EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2021
EMA/CHMP/444278/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of variations including an extension of indication

Invented name: Vaxchora

Common name: cholera vaccine, oral, live

Procedure No. EMEA/H/C/003876/II/0003/G

Marketing authorisation holder (MAH) Emergent Netherlands B.V.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
CFU	Colony Forming Unit
CI	Confidence Interval
CRF	Case Report Form
CT	Cholera Toxin
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMFI	Geometric Mean Fold Increase
GMO	Genetically Modified organism
GMT	Geometric Mean Titer
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IEP	Immunogenicity Evaluable Population
IPD	Important Protocol Deviation
IRB	Institutional Review Board
kDA	Kilodaltons
LLOQ	Lower Limit Of Quantification
LPS	Lipopolysaccharide
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary of Regulatory Activities
MM	Medical Monitor
mITT	Modified Intent To Treat
ORS	Oral rehydration salts
OSP	anti-O-specific polysaccharide
PBMC	Peripheral blood mononuclear cells
PCO	Placebo Crossover Study
PD	Protocol Deviation
PT	Preferred Term
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
SVA	Serum Vibriocidal Antibody
TCBS	Thiosulfate-citrate-bile salts-sucrose
TMB	Tetramethylbenzidine
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Emergent Netherlands B.V. submitted to the European Medicines Agency on 2 June 2020 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

C.I.6.a (type II): Extension of the indication for the active immunisation against disease caused by Vibrio cholerae serogroup O1, from the currently approved age range "adults and children aged 6 years and older" to "adults and children aged 2 years and older". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.
C.I.4 (type II): Update of section 5.1 of the SmPC to include long-term immunogenicity data supporting Vaxchora effectiveness at generating a protective immune response that persists for 2 years following vaccination; based on the final results from study PXVX-VC-200-006, a randomized, double-blind, placebo-controlled trial aimed to assess the safety and immunogenicity of Vaxchora in children 2 to <18 years of age.
In addition, the MAH took the opportunity to include editorial changes in the SmPC and Annex II.

The group of variations requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0381/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0381/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH sought scientific advice in 2017 (EMA/CHMP/SAWP/713319/2017) where there was one question related to the paediatric clinical trial PXVX-0200-006 regarding the proposed acceptance criteria for the clinical trial endpoints.

The primary objectives by cohort:

- Demonstrate that the seroconversion rate at Day 11 in paediatric subjects is non-inferior to the seroconversion rate at Day 11 in adults between the ages of 18 and 45 years.
- Demonstrate that the seroconversion rate in paediatric subjects is greater than or equal to 70% with 98.3% confidence.

The proposed acceptance criteria for the primary objectives:

- The lower bound of the two-sided 96.7% confidence interval on the difference in seroconversion rates between children and adults must be greater than -10 percentage points.
- The lower bound of the two-sided 98.3% confidence interval on the proportion of vaccinees who seroconvert between Day 1 and Day 11 must equal or exceed 70%.

Furthermore, a sequential testing strategy would be followed in which each of the two primary objectives will be tested first in the 12 - <18 age group, with formal testing of a given objective in the 6 - <12 age group occurring only if the corresponding objective was met in the older children, and formal testing of the 2 - <6 group occurring only if the corresponding objective was met in both the 6- <12 and 12- <18 groups. This sequential strategy and the indicated levels of the confidence intervals ensure that the overall alpha level across both primary objectives and across all three age groups is equal to 0.05.

A summary of the CHMP response was that since efficacy trials are not possible and since there is no established immune correlate of protection, it could be acceptable to support use in children based on comparison of serum vibriocidal antibody (SVA) seroconversion rates with adults. However, the Applicant should attend to the statistical analysis plan for the study and may need to reconsider the sample size.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Bjorg Bolstad

Timetable	Actual dates
Submission date:	2 June 2020
Start of procedure:	20 June 2020
CHMP Rapporteur's preliminary Assessment Report circulated on:	14 August 2020
PRAC Rapporteur's preliminary Assessment Report circulated on:	21 August 2020
PRAC Rapporteur's updated Assessment Report circulated on:	28 August 2020
PRAC RMP advice and assessment overview adopted by PRAC:	4 September 2020
CHMP Rapporteur's and PRAC Rapporteur's Joint Assessment Report circulated on:	10 September 2020
Request for supplementary information (RSI) adopted by the CHMP on:	17 September 2020

Timetable	Actual dates
MAH's responses submitted to the CHMP on:	25 November 2020
CHMP Rapporteur's preliminary Assessment Report on the MAH's responses circulated on:	22 December 2020
PRAC Rapporteur's preliminary Assessment Report on the MAH's responses circulated on:	04 January 2021
PRAC Rapporteur's updated Assessment Report on the MAH's responses circulated on:	n/a
PRAC RMP advice and assessment overview adopted by PRAC:	14 January 2021
CHMP Rapporteur's updated Assessment Report on the MAH's responses circulated on:	n/a
CHMP Opinion:	28 January 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The bacterium *Vibrio cholerae* is the etiological agent of cholera, an acute and potentially fatal toxigenic diarrhoeal illness. Humans are the only host for *V. cholerae*.

O1 vibrios contain an enterotoxin (cholera toxin - CT) which is responsible for causing diarrhoea.

V. cholerae O1 is divided into two biotypes, Classical and El Tor. Both biotypes contain two major serotypes, Inaba and Ogawa. Worldwide, *V. cholerae* O1 El Tor is currently the predominant biotype. (Vaxchora consists of live attenuated *V. cholerae* O1 Classical biotype).

