite	1 (1.1%)	1 (1.0%)
Dizziness	1 (1.1%)	1 (1.0%)
Gastrointestinal sounds abnormal	1 (1.1%)	1 (1.0%)
Hypertension	1 (1.1%)	1 (1.0%)
Oropharyngeal pain	1 (1.1%)	1 (1.0%)
Abdominal pain	1 (1.1%)	0
Arthralgia	1 (1.1%)	0
Eye pain	1 (1.1%)	0
Feeling hot	1 (1.1%)	0
Pyrexia	1 (1.1%)	0
Sinus congestion	1 (1.1%)	0
Sports injury	1 (1.1%)	0

Toothache	1 (1.1%)	0
Rhinorrhoea	0	3 (2.9%)
Cough	0	2 (2.0%)
Sneezing	0	2 (2.0%)
Back pain	0	1 (1.0%)
Chlamydial infection	0	1 (1.0%)
Feeling abnormal	0	1 (1.0%)
Frequent bowel movements	0	1 (1.0%)
Headache	0	1 (1.0%)
Musculoskeletal chest pain	0	1 (1.0%)
Musculoskeletal stiffness	0	1 (1.0%)
Myalgia	0	1 (1.0%)
Neck pain	0	1 (1.0%)
Rash	0	1 (1.0%)
Thirst	0	1 (1.0%)
Throat irritation	0	1 (1.0%)
Urinary tract infection	0	1 (1.0%)

Note: Percentages were based on the number of subjects in each treatment group. Subjects were counted once within each preferred term.

Note: Adverse events that emerged post-challenge were not included in this table. Thus, the table includes events from the 10-Day Challenge group only through Day 10.

a All AE terms were coded using MedDRA dictionary version 15.0.

Most AEs were mild. The most common AEs reported among vaccine recipients were upper respiratory infection, flatulence, and diarrhea. Statistical comparison was not performed due to small numbers of AEs in each category. Mild diarrhea was reported in 2 vaccine recipients 8-10 days and 3-10 days post-vaccination. No diarrhea was reported in placebo recipients. Evaluation of AEs by System Organ Class (SOC) did not reveal any significant trends in AEs. Gastrointestinal disorders were the most common AEs and were reported in 6.3% of the vaccine recipients and 2.9% of the placebo recipients.

Serious Adverse Events

There was one SAE reported in a placebo recipient. This concerned a 45-year old male who experienced diarrhea and fever after challenge and later, 57 days after the challenge experienced an MVA with tibial fracture. This event was not considered related to the study therapy.

Additionally, a placebo recipient developed hyperkalemia 3 days after challenge and it was considered unrelated to the vaccine product.

Deaths

No subjects died during this study.

iii. Trial PXVX-VC-200-004

This is a phase 3 randomized, double-blind, placebo-controlled three-lot consistency study in healthy adult volunteers to assess immunogenicity, and clinical acceptability of a single-dose of PXVX0200. This study was conducted across 19 sites in the US and 6 sites in Australia, from 12 May 2014 to 23 February 2015.

In this study, 3146 subjects were enrolled (2,795 in the vaccine group [2789 received the vaccine] and 351 in the placebo group).

Reactogenicity

Reactogenicity signs and symptoms after vaccine administration were reported by 51.90% (95% CI, 50.01% - 53.79%) of the vaccine recipients and 43.15% (95% CI, 37.84% - 48.58%) of placebo recipients (p=0.0024). The most common signs and symptoms of reactogenicity among vaccine and placebo recipients were tiredness, headache, and abdominal pain. Headache was reported in 28.93% (95% CI, 27.24% - 30.67%) of vaccine recipients and 23.62% (95% CI, 19.22% - 28.47%) of placebo recipients (p=0.0419). Diarrhea (defined as ≥ 4 loose stools per 24 hours) was reported in 3.88% (95% CI, 3.18% - 4.67%) of vaccine recipients and 1.17% (95% CI, 0.32% - 2.96%) of placebo recipients (p=0.0079). Most reactogenicity was mild and resolved within 3 days. The reactogenicity signs and symptoms by highest reported severity are summarized in Table 5.

Table 5. Reactogenicity Signs and Symptoms by Highest Reported Severity: Vaccine vs. Placebo – Safety Population

Signs and Symptoms	PXVX0200 All Lots N=2789	Placebo N=350	P-value ^a
No. of Subjects Assessed	2734	343	
Any Reactogenicity ^b	1419 (51.90%)	148 (43.15%)	0.0024
95% CI ^c	[50.01%, 53.79%]	[37.84%, 48.58%]	
Tiredness ^d	856 (31.31%)	94 (27.41%)	0.1538
95% CI ^c	[29.57%, 33.09%]	[22.75%, 32.45%]	
Mild	510 (18.65%)	56 (16.33%)	
Moderate	328 (12.00%)	34 (9.91%)	
Severe	18 (0.66%)	4 (1.17%)	
Potentially Life-Threatening	0	0	
Headache ^d	791 (28.93%)	81 (23.62%)	0.0419
95% CI ^c	[27.24%, 30.67%]	[19.22%, 28.47%]	
Mild	516 (18.87%)	50 (14.58%)	
Moderate	261 (9.55%)	30 (8.75%)	
Severe	14 (0.51%)	1 (0.29%)	
Potentially Life-Threatening	0	0	
Abdominal Pain ^d	510 (18.65%)	58 (16.91%)	0.4609
95% CI ^c	[17.21%, 20.17%]	[13.10%, 21.30%]	
Mild	330 (12.07%)	41 (11.95%)	
Moderate	169 (6.18%)	17 (4.96%)	
Severe	11 (0.40%)	0	
Potentially Life-Threatening	0	0	