The claimed the therapeutic indication

Vaxchora is indicated for active immunisation against disease caused by Vibrio cholerae serogroup O1 in adults and children aged 2 years and older. This vaccine should be used in accordance with official recommendations.

Epidemiology

Although cholera can occur in Europe e.g. in contaminated shellfish (there have been cases in Italy, and Eastern European countries such as Romania and Ukraine), the large majority of cholera cases are imported from EU nationals travelling to cholera endemic areas. Popular cholera-endemic travel destinations for Europeans include countries in Asia (India, Pakistan, Vietnam, Malaysia, and the

Philippines), Africa (Morocco, Tanzania, Kenya) and the Caribbean (Cuba, Haiti, the Dominican Republic). These include poverty affected regions with poor infrastructure and sanitation.

Cholera epidemics can also arise sporadically, for example due to flooding following natural disasters such as the recent cyclone Idai in Mozambique, Zimbabwe, Malawi and Madagascar in March 2019. European travellers to these cholera affected regions include aid workers and military personnel.

In general, European travellers should be informed about the availability of a cholera vaccine before travelling and should follow good personal hygiene practices and drink only bottled water to prevent or minimise the risk for *Vibrio cholerae* infection when residing in endemic areas.

Globally, in 2017, 34 countries reported 227,391 cases and 5,654 deaths (WHO 2018b) due to cholera. However, due to limited diagnostic capability and other factors contributing to underreporting (Ali 2015), these figures are considered to represent only a small fraction of actual cholera cases and deaths. Correcting for this underreporting, WHO estimates that 1.3-4.0 million cases and 21,000 to 143,000 deaths occur each year around the world (WHO 2018a[1]).

Aetiology and pathogenesis

Contaminated water supplies are the main source of infection, although raw shellfish, uncooked fruits and vegetables and other foods can harbour *V. cholerae* and therefore also present a risk of infection.

Cholera toxin secreted by *V cholerae* O1 confers pathogenicity to the organisms. Injection of as little as 5 µg of purified cholera toxin can elicit severe cholera diarrhoea. The toxin is an 84 kDa polymeric protein consisting of two subunits. The A subunit (28 kDa) is responsible for the biological activity of the toxin (diarrhoea). It is linked by non-covalent interactions to five identical B subunits (11.5 kDa each). The B subunit aids pathogenicity by binding the toxin to receptors on intestinal cell membranes. Since the A subunit is surrounded by B subunits, the latter form the immunologically dominant portion of cholera toxin, and the predominant antitoxin immune response is elicited against the B subunit. The A subunit is the enzymatically active portion of the toxin while the B subunit is the immunologically dominant portion which binds CT to its receptor, the monosialosyl ganglioside GM-1 receptor, on host cell membranes. The A subunit is taken up by cells and leads to hypersecretion of chloride, bicarbonate and water from epithelial cells into the lumen of the small intestine. This results in the characteristic voluminous stool and a rapid loss of body fluid and electrolytes. *V. cholerae* is also shed in high concentrations in the stool of severely ill patients.

Infection with wild-type V. cholerae provides prolonged protective immunity against subsequent infection. Protection against cholera is serogroup specific; hence infection with V. cholerae O1 provides no cross-protection from cholera caused by V. cholerae O139, and vice versa. The immunity is mediated by local mucosal secretory IgA (sIgA) produced in the small intestine, which is the anatomical site of colonization.

Specifically, sIgA targets both the lipopolysaccharide (LPS) coat of the bacterium and the cholera toxin (CT). Antibodies directed against LPS appear to confer more robust protection than those against CT. The anti-LPS response is mostly addressed against the O-specific polysaccharide (OSP) component of the LPS and may mediate protection against V. cholerae via multiple mechanisms including inhibition of motility. The presence of naturally acquired serum vibriocidal antibodies (SVA) correlates with protection against subsequent cholera infection at both the individual and population level. Also, SVA responses are directed primarily against OSP. Recently, plasma antibody responses against OSP have been shown to correlate with protection against cholera in household contacts, strengthening the mechanistic link between the SVA correlate and the OSP-specific mucosal antibodies that directly mediate protection. In addition,

[1] WHO (2018a) Outbreak update – Cholera in Yemen, 19 July 2018. Retrieved from http://www.emro.who.int/pandemic-epidemic-diseases/cholera/outbreak-update-cholera-inyemen-19-july-2018.html

naturally acquired peripheral memory B cell responses against OSP have also been shown to correlate with protection.

Clinical presentation, diagnosis

Clinical symptoms are usually sufficient to diagnose cholera and begin treatment. However, laboratory diagnosis of *V cholerae* in stool specimens is required to confirm the presence of cholera, characterise the organism, and determine its antibiotic sensitivity pattern. The selective medium for identifying *Vibrio species* is thiosulfate-citrate-bile salts-sucrose (TCBS).

Laboratory diagnosis is important in the initial cases, for the purpose of official notification and for monitoring the progress of the disease or epidemic. Rapid diagnostic tests kits for detecting *V cholerae* O1 and O139 are available.

Management

Clinical infection with cholera is often mild but can be severe and life-threatening. Cholera can be successfully treated with prompt and adequate replacement of lost fluid and electrolytes. Individuals with mild and moderate cholera can usually be treated with oral rehydration salts (ORS), pre-packaged mixtures of glucose and salts mixed with safe drinking water and orally administered.

Approximately 5 percent of infected persons will have severe disease (cholera gravis), characterized by profuse watery diarrhoea, vomiting and leg cramps. In these people, rapid loss of body fluids leads to dehydration and pre-renal azotaemia. These individuals typically require intravenous fluid replacement. Without treatment, death can occur within hours and mortality rates may exceed 70%. Prompt rehydration dramatically reduces cholera mortality; fewer than 1% of cholera patients may die with appropriate hydration. Antibiotics may shorten the course of the diarrhoea and/or diminish the severity of the illness (i.e. the total diarrhoeal stool volume), but do not substitute for rapid rehydration.

In Europe an inactivated cholera vaccine is available for travellers over 2 years of age (Dukoral). It was approved in Europe in 2004. It contains inactivated *V. cholerae* Classical and El Tor biotypes and the Inaba and Ogawa serotypes for each biotype. In addition, recombinant cholera toxin B subunit is also included from *V. cholerae* O1 Classical Biotype, serotype Inaba.

2.1.2. About the product

Vaxchora (cholera vaccine, live), is a live attenuated bacterial vaccine containing the CVD 103-HgR vaccine strain of *Vibrio cholerae* serogroup O1, biotype classical, serotype Inaba.

Vaxchora is administered orally where the proposed mechanism of action is to induce a broadly protective mucosal immune response similar to that induced by natural *V. cholerae* infection. This response includes induction of antigen-specific mucosal antibodies and memory B cells. Immune responses to Vaxchora can be reliably assessed by the measurement of serum vibriocidal antibodies (SVA).

The product was approved in 2020 for the following indication:

Vaxchora is indicated for active immunisation against disease caused by Vibrio cholerae serogroup O1 in adults and children aged 6 years and older. This vaccine should be used in accordance with official recommendations.

This approval was based on five randomised, double-blind, placebo-controlled clinical trials conducted with Vaxchora in healthy volunteers (Table 1). All trials used a single oral dose of Vaxchora. This

development program was designed as a standalone program to support the licensure of Vaxchora using the combination of a human challenge trial and an immunologic correlate of protection, without a field efficacy trial. Protective efficacy data against cholera challenge, clinical lot consistency, and non-inferiority of the immune response in both older adults and children aged 6 to <18 years, coupled with a safety data in 3563 vaccine recipients supported proposed indication.

Table 1: Listing of clinical studies

Type of Trial	Trial No[a].	Location of Trial Report	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	Trial Status; Type of Report
Phase 1	PXVX-VC-200-002	Synopsis 5.3.5.1 Report	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	4.43 x 10^8 CFU/dose; oral	66 55 vaccine, 11 placebo *(55 vaccine, 11 placebo)*	Healthy Subjects	Single dose	Complete; full report
Challenge Phase 3	PXVX-VC-200-003	Synopsis 5.3.5.1 Report	Demonstrate protection from live cholera challenge	Randomized, double-blind, placebo-controlled	5 x 10^8 CFU/dose; oral	197 95 vaccine, 102 placebo *(95 vaccine, 102 placebo)*	Healthy Subjects	Single dose	Complete; full report
Lot Consistency Phase 3	PXVX-VC-200-004	Synopsis 5.3.5.1 Report	Demonstrate clinical lot consistency	Randomized, double-blind, placebo-controlled	1 x 10^9 CFU/dose; oral	3146 2795 vaccine, 351 placebo *(2789 vaccine, 350 placebo)*	Healthy Subjects	Single dose	Complete; full report
Older Adults Phase 3	PXVX-VC-200-005	Synopsis 5.3.5.1 Report	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	1 x 10^9 CFU/dose; oral	398 299 vaccine, 99 placebo *(296 vaccine, 99 placebo)*	Healthy Subjects	Single dose	Complete; full report
Paediatric Phase 4	PXVX-VC-200-006	Synopsis 5.3.5.1 Report	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	1 x 10^9 CFU/dose; oral	550 471 vaccine, 79 placebo *(468 vaccine, 75 placebo)*	Healthy Subjects	Single dose	Complete; full report

[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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The type II variation C.I.6.a in this application seeks to extend the indication to children and adults over the age of two years. Support for this indication is based on data from a single paediatric phase 4 clinical trial (PXVX-VC-200-006). At the time of approval, only data for the age groups above 6 years were available for evaluation. The clinical **study PXVX-VC-200-006** has since been completed allowing for the evaluation of data for the paediatric population aged 2-6 years (Table 1). This was a randomised, placebo-controlled, double-blind, single cross-over design with two treatment groups across three cohorts. Seroconversion rates in children aged 2 to <6 years in the study PXVX-VC-200-006 were compared to healthy adults 18 to 45 years from the study PXVX-VC-200-004.

The MAH sought scientific advice in 2017 (EMA/CHMP/SAWP/713319/2017) where there was one question related to the paediatric clinical trial PXVX-0200-006 regarding the proposed acceptance criteria for the clinical trial endpoints. In general, the MAH has followed the Scientific Advice obtained.

The study that forms the basis for the application to extend the indication, PXVX-VC-200-006, is contained in the agreed Paediatric Investigation Plan (P/0381/2018).

2.1.4. General comments on compliance with GCP

According to the MAH, the paediatric clinical trial PXVX-200-006 was carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Part 50, 54, 56 and 312 (for studies conducted in the U.S. only), the principles enunciated in the latest version of The Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (ICH E6).