Nausea/Vomiting ^d	501 (18.32%)	52 (15.16%)	0.1569
95% CI ^c	[16.89%, 19.83%]	[11.53%, 19.40%]	
Mild	364 (13.31%)	39 (11.37%)	
Moderate	129 (4.72%)	13 (3.79%)	
Severe	8 (0.29%)	0	
Potentially Life-Threatening	0	0	
Lack of Appetite ^d	451 (16.50%)	57 (16.62%)	0.9386
95% CI ^c	[15.12%, 17.94%]	[12.84%, 20.99%]	
Mild	321 (11.74%)	42 (12.24%)	
Moderate	121 (4.43%)	15 (4.37%)	
Severe	9 (0.33%)	0	
Potentially Life-Threatening	0	0	
Diarrhea ^d	106 (3.88%)	4 (1.17%)	0.0079
95% CI ^c	[3.18%, 4.67%]	[0.32%, 2.96%]	
Mild	65 (2.38%)	3 (0.87%)	
Moderate	18 (0.66%)	1 (0.29%)	
Severe	22 (0.80%)	0	
Potentially Life-Threatening	1 (0.04%)	0	
Fever ^d	17 (0.62%)	4 (1.17%)	0.2828
95% CI ^c	[0.36%, 0.99%]	[0.32%, 2.96%]	
Mild	6 (0.22%)	1 (0.29%)	
Moderate	8 (0.29%)	3 (0.87%)	
Severe	2 (0.07%)	0	
Potentially Life-Threatening	1 (0.04%)	0	

Note: The number of subjects assessed was the number of subjects who completed a memory aid following the vaccination

Note: Percentages were calculated using the number of subjects assessed in the given treatment arm as the denominator

a The p-value was from a Fisher's exact test comparing the frequency of the corresponding reactogenicity sign and symptom between the vaccine and placebo recipients

b Counted subjects who reported reactogenicity of any severity at any time within 8 days following vaccination

c Exact confidence interval was for the percentage of subjects in the given treatment arm who recorded the reactogenicity event(s) on the memory aid

d Subjects were counted at most once at the highest severity level reported for the corresponding sign or symptoms at any time within 8 days following vaccination

Reactogenicity signs and symptoms of at least moderate severity were reported by 23.81% (95% CI, 22.23% - 25.45%) of vaccine recipients and 18.37% (95% CI, 14.41% - 22.88%) of placebo recipients (p=0.0250). There was a trend towards greater frequency of moderate (defined as 5 loose stools per 24 hours) and severe (defined as ≥ 6 loose stools per 24 hours) diarrhea in vaccine recipients when compared to placebo recipients (p=0.0809). For other reactogenicity categories, the difference between vaccine and placebo recipients did not reach statistical significance.

The distribution of the day of onset of signs and symptoms of reactogenicity was similar in both groups. Three times as many subjects in both groups reported onset on day 1 as on day 2 and the frequency then decreased from day 3 through Day 8 in both groups.

Severe diarrhea (defined as ≥ 6 loose stools per 24 hours) was reported in 22 of the 2,789 (0.80%) of the vaccine recipients compared with 0 of the 350 (0.00%) of the placebo recipients.

Reactogenicity was reported at similar rates across the three different vaccine lots. Female vaccine recipients reported reactogenicity more frequently than male vaccine recipients: 57.23% (95% CI, 54.69% - 59.74%) females reported at least one sign or symptom compared to 45.3 % (95% CI, 42.54% - 48.19%) males. Differences in reactogenicity were also noted between races. White vaccine recipients reported reactogenicity more frequently than African-American or black vaccine recipients: 54.37% (95% CI, 52.09% - 56.64%) of white vaccine recipients reported at least one sign or symptom compared to 43.24% (95% CI, 39.47% - 47.05%) of African-American or black vaccine recipients. A similar pattern was observed in placebo group although the difference between races was smaller: 45.07% (95% CI, 38.26% - 52.2%) of white placebo recipients reported reactogenicity compared to 39.82% (95% CI, 30.73% - 49.46%) of African-Americans or blacks. No apparent difference in reactogenicity was observed between vaccine recipients of different blood groups. In summary, reactogenicity was more common in vaccine recipients (51.90%) than placebo recipients (43.15%) ($p=0.0024$). Although diarrhea occurred in less than 5 % of subjects in both groups (vaccine 3.88%; placebo 1.17%), it was reported three times more frequently in vaccine recipients ($p=0.0079$). Also, diarrhea was of greater severity (vaccine 1.50%; placebo 0.29%) and greater duration (vaccine 1.4 days; placebo 1.0 days) in vaccine recipients than placebo recipients. Headache was significantly more common in vaccine recipients (28.93%) than placebo recipients (23.62%) ($p=0.0419$).

Adverse Events

Unsolicited AEs post-vaccination administration through Day 29 were reported in 22.98% of vaccine recipients and 24.00% of placebo recipients. The most common AEs reported in both groups were headache (2.74%), fatigue (2.13%), and upper respiratory tract infection (1.98%). Statistical analyses were not performed to compare the AEs in both groups because of the small number of AEs in each category. The data by PT in descending order of incidence are summarized in Table 6 below.