2.2. Quality aspects

The vaccine Drug Product packet containing lactose and lyophilized live attenuated *V.cholerae* strain CVD 103-HgR bacteria is co-packaged with the buffer packet (sodium bicarbonate/sodium carbonate, ascorbic acid and dried lactose). The reconstitution procedure begins with removing the carton containing the vaccine and buffer packet from the refrigerator and reconstituting the contents of the buffer packet in 100mL of non-carbonated bottled spring or purified bottled water. The resulting solution is stirred until the powder is dissolved, after which the contents of the vaccine packet are added and mixed. The solution is then administered orally. This procedure helps to ensure that the vaccine, when administered, meets the potency acceptance criterion. Steps in the vaccine reconstitution procedure that potentially affect vaccine potency were identified, and experiments were performed to institute acceptable vaccine preparation conditions. The Global manufacturing of the active and buffer components have been transferred and scaled-up at Emergent BioSolutions Berna GmbH (Thoerishaus, Switzerland). No impact on the changes with the vaccine in regard to its compatibility and/or reconstitution procedures with the buffer were indicated. Both the active and buffer component are stored at 2ºC to 8ºC. The historical data for the buffer preparation remains still relevant since no changes were essentially made with the buffer component.

Compatibility of Vaxchora with stevia and sucrose

For the Phase 4 paediatric study (PXVX-VC-200-006), specifically for the youngest children between the ages of 2 to < 6 years old, the buffer was reconstituted in 100 mL of bottled water and then 50 mL was discarded prior to adding the contents of the vaccine sachet. Stevia or sucrose may also have been added to improve taste.

Orochol, the precursor to the Vaxchora vaccine, contained aspartame as a sweetener and lower volume of 50 mL was used in children aged 2 to 6 years in one study. A reduced concentration of buffer is justified for use in the 2 to <6 age cohort in the Emergent BioSolutions paediatric study based on the naturally occurring higher gastric pH in children. This pharmaceutical development study was performed to test the stability of the vaccine in different volumes of reconstituted Vaxchora (in buffer) and the compatibility of the vaccine with the sweetener stevia (various manufacturing formulations) or sucrose. Potency (Table 2 and Table 3), pH, and buffer capacity (Table 4) analyses were performed, where appropriate.

Table 2. Potency Results for Reconstitution in Different Volumes and Stevia (PureVia)

DP Lot#	DP Stability Titer	Buffer Reconstitution Volume	CFU/dose Post Reconstitution (Spec: 4×10^8 to 2×10^9)		
			T_0	15 min	30 min
6000001	8.43×10^8	150 mL	6.32×10^8	4.58×10^8	4.12×10^8
		125 mL	7.58×10^8	8.01×10^8	7.44×10^8
		75 mL	6.23×10^8	7.84×10^8	7.21×10^8
		50 mL	4.56×10^8	3.52×10^8	2.10×10^{8a}
6000003	4.51×10^8	100 mL (Discard 50 mL)	5.49×10^8	5.30×10^8	4.98×10^8
		200 mL (Discard 100 mL)	4.88×10^8	4.52×10^8	3.87×10^8
		100 mL + stevia (PureVia®)	6.94×10^8	6.83×10^8	6.27×10^8
		100 mL (Discard 50 mL) + stevia (PureVia®)	4.94×10^8	4.25×10^8	3.60×10^8
6000016	1.06×10^9		1.16×10^9	1.12×10^9	1.09×10^9
6000014	1.18×10^9		5.62×10^8	5.59×10^8	5.12×10^8
[a] Below specification					

The vaccine potency remains within specification following reconstitution at different volumes and in the presence of Stevia (PureVia). Vaccine reconstituted in 50 mL of water is the only condition that falls below the specification and may be due to osmotic shock since the buffer and vaccine components are twice as concentrated as the adult formulation for Vaxchora.

Additional experiments were performed with Vaxchora (Lot 5003076 which was > 12months old at the time of the study), looking at different brands of stevia and also sucrose. Results are presented in Table 3. The results confirm that any brand of stevia (powdered or crystalline forms) or sucrose can be used to sweeten Vaxchora prior to administration.

Table 3. Potency Results for Reconstitution of Vaxchora with Sucrose or Various Brand Stevia Sweeteners

Sample	Replicate	CFU/dose Post Reconstitution (Spec: 4×10^8 to 2×10^9)		
		T_0	15 min	30 min
Sucrose	1	7.18×10^8	5.14×10^8	6.35×10^8
	2	7.32×10^8	6.92×10^8	5.90×10^8
Truvia®	1	7.90×10^8	7.34×10^8	6.02×10^8
	2	6.27×10^8	5.20×10^8	4.77×10^8
Splenda Naturals®	1	6.91×10^8	5.99×10^8	5.84×10^8
	2	7.30×10^8	5.91×10^8	5.97×10^8
Sweetleaf®	1	6.74×10^8	6.22×10^8	5.55×10^8
	2	6.95×10^8	6.20×10^8	5.74×10^8
Sweet Additions®	1	7.40×10^8	6.26×10^8	5.96×10^8
	2	7.57×10^8	6.40×10^8	5.67×10^8

Table 4. Results of pH and Buffer Capacity after Reconstitution of Buffer at Different Volumes and with Stevia (PureVia®)

Variable	Expt. #	Buffer Lot	Buffer Reconstitution Volume (mL)	Buffer (g)	pH (Spec 6.9 ± 0.2)	Buffer Capacity > 21.0 mL, 1M HCl neutralised
Volume	1	6000004	100	4.776	7.00	25.1
	2		75	4.549	7.02	25.0
	3		50	4.495	7.16[a]	24.3
	4		100 (Discard 50 mL)	4.438	7.02	12.2[a]
	5	P720.550-5HA03	200 (Discard 100 mL)	4.427	7.01	12.2[a]
Flavouring	6	P720.550-5HA03	100 (+stevia, 1g)	4.482	7.03	25.9
[a] Below Specification						

Experiments 4 and 5 in which buffer is below specification can be explained since half of the buffer has been removed with the discarded solution. The high starting pH in experiment 3 is likely due to the decreased capacity for carbonic acid, which is created when CO_2 from the Vaxchora bicarbonate buffer is dissolved in water. Carbonic acid (H_2CO_3) makes carbonated solutions acidic but exists in small quantities and will continue to react forming H_2O and CO_2 ($CO_2 + H_2O \leftrightarrow H_2CO_3$). As in experiment 3, less water will have a lower capacity for carbonic acid, and the solution will be less acidic. Stevia did not affect the starting pH or buffer capacity.

Results showed that the vaccine is stable for at least 30 minutes under the following reconstitution scheme depicted in Figure 1. The resulting dose is half the normal volume (50 mL vs 100 mL) and the stevia or sucrose sweetener will make the flavour more appealing to young children and make the vaccine easier to take.

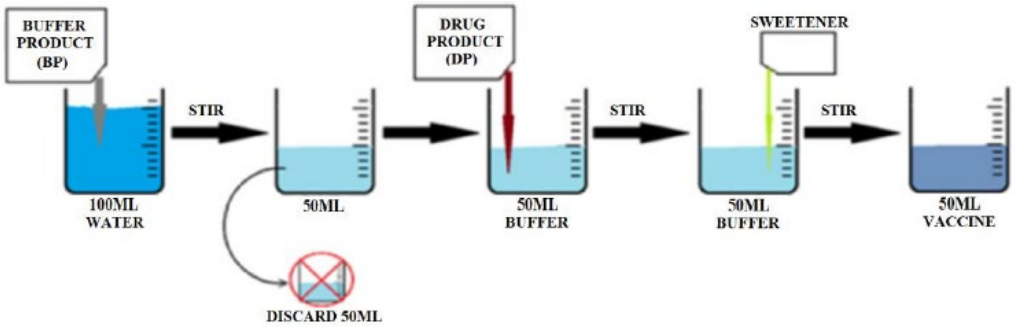

Figure 1. Reconstitution Scheme for Paediatrics, Including Stevia

2.2.1. Discussion on quality aspects

The proposed update in module 3 is for an additional reconstitution step for paediatric patients between the ages of 2 to < 6 years old. Following reconstitution of the buffer in 100 mL of bottled water, 50 mL of the solution is discarded prior to adding the contents of the DP sachet. Addition of a sweetener can also be performed to improve taste. To demonstrate compatibility of the additional reconstitution steps, a development study testing the stability of the vaccine in different volumes of reconstituted Vaxchora (in buffer) and the of the vaccine with the sweetener stevia or sucrose, is presented.

The stability study demonstrates stability of product potency when the buffer is reconstituted in at a range of 75ml to 150ml, and pH when the buffer is reconstituted in at a range of 75ml to 100ml. The

study also demonstrates product stability when half the reconstituted buffer is discarded with or without stevia sweeteners. The Applicant has provided additional data indicating the reconstitution protocol is sufficiently robust for self-administration, with an adequate dose achieved when reconstituted in as little as 10 ml buffer, and up to 4g sucrose. The relevant batch data is provided.

2.2.2. Conclusion on quality aspects

The editorial changes in module 3 are acceptable.
Further, the updated instructions in the Package Leaflet on how to prepare the vaccine are agreed. These updates concern the optional addition of a sweetener and the advice, for children age 2 to <6 years only, to pour away and discard half of the buffer solution before adding the contents of the DP sachet.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

No risk to the environment was identified. However, since Vaxchora is a GMO, the waste should be disposed of according to standard procedures for medical waste in order to minimize any potential risks to the environment.

2.3.1. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is acceptable to the CHMP.

2.3.2. Conclusion on the non-clinical aspects

The updated data submitted in this application, do not lead to a significant increase in environmental exposure further to the use of CVD 103-HgR. However, since Vaxchora is a GMO, the waste should be disposed of according to standard procedures for medical waste in order to minimize any potential risks to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trial in children aged 2-<18 years, (PXVX-VC-200-006) was performed in accordance with GCP as claimed by the MAH. The seroconversion rate observed in the PXVX-VC-200-006 was compared to that of the lot consistency clinical study in adults (18-45 years), PXVX-VC-200-004. This latter study was also carried out in accordance with GCP as claimed by the MAH (Table 5).

2.4.2. Pharmacokinetics

Pharmacokinetics studies are not required for an oral vaccine which is not absorbed systemically, such as Vaxchora (EMEA/CHMP/VWP/164653). No pharmacokinetic studies are included in this application for a type II variation.

2.4.3. Pharmacodynamics

According to the Guideline on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/2005), pharmacodynamic studies for vaccines are essentially comprised of the immunogenicity studies that characterise immune responses to the vaccine. This section will therefore focus on the bioanalytical methods used for evaluating the immunogenicity endpoints in the Vaxchora clinical trials.