Table 6. Adverse Events Through Day 29 by Preferred Term in Descending Order of Incidence of $\geq 0.20\%$ - Safety Population

Preferred Term^a	PXVX0200 N=2789	Placebo N=350	Total N=3139
Number of subjects with at Least One AE	641 (22.98%)	84 (24.00%)	725 (23.10%)
Headache	75 (2.69%)	11 (3.14%)	86 (2.74%)
Fatigue	59 (2.12%)	8 (2.29%)	67 (2.13%)
Upper respiratory tract infection	57 (2.04%)	5 (1.43%)	62 (1.98%)
Back pain	38 (1.36%)	3 (0.86%)	41 (1.31%)
Flatulence	32 (1.15%)	4 (1.14%)	36 (1.15%)
Abdominal pain	29 (1.04%)	2 (0.57%)	31 (0.99%)
Nausea	25 (0.90%)	3 (0.86%)	28 (0.89%)
Arthralgia	24 (0.86%)	1 (0.29%)	25 (0.80%)
Decreased appetite	23 (0.82%)	4 (1.14%)	27 (0.86%)
Oropharyngeal pain	20 (0.72%)	3 (0.86%)	23 (0.73%)

Viral upper respiratory tract infection	17 (0.61%)	3 (0.86%)	20 (0.64%)
Constipation	16 (0.57%)	3 (0.86%)	19 (0.61%)
Dizziness	16 (0.57%)	0	16 (0.51%)
Musculoskeletal pain	16 (0.57%)	0	16 (0.51%)
Abnormal faeces	15 (0.54%)	0	15 (0.48%)
Neck pain	13 (0.47%)	2 (0.57%)	15 (0.48%)
Cough	12 (0.43%)	1 (0.29%)	13 (0.41%)
Dysmenorrhoea	12 (0.43%)	0	12 (0.38%)
Rhinorrhoea	11 (0.39%)	3 (0.86%)	14 (0.45%)
Dyspepsia	11 (0.39%)	2 (0.57%)	13 (0.41%)
Pain	11 (0.39%)	0	11 (0.35%)
Pain in extremity	10 (0.36%)	3 (0.86%)	13 (0.41%)
Myalgia	10 (0.36%)	2 (0.57%)	12 (0.38%)
Diarrhoea	10 (0.36%)	1 (0.29%)	11 (0.35%)
Rash	9 (0.32%)	2 (0.57%)	11 (0.35%)
Abdominal distension	9 (0.32%)	1 (0.29%)	10 (0.32%)
Insomnia	9 (0.32%)	1 (0.29%)	10 (0.32%)
Urinary tract infection	9 (0.32%)	0	9 (0.29%)
Toothache	8 (0.29%)	2 (0.57%)	10 (0.32%)
Influenza	8 (0.29%)	1 (0.29%)	9 (0.29%)
Influenza like illness	8 (0.29%)	1 (0.29%)	9 (0.29%)
Muscle strain	7 (0.25%)	1 (0.29%)	8 (0.25%)
Gastroenteritis	7 (0.25%)	0	7 (0.22%)
Pharyngitis	7 (0.25%)	0	7 (0.22%)
Ligament sprain	6 (0.22%)	3(0.86%)	9 (0.29%)
Musculoskeletal stiffness	6 (0.22%)	1 (0.29%)	7 (0.22%)
Nasopharyngitis	6 (0.22%)	1 (0.29%)	7 (0.22%)
Abdominal pain upper	6 (0.22%)	0	6 (0.19%)
Migraine	6 (0.22%)	0	6 (0.19%)
Muscle spasms	6 (0.22%)	0	6 (0.19%)
Rhinitis	5 (0.18%)	1 (0.29%)	6 (0.19%)
Abdominal discomfort	5 (0.18%)	0	5 (0.16%)
Dry mouth	5 (0.18%)	0	5 (0.16%)
Nasal congestion	5 (0.18%)	0	5 (0.16%)
Viral infection	5 (0.18%)	0	5 (0.16%)
Procedural pain	4 (0.14%)	3 (0.86%)	7 (0.22%)

Note: Percentages were based on the number of subjects in each treatment group. Subjects were counted once within each preferred term.
Note: Preferred terms were listed in order of descending incidence in the vaccine group. Ties are ordered by incidence in the placebo group. Any remaining ties are listed alphabetical order.
a All adverse event terms were coded using MedDRA dictionary version 15.0

For the AEs of moderate or higher severity, the most common AEs in both groups were similar to all AEs: fatigue (vaccine 1.18%; placebo 0.86%), headache (vaccine 1.08%; placebo 0.86%), and upper respiratory tract infection (vaccine 0.65%; placebo 0.86%).

AEs by SOC or PT did not reveal any meaningful differences in type or incidence between the two groups. AEs in Gastrointestinal Disorders SOC were the commonest in both groups (vaccine 6.17%; placebo 6.00%).

Serious Adverse Events

The incidence of SAEs through Day 181 was similar in both groups (vaccine 0.61%; placebo 0.86%). In this study, 20 subjects (vaccine 17; placebo 3) reported SAEs other than death. None of these SAEs were considered related to the study product and all but 2 resolved by day 181. The 2 events that did not resolve by Day 181 were exacerbation of depression and fracture of left patella.

Deaths

There was one death in this study, on Day 85. A 38-year old male who was randomized to receive the vaccine committed suicide. Death certificate was not available. The event was not considered related to the vaccine.

iv. Trial PXVX-VC-200-0005

This is a phase 3 randomized, double-blind, placebo-controlled study in older adults to assess immunogenicity and clinical acceptability of a single-dose of PXVX0200. The study was conducted at 16 sites in the US from 19 May 2014 to 15 January 2015.

The main safety objective was to evaluate the safety of PXVX0200 in older adults aged 46-64 years. Safety endpoints were: incidence and severity of signs and symptoms of reactogenicity such as diarrhea, vomiting, and fever, and incidence and severity of unsolicited AEs.

A total of 398 subjects were enrolled in this study: 299 to vaccine and 99 to placebo. A vaccine dose of 1×10^9 CFU/dose was used and placebo consisted of physiological saline administered orally.

Reactogenicity

Solicited signs and symptoms of reactogenicity in the 7-day period following vaccination were reported in 36.3% of vaccine recipients and 50.5% of placebo recipients ($p=0.0174$). The data ordered by highest reported severity are summarized in Table 7 below.

Table 7. Reactogenicity Signs and Symptoms by Highest Reported Severity – Safety Population

Signs and Symptoms	PXVX0200 N=296	Placebo N=99	Total N=395	P-value ^a
No. of Subjects Assessed	295	99	394	
Any Reactogenicity by Highest Reported Severity ^b	107 (36.3%)	50 (50.5%)	157 (39.8%)	0.0174
95% CI ^c	[30.8%, 42.0%]	[40.3%, 60.7%]	[35.0%, 44.9%]	
Headache ^d	60 (20.3%)	30 (30.3%)	90 (22.8%)	0.0522
95% CI ^c	[15.9%, 25.4%]	[21.5%, 40.4%]	[18.8%, 27.3%]	
Mild	41 (13.9%)	19 (19.2%)	60 (15.2%)	

Moderate	17 (5.8%)	11 (11.1%)	28 (7.1%)	
Severe	2 (0.7%)	0	2 (0.5%)	
Potentially Life-Threatening	0	0	0	
Tiredness ^d	59 (20.0%)	36 (36.4%)	95 (24.1%)	0.0017
95% CI ^c	[15.6%, 25.0%]	[26.9%, 46.6%]	[20.0%, 28.6%]	
Mild	37 (12.5%)	20 (20.2%)	57 (14.5%)	
Moderate	20 (6.8%)	16 (16.2%)	36 (9.1%)	
Severe	2 (0.7%)	0	2 (0.5%)	
Potentially Life-Threatening	0	0	0	
Abdominal Pain ^d	42 (14.2%)	13 (13.1%)	55 (14.0%)	0.8679
95% CI ^c	[10.5%, 18.8%]	[7.2%, 21.4%]	[10.7%, 17.8%]	
Mild	34 (11.5%)	10 (10.1%)	44 (11.2%)	
Moderate	7 (2.4%)	3 (3.0%)	10 (2.5%)	
Severe	1 (0.3%)	0	1 (0.3%)	
Potentially Life-Threatening	0	0	0	
Nausea/Vomiting ^d	35 (11.9%)	12 (12.1%)	47 (11.9%)	1.0000
95% CI ^c	[8.4%, 16.1%]	[6.4%, 20.2%]	[8.9%, 15.5%]	
Mild	27 (9.2%)	9 (9.1%)	36 (9.1%)	
Moderate	7 (2.4%)	3 (3.0%)	10 (2.5%)	
Severe	1 (0.3%)	0	1 (0.3%)	
Potentially Life-Threatening	0	0	0	
Lack of Appetite ^d	24 (8.1%)	12 (12.1%)	36 (9.1%)	0.2320
95% CI ^c	[5.3%, 11.9%]	[6.4%, 20.2%]	[6.5%, 12.4%]	
Mild	14 (4.7%)	11 (11.1%)	25 (6.3%)	
Moderate	8 (2.7%)	1 (1.0%)	9 (2.3%)	
Severe	2 (0.7%)	0	2 (0.5%)	
Potentially Life-Threatening	0	0	0	
Diarrhea ^d	7 (2.4%)	2 (2.0%)	9 (2.3%)	1.0000
95% CI ^c	[1.0%, 4.8%]	[0.2%, 7.1%]	[1.0%, 4.3%]	
Mild	4 (1.4%)	1 (1.0%)	5 (1.3%)	
Moderate	2 (0.7%)	0	2 (0.5%)	
Severe	1 (0.3%)	1 (1.0%)	2 (0.5%)	
Potentially Life-Threatening	0	0	0	
Fever ^d	2 (0.7%)	0	2 (0.5%)	1.0000
95% CI ^c	[0.1%, 2.4%]	[0.0%, 3.7%]	[0.1%, 1.8%]	

Mild	2 (0.7%)	0	2 (0.5%)	
Moderate	0	0	0	
Severe	0	0	0	
Potentially Life-Threatening	0	0	0	

Note: The number of subjects assessed was the number of subjects who completed a memory aid following the vaccination

Note: Percentages were calculated using the number of subjects assessed in the given treatment arm as the denominator

a P-value was from a Fisher's exact test comparing the frequency of the corresponding reactogenicity sign or symptom between the vaccine and placebo recipients

b Counts subjects who reported reactogenicity of any severity at any time within 8 days following vaccination

c Exact confidence interval was for the percentage of subjects in the given treatment arm who recorded the reactogenicity event(s) on the memory aid

d Subjects were counted at most once at the highest severity level reported for the corresponding sign or symptom at any time within 8 days following vaccination

The most common signs and symptoms of reactogenicity among vaccine recipients in order of frequency were headache, tiredness, and abdominal pain. Greater proportion of placebo recipients reported tiredness (placebo 36.4% vs. vaccine 20.0%, $p=0.0017$) and headache (placebo 30.3%; vaccine 20.3%, $p=0.0522$) than vaccine recipients. For other reactogenicity categories, the differences between vaccine and placebo groups did not reach statistical significance. Diarrhea (defined as ≥ 4 loose stools per 24 hours) was reported in 2.4% of vaccine recipients compared with 2.0% of placebo recipients ($p=1.0000$). Most reactogenicity was mild and lasted for 1-2 days.

Reactogenicity of at least moderate severity was reported by 11.9% of vaccine recipients and 23.2% of placebo recipients ($p=0.0084$). The most common signs and symptoms for at least moderately severe reactogenicity in both groups were tiredness, headache, and lack of appetite.

The frequency for subgroup analysis by blood type (O and non-O), sex (female and male), and race (black and white) did not reveal any trends in reactogenicity between vaccine and placebo recipients.