The serum vibriocidal antibody assay (SVA)

The serum vibriocidal antibody (SVA) assays for all Classical Inaba; El Tor Inaba, Classical Ogawa and El Tor Ogawa respectively, were used to measure vibriocidal antibody levels in serum. Briefly, serial dilutions of serum were mixed and incubated at 37°C with equal volumes of standardized *V. cholerae* (including guinea pig complement). Titres were expressed as the reciprocal of the dilution of the most diluted sample associated with bacterial growth of 75% or less compared with the negative control. To achieve validation of the assay, intra- and inter-assay precision, accuracy/dilutability, specificity, sample stability, and robustness were evaluated.

The cholera toxin (CT) ELISA assay

The CT ELISA assay measured serum antibodies against cholera toxin. Briefly, samples were serially diluted from 1:200 to 1:12800 in duplicate. Following incubation on CT coated wells, antibodies to CT are detected with a peroxidase labelled goat anti-human IgG and a tetramethylbenzidine (TMB) substrate. The titre is equal to the reciprocal of the dilution of the least diluted sample with an OD_{450} greater than or equal to 0.2. To achieve validation of the assay, intra and inter-assay precision, accuracy/dilutability, specificity, sample stability, and robustness were evaluated.

Memory B-cells specific for CT and LPS, Inaba strain ELISPOT assay

Percentages of memory B-cells that are specific for *V. cholerae* toxin B (CT) and lipopolysaccharide (LPS, Inaba strain) in the peripheral blood mononuclear cells (PBMC) of clinical trial subjects were measured using an enzyme-linked immunospot (ELISPOT) assay.

Spots appearing in assay wells corresponding to B-cells within a PBMC sample that secreted IgG or IgA antibody specific for CT or LPS were enumerated. PBMC isolated from blood samples collected from each subject are cryopreserved in liquid nitrogen and then batch tested in the same experiment.

The ELISPOT assay was conducted at the site of the Applicant. Since the memory B cell evaluation was only an exploratory endpoint in the clinical studies, this assay was qualified rather than validated.

O-specific polysaccharide antibody ELISA assay

A research study was conducted post-hoc using samples from the PXVX-VC-200-003 trial (challenge study), using an ELISA assay to detect different anti-O-specific polysaccharide (OSP) antibody subclasses directed against the lipopolysaccharide of *V. cholerae* serogroup O1. The seroconversion threshold was

defined as a >1.5 fold increase from baseline. The findings from this study were included and discussed by the sponsor based on a publication by Islam et al. (2018[2]).

2.4.4. Discussion on clinical pharmacology

Vaxchora is a live attenuated oral vaccine. The mode of administration therefore corresponds to the natural mode of infection. The bacterium *Vibrio cholerae* is the etiological agent of cholera, an acute and potentially fatal toxigenic diarrhoeal illness. Humans are the only host for *V. cholerae*. The vibrio predominantly associated with epidemic cholera is *V. cholera* serogroup O1. The mode of administration for Vaxchora corresponds to the natural mode of transmission with the aim of providing protection at the site of infection.

Humoral immunity, induced by *V. cholerae* infection, specifically, sIgA targets both the lipopolysaccharide (LPS) coat of the bacterium and the cholera toxin (CT). Antibodies directed against LPS appear to confer more robust protection than those against CT (Apter 1993[3]). The anti-LPS response is focused on the O-specific polysaccharide (OSP) (Wang 1998[4], Villeneuve 2000[5], Johnson 2012[6]). The serum vibriocidal antibody (SVA) assay and measures lysis of standardised *V. cholera* (according to serotype). SVA seroconversion was pre-specified in the protocol as a $\geq$4 fold increase over baseline.

All analyses of immunogenicity are based on samples taken from peripheral blood (serum and B-cells).

Immunogenicity analyses used assays that were validated and carried out at a central laboratory for determining serum vibriocidal antibodies (SVA) and anti-cholera toxin (CT) antibodies. The only assay that was not validated was the ELISPOT assay to measure memory B-cells, which was carried out In House by the Sponsor.

The serum vibriocidal antibodies correspond to a simple means of assessing the induction of functional vibriocidal antibodies. SVA measurements in serum may not adequately reflect immune responses produced locally in the mucosa. Assessment of the duration of immunity was limited to detecting B-cell memory responses up to 6 months post-vaccination. Since the assay used was not validated, findings from this assay are considered exploratory.

2.4.5. Conclusions on clinical pharmacology

Serum vibriocidal antibodies (SVA) were detected using a validated functional assay that involved complement-mediated bacteriolysis. The SVA assay detected mainly IgM antibodies, which correspond mainly to *de novo* immune responses. Detection of anti-CT antibodies used a validated ELISA assay specific for detecting IgG antibodies, which are usually induced approximately 2 weeks after exposure to antigen. Detection of memory B-cells involved a qualified but not validated ELISPOT assay using frozen

[2] Islam, K. et al. (2018). Anti-O-specific polysaccharide (OSP) immune responses following vaccination with oral cholera vaccine CVD 103-HgR correlate with protection against cholera after infection with wild-type Vibrio cholerae O1 El Tor Inaba in North American volunteers. PLoS neglected tropical diseases, 12(4), e0006376.

[3] Apter, FM et al. (1993) Analysis of the roles of antilipopolysaccharide and anti-cholera toxin immunoglobulin A (IgA) antibodies in protection against Vibrio cholerae and cholera toxin by use of monoclonal IgA antibodies in vivo. Infection and immunity, 61(12), 5279-5285.

[4] Wang, J, et al. (1998). On the antigenic determinants of the lipopolysaccharides of Vibrio cholerae O: 1, serotypes Ogawa and Inaba. Journal of Biological Chemistry, 273(5), 2777-2783.