Adverse Events

Unsolicited AEs through 28 days following vaccination were reported in 20.6% of vaccine recipients and 27.3% of placebo recipients. The most common AEs reported by vaccine recipients were fatigue (3.7%), back pain (2.0%), and decreased appetite (1.7%). All other AEs were reported $\leq 1.0\%$ of vaccine recipients. AEs considered related to the study product were reported in 7.1% of vaccine recipients and 9.1% of placebo recipients. These AEs were: fatigue (vaccine 1%; placebo 1%), pain and decreased appetite (vaccine 0.7%), upper abdominal pain, vomiting, malaise, and neck pain (vaccine 1%), musculoskeletal pain and extremity pain (placebo 1%).

Serious Adverse Events

No SAEs were reported in either group through Day 29 after vaccination. By Day 181 follow-up, 3 SAE reports, which occurred more than 119 days after vaccination, were received in the vaccine group: atrial fibrillation, myocardial infarction, and spinal compression fracture. They were not considered to be related to the study vaccine.

Deaths

There were no deaths during this study.

v. Integrated Summary of Safety

This summary integrates the results obtained from the four studies noted above. The studies are summarized in Table 8 below. A total of 3,797 subjects were included in the Safety Population (3,235 subjects in the vaccine group and 562 in the placebo group).

Table 8. Design of the Clinical Trials for PXVX0200

Type of Trial	Trial No ^a	Objectives of Trial	Trial Design	Test product and route of administration	Number of Subjects	Healthy subjects vs. patients	Duration of treatment
Phase 1	PXVX-VC-200-002	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	4.43 x 10 ⁸ CFU/dose, oral	66 55 vaccine, 11 placebo	Health subjects	Single dose
Challenge Phase 3	PXVX-VC-200-003	Demonstrate protection from live cholera challenge	Randomized, double-blind, placebo-controlled	5 x 10 ⁸ CFU/dose, oral	197 95 vaccine, 102 placebo	Health subjects	Single dose
Lot Consistency Phase 3	PXVX-VC-200-004	Demonstrate clinical lot consistency	Randomized, double-blind, placebo-controlled	1 x 10 ⁹ CFU/dose, oral	3146 2795 vaccine, 350 placebo	Health subjects	Single dose
Older adults Phase 3	PXVX-VC-200-005	Demonstrate equivalence in immune response of older and younger adults	Randomized, double-blind, placebo-controlled	1 x 10 ⁹ CFU/dose, oral	398 296 vaccine, 99 placebo	Health subjects	Single dose

^a There was no trial with the suffix 001; this was assigned to a protocol that was not performed

^b Italics show the number of subjects who actually received vaccine or placebo. A total of 3235 subjects received PXVX0200 vaccine

^c Placebo in the Phase 1 trial was lactose powder in water. Placebo was physiological saline in all other trials

One subject in the lot consistency trial was reenrolled in error and received a second dose of the vaccine 2 months after the first dose. The subject did not report any reactogenicity or AEs with either administration.

Reactogenicity

Reactogenicity signs and symptoms were reported 4% more frequently by vaccine recipients 50.08% [48.32%, 51.83%] than placebo recipients 45.75% [41.54%, 50.01%] (p=0.0652). In both groups most reactogenicity was mild, occurred within 1 to 3 days of vaccination, and resolved within 3-5 days following vaccination. The most common signs and symptoms of reactogenicity in both groups were tiredness and headache. A statistically significant difference between the two groups was found only for diarrhea. Diarrhea (defined as ≥ 4 loose stools per 24 hours) was reported in 115/3177 = 3.62% [3.00%, 4.33%] of vaccine recipients and 9/553 = 1.63% [0.75%, 3.07%] of placebo recipients (p=0.0140). The Reactogenicity signs and symptoms are summarized in Table 9 below.

Table 9. Summary of Reactogenicity Days 1-8 – safety Population

Reactogenicity Day 1 through Day 8 Post-Vaccination	PXVX0200 (N=3235)	Placebo (N=562)
No. of Subjects Assessed	3177	553
Tiredness	953 (30.00%)	163 (29.48%)
Headache	882 (27.76%)	144 (26.04%)
Abdominal Pain	582 (18.32%)	94 (17.00%)

Nausea/Vomiting	554 (17.44%)	86 (15.55%)
Lack of Appetite	495 (15.58%)	93 (16.82%)
Diarrhea	115 (3.62%)	9 (1.63%) ^a
Fever ^b	22 (0.69%)	6 (1.08%)

Note: The number of subjects assessed is the number of subjects who completed a memory aid following vaccination in PXVX-VC-200-002 (Phase 1), PXVX-VC-200-003 (Challenge), PXVX-VC-200-004 (Lot), and PXVX-VC-200-005 (Older)

Note: Percentages are based on the number of subjects in PXVX-VC-200-002 (Phase 1), PXVX-VC-200-003 (Challenge), PXVX-VC-200-004 (Lot), and PXVX-VC-200-005 (Older). The denominator represents the total number of subjects who received treatment and were assessed (ie completed a memory aid)

a p = 0.0140

b Fever was defined as a body temperature greater than 100.4°F measured by oral thermometer

The proportion of vaccine recipients reporting any reactogenicity decreased with increasing age. No consistent trend with age was apparent in the placebo group, although a smaller sample size may have limited the power to detect such a difference.

Reactogenicity was lower in male than in female vaccine recipients: 43.63% [41.05%, 46.22%] of males vs. 55.50% [53.12%, 57.87%] of females. This trend was also seen in placebo recipients.

Frequency of any reactogenicity was lower in blacks than in whites or in subjects of race other than white or black: 52.46% [50.34%, 54.58%] among whites and 41.71% [38.31%, 45.17%] among blacks, and 59.24% [51.77%, 66.41%] among subjects of race other than white or black. This difference was observed in placebo recipients as well, although the sample size was smaller.

Reactogenicity by ethnicity showed that Hispanic vaccine recipients reported less reactogenicity than non-Hispanics: 44.70% [39.01%, 50.50%] of Hispanic vaccine recipients reported at least one sign and symptoms of reactogenicity compared to 50.61% [48.76%, 52.45%] of non-Hispanic vaccinees. When reactogenicity of only moderate or high severity was evaluated, no difference between ethnic groups was noted. Placebo recipients did not show any difference between ethnic groups.

There was little difference between vaccine recipients with blood type O and non-O in frequency of reactogenicity.

Adverse Events

Unsolicited AEs were recorded through Day 181 following vaccination in Phase 1 trial and through Day 29 for the three Phase 3 trials. AEs in the challenge trial are not included in the integrated summary. Unsolicited AEs were reported in 23.7% of vaccine recipients and 27.4% of placebo recipients. The only AEs reported in ≥2.0% of vaccine or placebo recipients were headache, fatigue, and upper respiratory tract infection. Statistical comparisons of the frequency of AEs in the two groups were not conducted due to small numbers of AEs in each category. AEs ordered by incidence are summarized in Table 10 below.

Table 10. Adverse Events by Decreasing Order of Incidence (≥0.2% of Vaccine Recipients) – Safety Population

Preferred Term^a	PXVX0200 N=3235	Placebo N=562
Number of subjects with at Least One AE	767 (23.7%)	154 (27.4%)
Headache	80 (2.5%)	15 (2.7%)
Fatigue	71 (2.2%)	18 (3.2%)
Upper respiratory tract infection	67 (2.1%)	12 (2.1%)
Back pain	45 (1.4%)	6 (1.1%)
Flatulence	37 (1.1%)	7 (1.2%)
Abdominal pain	35 (1.1%)	5 (0.9%)

Decreased appetite	29 (0.9%)	6 (1.1%)
Nausea	28 (0.9%)	5 (0.9%)
Arthralgia	27 (0.8%)	2 (0.4%)
Oropharyngeal pain	24 (0.7%)	5 (0.9%)
Musculoskeletal pain	19 (0.6%)	5 (0.9%)
Constipation	18 (0.6%)	5 (0.9%)
Dizziness	18 (0.6%)	3 (0.5%)
Viral upper respiratory tract infection	18 (0.6%)	3 (0.5%)
Abnormal faeces	17 (0.5%)	2 (0.4%)
Diarrhoea	16 (0.5%)	6 (1.1%)
Neck pain	15 (0.5%)	4 (0.7%)
Rhinorrhoea	14 (0.4%)	7 (1.2%)
Pain in extremity	14 (0.4%)	4 (0.7%)
Myalgia	13 (0.4%)	5 (0.9%)
Cough	13 (0.4%)	4 (0.7%)
Dysmenorrhoea	13 (0.4%)	0
Pain	13 (0.4%)	0
Rash	12 (0.4%)	5 (0.9%)
Dyspepsia	12 (0.4%)	2 (0.4%)
Urinary tract infection	11 (0.3%)	2 (0.4%)
Abdominal distension	9 (0.3%)	3 (0.5%)
Muscle strain	9 (0.3%)	3 (0.5%)
Insomnia	9 (0.3%)	2 (0.4%)
Toothache	9 (0.3%)	2 (0.4%)
Pharyngitis	9 (0.3%)	0
Ligament sprain	8 (0.2%)	3 (0.5%)
Gastroenteritis	8 (0.2%)	1 (0.2%)
Influenza	8 (0.2%)	1 (0.2%)
Influenza like illness	8 (0.2%)	1 (0.2%)
Sinusitis	7 (0.2%)	2 (0.4%)
Vomiting	7 (0.2%)	1 (0.2%)
Abdominal pain upper	7 (0.2%)	0
Dry mouth	7 (0.2%)	0
Musculoskeletal stiffness	6 (0.2%)	2 (0.4%)
Nasal congestion	6 (0.2%)	2 (0.4%)
Dermatitis contact	6 (0.2%)	1 (0.2%)
Nasopharyngitis	6 (0.2%)	1 (0.2%)
Abdominal discomfort	6 (0.2%)	0
Migraine	6 (0.2%)	0
Muscle spasms	6 (0.2%)	0

Arthropod bite	5 (0.2%)	3 (0.5%)
Hypertension	5 (0.2%)	2 (0.4%)
Gastroesophageal reflux disease	5 (0.2%)	1 (0.2%)
Pharyngitis streptococcal	5 (0.2%)	1 (0.2%)
Rhinitis	5 (0.2%)	1 (0.2%)
Viral infection	5 (0.2%)	0

Note: Percentages are based on the number of subjects in PXVX-VC-200-002 (Phase I), PXVX-VC-200-003 (Challenge), PXVX- VC-200-004 (Lot), and PXVX-VC-200-005 (Older). The denominator represents the total number of subjects who received treatment combined from all trials. Only treatment-emergent adverse events are presented. Challenge-emergent adverse events are excluded.

Note: Subjects are counted once within each preferred term. Preferred terms are listed in order of descending incidence in all vaccine recipients, then all placebo recipients, and remaining ties are ordered alphabetically.

a. All adverse event terms were coded using MedDRA dictionary version 15.0.

Serious Adverse Events

There were 27 SAEs reported by 23 subjects, none of which were considered to be related to the vaccine or placebo.