[5] Villeneuve, S, et al. (2000). Crystal structure of an anti-carbohydrate antibody directed against Vibrio cholerae O1 in complex with antigen: molecular basis for serotype specificity. Proceedings of the National Academy of Sciences, 97(15), 8433-8438.

[6] Johnson, RA et al. (2012). Comparison of immune responses to the O-specific polysaccharide and lipopolysaccharide of Vibrio cholerae O1 in Bangladeshi adult patients with cholera. Clinical and Vaccine Immunology, CVI-00321.

peripheral blood lymphocytes. No criteria for cell recovery and viability were used, however, the viability of the cells was acceptable.

Based on the acceptance of the original MAA, the omission of non-clinical and clinical pharmacology studies is considered acceptable.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose response studies have been carried out in this application for a type II variation.

2.5.2. Main study

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

The randomised, double-blind, placebo-controlled PXVX-VC-200-006 trial was designed to evaluate the immunogenicity of Vaxchora in children aged ≥12 to <18 (Cohort 1); ≥6 to <12 (Cohort 2); and 2 to <6 years (Cohort 3), demonstrate a seroconversion rate of greater than 70%, and demonstrate non-inferiority to the immune response seen in adults using a 10% margin. Vaxchora is already approved for children over 6 years of age. The assessment of this application focused on Cohort 3, and the overall study population. Findings for Cohort 3 were evaluated also in relation to the findings for Cohorts 1 and 2.

Immunogenicity was assessed in all cohorts by analysing classical Inaba SVA responses on Day 1 and post-vaccination on Days 11 and 29. Subjects in all cohorts were monitored out to Day 181, at which point, placebo subjects had an option to crossover to the Vaxchora treatment group (Placebo Crossover [PCO]) for an additional 6 months.

Cohort 1 subjects were also assessed for immune response at Days 91 and 181. A subset of Cohort 1 subjects was also assessed for a long-term study of classical Inaba SVA responses at Days 365, 547 and 730.

To demonstrate non-inferiority in the immune response of paediatrics compared to adults, subjects from the PXVX-VC-200-004 lot consistency study were selected as the bridging population (Table 5). This choice was justified because the lot consistency study had a large sample size (n=2687) and afforded high power to demonstrate non-inferiority. The non-inferiority criterion for bridging required that the lower bound of the two-sided 96.7% CI on the difference in the seroconversion rate between paediatrics and adults 18 - 45 years must be greater than -10 percentage points.

Table 5: Clinical studies involved in this variation

Trial No.	Objectives	Trial Design	Route of Admin.	Number of subjects	Subjects	Duration of Treatment
PXVX-VC-200-004	Demonstrate clinical lot consistency (Phase 3)	Randomised Double blind Placebo-controlled	1 x 10^9 CFU/dose; oral	3146 2795 vaccine, 351 placebo *(2789 vaccine, 350 placebo)**	Healthy	Single dose
PXVX-VC-200-006	Safety and Immunogenicity (Phase 4)	Randomised, Double blind Placebo-controlled	1 x 10^9 CFU/dose; oral	550 471 vaccine, 79 placebo *(468 vaccine, 75 placebo)**	Healthy	Single dose

*Italics show number of subjects who actually received vaccine or placebo. (Table by Assessor, modified from Table 1 (Section 5.2.1 in the dossier)).

This same bridging population had been used previously for the non-inferiority analysis to older adults 46 - 64 years (Study PXVX-VC-200-005).

Methods

The study started with the first informed consent form signed on the 21 July 2017. The study concluded with the last patient last visit on the 10 September 2019.

The study was conducted using a randomised, placebo-controlled, double-blind, single crossover design with two treatment groups across 3 cohorts. The study included a long-term follow-up through to Day 750 (Figure 2).

This study consisted of a screening period of 30 days. Eligible subjects were randomised to the Vaxchora or Placebo treatment groups in a 6:1 ratio. A single-dose vaccination was administered orally in each group on Day 1. To maintain blinding, subjects were asked not to discuss the taste of the administered treatment with other study participants.