Administration During Pregnancy

Eight vaccine recipients in the lot consistency trial were found to be pregnant following vaccination. Based on the last menstrual period, seven of these women would not have been pregnant at the time of vaccination; however, one woman may have been pregnant at the time of the vaccination. Each pregnancy was followed to term and resulted in a healthy baby. No vaccine related unsolicited AEs or SAEs were noted in these eight women.

Deaths

There was one death due to suicide during the study. This occurred on Day 85 in a vaccine recipient and was not considered related to vaccine.

b. Safety concerns

The sponsor has summarized the important identified safety issues, potential safety issues, and missing information in Table 11 below.

Table 11. Summary of ongoing safety Issues

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> Hypersensitivity* to any of the components of vaccine or buffer Lack of protection against non-O1 cholera serogroup Lack of 100% protection against <i>V. cholerae</i> O1 Reduction in efficacy when stored above the recommended temperature, or when administered >30 minutes after reconstitution

Important potential risks	<ul style="list-style-type: none"> • Reduced immune response/decreased vaccine effectiveness when used concomitantly with sulphonamides or other antibiotics • Reduced immune response/decreased vaccine effectiveness when used in immunocompromised patients or along with immunosuppressive therapies • Exacerbation of gastrointestinal or febrile illness
Missing information	<ul style="list-style-type: none"> • Use in adults aged 65 years or older • Unproven safety and efficacy in pediatric population • Use during pregnancy

*Hypersensitivity defined by the sponsor as an allergic reaction or anaphylaxis to the bacterial component, or the buffer including milk protein

c. Sponsor's proposed actions and timelines

i. Routine Pharmacovigilance

The sponsor has proposed routine pharmacovigilance activities for the following risks noted in Table 11.

For all identified risks noted in table 11, the sponsor has proposed routine pharmacovigilance activities, with the justification that the risks are adequately covered in the Package Insert (PI).

For all potential risks noted in table 11, the sponsor has proposed routine pharmacovigilance activities, with the justification that the risks are adequately covered in the Package Insert (PI).

For use in adults aged 65 and older, the sponsor has proposed routine pharmacovigilance with the justification that collection and analysis of reported information on use of VAXCHORA in adults aged 65 and older would enable further assessment of any impact over existing benefit-risk balance.

Reviewer comment: The sponsor has not submitted any data on safety and efficacy of VAXCHORA in adults aged 65 and older. Based on review of submitted safety data from adults 18 through 64 years old, there are no identified safety risks that can be expected to arise or be worse among older vaccinees. However, additional studies or pharmacovigilance activities beyond routine monitoring should be considered if the indication is approved as proposed by the sponsor (in adults 18 years of age and older).

For use in Pediatric population, the sponsor has proposed additional Phase 3 studies in children ≥ 2 to < 18 years old.

For use during pregnancy, the sponsor has proposed a pregnancy registry.

ii. Review of Pregnancy registry protocol

V. cholera is a non-invasive bacterium and remains in the intestinal lumen, and is thus not expected to have a direct effect on the developing fetus. The sponsor has proposed an observational prospective study of safety of VAXCHORA exposure during pregnancy. Final protocol submission is planned by July 1, 2016. The sponsor anticipates study completion by 5 years after registry initiation, by September 1, 2021. At that time an evaluation will be done to assess the need to keep the registry open. The final study report is anticipated to be submitted by September 1, 2022.

1. Objectives

The objective of the registry is to detect and describe pregnancy outcomes in women vaccinated with VAXCHORA at any time during pregnancy and within 28 days prior to conception, and the health of the infant. The sponsor has proposed the following primary and secondary outcomes:

Primary outcomes:

- Spontaneous abortions
- Fetal deaths/Stillbirths
- Preterm births
- Low birth weight

Secondary outcome:

- Major congenital anomalies

2. Source and study populations

The study population will include pregnant women within the US who are inadvertently vaccinated with VAXCHORA within 28 days prior to conception or anytime during pregnancy, and who are volunteering to participate in the registry before the outcome of the pregnancy is known.

3. Design

The sponsor proposes to enroll pregnant women prospectively in routine clinical setting. A woman may self-enroll by calling the registry telephone number (1-888-483-9053), or her healthcare provider can enroll her with her consent.

4. Exposure assessment

Exposure to VAXCHORA and other data such as exposures to other vaccines, medications, and countries traveled during pregnancy, will be collected prospectively using questionnaires sent to the reporter at the time of enrollment.

5. Outcome assessment

The sponsor proposes to conduct outcome assessment via questionnaires within a month of the estimated date of delivery.

6. Statistical analysis

The sponsor proposes to evaluate the prevalence rates with 95% Confidence Intervals will be calculated for each of the primary outcomes and the secondary outcome noted above. When feasible, rates will be broken down by the timing of the event relative to vaccine exposure. Comparison data will be derived from external databases such as CDC and Metropolitan Atlanta Congenital Defects Program.

7. Power calculation

The sponsor proposes to use one-sided Fisher's exact test with 80% power and $\alpha=0.05$.

8. Sensitivity analyses and plans for missing data

The sponsor has not provided any information regarding sensitivity analyses or plans for dealing with missing data.

4. Postlicensure Safety Review

a. Worldwide

VAXCHORA is currently not licensed in any country.

The sponsor-submitted Berna Biotech Ltd.'s PSUR Report 5, dated May 2, 2003, which covered the reporting period January 1, 1998 to December 31, 2002, shows that during these five years [REDACTED] doses of Orochol were distributed world-wide. There were two spontaneous case reports of adverse drug reactions (ADRs) resulting in a reporting rate of [REDACTED] case reports per [REDACTED] doses distributed. These two cases were as follows:

- i. Serious unlabeled ADR: A report from Germany regarding a 35 year old male who received Orochol concomitantly with Stamaril, Typhim Vi, Diphtheria

toxoid, and IPV and developed a polyradiculoneuritis (Guillain-Barré syndrome) involving cranial nerves. In view of the concomitant vaccines that have been associated with Guillain-Barré syndrome and the mechanism of action and adverse event profile of Orochol, Berna Biotech Ltd. did not consider this AE to be related to Orochol.

Reviewer Comment: Although Guillain Barré syndrome is a rare condition, it has a regular background rate and it can be related to an infectious process. One reported case in (b) (4) doses distributed is not suggestive of a vaccine related effect.

- ii. Non-serious unlabeled ADR: A spontaneous report from Germany regarding a 27 year old female who experienced hair loss starting 3 days post-vaccination with Orochol.

During this 5-year reporting period, there were no other safety-related information from any studies and no spontaneous reports of drug interactions. Also, with only two spontaneous AE reported between 1998 and 2002, there was no evidence of an increase in the frequency of any listed AEs compared with the company core safety information.

In a Safety memo, Berna Biotech Ltd. also noted that in the first 4 years of marketing (from January 1994 to December 1997), a total of (b) (4) doses were distributed world-wide and a total of 2 case reports involving 3 AEs were reported. This yields a reporting rate of (b) (4) doses distributed. These two cases were as follows:

- i. Serious labeled ADR: A spontaneous report from Germany regarding a 2 year old girl who inadvertently ingested half of her mother's Orochol and presented a day later with vomiting and gastroenteritis with blood stained diarrheal fluid. The child had received ½ dose of a yellow fever vaccine on the same day. The child was hospitalized but recovered fully within a few days.
- ii. Non-serious unlabeled ADR: A spontaneous report from Switzerland regarding a 50 year old female who presented a day after intake of Orochol with redness and swelling of face and throat, and breathlessness. Her clinical picture resembled allergic angioedema. The interval between intake of Orochol and onset of symptoms of angioedema was not typical of a causal relationship. However, since the cause of angioedema could not be determined, a causal relationship with Orochol could not be excluded.

Reviewer Comment: No information is provided whether this patient was hospitalized or not, therefore it is difficult to classify this event as "serious" based on that criterion. However, allergic angioedema often has a serious outcome and has the potential of progressing to anaphylaxis if not treated promptly; additionally, the "breathlessness" described in his case could represent life threatening symptoms, another criterion for a serious AE in this case. However, it is reassuring that only one case was reported in four years during which (b) (4) doses were distributed.

No doses of Orochol were distributed in the calendar year 1993 and between January and March 2004. Berna Biotech Ltd. did not receive any AE reports from the market in 2003 or in the period January to March 2004.

One case was reported in January 2004 from a clinical trial, which was not sponsored by Berna Biotech Ltd. Five weeks after Orochol vaccination, an 11-month old male in the study needed to be hospitalized for dehydration and fever due to diarrhea and vomiting. The differential diagnoses were gastroenteritis, meningitis, or malaria infection. Laboratory tests revealed hemorrhagic CSF and mild anemia. The child recovered with treatment and causality was assessed as unlikely for Orochol.

In summary, from January 1994 until March 2004, a total of [REDACTED] doses of Orochol were distributed. During this time, 4 spontaneous reports were received by Berna Biotech Ltd. – one serious labeled, one serious unlabeled, and two non-serious reports with a total of 5 AEs. This yields a reporting rate of [REDACTED] cases per [REDACTED] doses distributed. The sponsor concluded that this low reporting rate confirms good tolerability of Orochol in the period from 1994 to 2002.

b. U.S.

VAXCHORA is currently not marketed or licensed in the US.

5. Integrated Risk Assessment

This reviewer has identified the following risks:

- a. **Adults aged ≥ 65 :** Safety assessment and corresponding pharmacovigilance recommendations in people aged > 64 years is limited because subjects in that age group were not included in the trials. Safety experience in vaccinees aged ≥ 65 could be different from that in people < 65 years of age. Additional studies or pharmacovigilance activities beyond routine monitoring should be considered if the indication is approved as proposed by the sponsor (in adults 18 years of age and older).
- b. **Revaccination:** The data provided by the sponsor do not address the safety, or effectiveness of revaccination. This is noted in the package insert. At this time, this reviewer does not recommend any mitigating activity beyond routine pharmacovigilance activities for this potential risk.
- c. **Immunocompromised individuals:** As noted in the label, safety and effectiveness of VAXCHORA have not been established in immunocompromised persons. The potential risk to immunocompromised household contacts (HHC) of vaccinees is unknown. Adverse events in immunocompromised vaccinees and HHCs will be monitored in routine surveillance.
- d. **Pregnancy:** VAXCHORA is not contraindicated in pregnancy, and the indicated age group includes women of child-bearing age. Safety of VAXCHORA in pregnant women has not been established. This reviewer agrees with the sponsor's plan to establish a Pregnancy Registry.
- e. **Shedding:** Fecal shedding of the vaccine strain occurred for at least 7 days after vaccination. No HHCs seroconverted or had an appreciable rise in vibriocidal antibodies. However, the sample size was small (53 vaccinees) and thus there remains a theoretical risk of exposure to HHCs (e.g., pregnant women, immunocompromised persons). This potential transmission is addressed in the package insert, and caution is advised when administering VAXCHORA to individuals with immunocompromised HHCs.

6. Recommendations

- a. Routine pharmacovigilance
This reviewer recommends routine pharmacovigilance.
- b. Pregnancy Registry (PMC)
This reviewer agrees with the sponsor's plan to establish a pregnancy registry to evaluate the safety of VAXCHORA in women who may inadvertently receive the vaccine during pregnancy.
- c. This reviewer does not recommend PMR or Risk Evaluation and Mitigation Strategy (REMS) at this time.