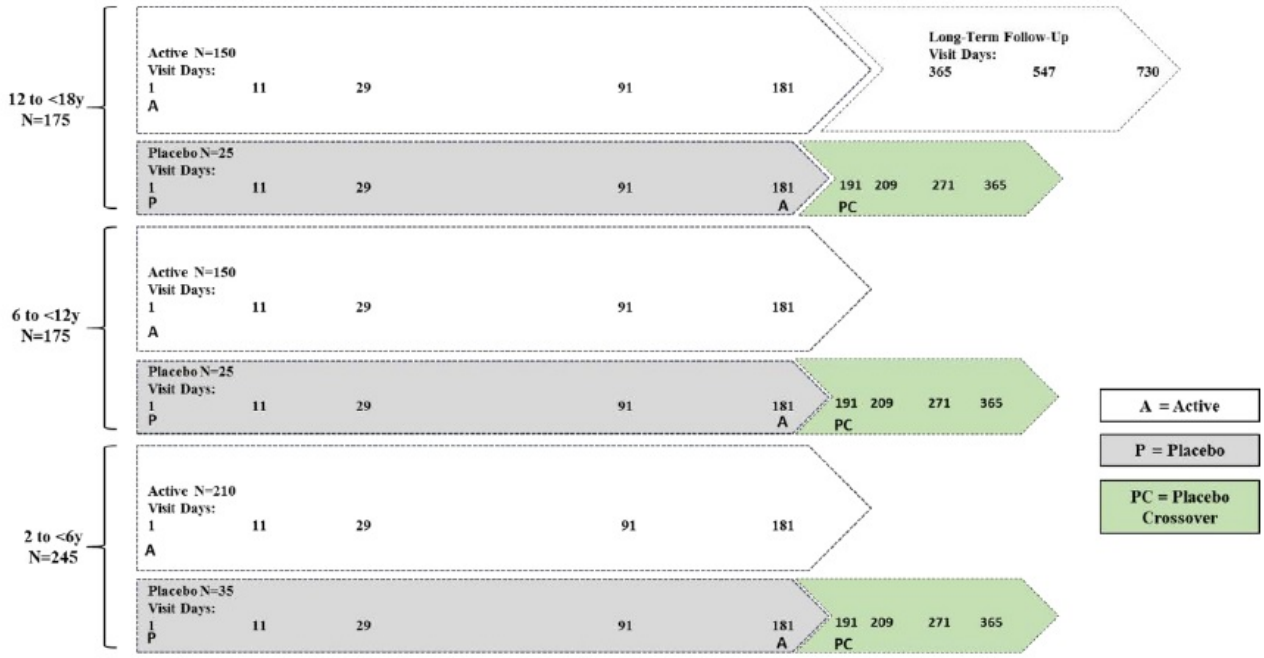

Figure 2: Study Design

There was an observation period from Day 1 to Day 29, and a follow-up period through Day 181. Following this period, subjects that opted for the placebo-crossover group at Day 181 were monitored through Day 365 (approximately 6 months post-Vaxchora vaccination. The planned patient numbers to receive Vaxchora including cross-over subjects is shown in Table 6. Additionally, subjects in Cohort 1 that opted for the sub-study, were monitored out to Day 730.

Table 6: PXVXVC-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
		Placebo-Crossover	25	Placebo	VAXCHORA
2	6 to <12	Active	150	VAXCHORA	None
		Placebo-Crossover	25	Placebo	VAXCHORA
3	2 to <6	Active	210	VAXCHORA	None
		Placebo-Crossover	35	Placebo	VAXCHORA
		Total	**595**		

The primary immunogenicity comparator group for all 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 (See Table 5).

Study participants

The healthy male and female participants aged 2 to <18 were selected from the general population and represent an under-researched age group with respect to the safety and immunogenicity of Vaxchora. This choice of population enabled a robust assessment of the immunogenicity of Vaxchora in a population that may respond differently to vaccination when compared to healthy adults.

Inclusion criteria:

1. Male or female.
2. Age 2 to <18 years of age on Day 1.
3. In general, good health.
4. Using an acceptable method of contraception through Day 29 (for females of childbearing potential).
5. Able and willing to provide informed consent for study participation.
6. Primary caregiver is able and willing to provide informed consent for study participation.

Exclusion criteria:

1. Current acute gastrointestinal illness or loose stools within 3 days of Day 1 visit.
2. Current acute febrile illness.
3. History of cholera infection.
4. Pregnant or nursing, or who plan to become pregnant or nurse during the study (for females of childbearing potential).
5. History of cholera vaccination.
6. History of severe allergic reaction (i.e. anaphylaxis) to any component of Vaxchora.
7. Congenital or acquired immunodeficiency.
8. Any other condition that, in the opinion of the Investigator, creates an unacceptable risk to the subject.
9. Any other condition that, in the opinion of the Investigator, will interfere with the conduct of the study or the validity of the data.

10. Duration of >2 weeks of abnormal stool pattern, defined as <3 stools per week or >2 stools per day in the past 6 months.
11. Regular use of laxatives in the past 6 months.
12. History of enterotoxigenic *E. coli* infection.
13. Travel to a cholera-endemic area in the previous 5 years.
14. Received or plans to receive the following from 14 days prior to the study vaccination through 11 days after vaccination:
    - Any other licensed vaccines
    - Antibiotics or chloroquine or any other investigational agents.
15. Received or plans to receive any other investigational agent throughout the main study (Day 1 through Day 181).

Treatments

Study subjects were randomised to receive either Vaxchora or Placebo (saline solution). These treatments were to be taken orally and were administered by the site's designated unblinded dose administrator, following reconstitution. The subject or healthcare provider had the option to add PureVia Stevia Sweetener to the oral solution. The use of sweetener was intended to increase the palatability of the oral solution for the paediatric study subjects and to increase the likelihood that each subject would consume the full dose. Subjects were to take no food or drink for 60 minutes before or after vaccine administration. It was intended that the study product was to be administered within 15 minutes of reconstitution by the unblinded study staff member.

- Vaxchora:

Vaxchora was provided as two packets containing a single dose of buffer and a single dose of active component. These packets were then reconstituted in purified bottled water and stirred for 30 seconds. After reconstitution, Vaxchora contained 4×10^8 to 2×10^9 colony forming units (CFU) of live attenuated *V. cholerae* CVD 103-HgR with lyophilisation and bulking reagents.

Vaxchora has been formulated using a lyophilisation buffer containing excipients to protect the drug substance during the lyophilisation process, while also helping with product stability. The anhydrous lactose was added during the blending process as a bulking agent.

For participants 6 years and older, Vaxchora was reconstituted in 100 mL buffer solution. For children 2-<6 years, Vaxchora was reconstituted in 50 mL of the buffer in an opaque cup. The subject or healthcare provider had the option to add 1g sucrose or PureVia Stevia Sweetener to the oral solution to potentially improve palatability. For Cohort 3 only half of the buffer (50 mL) was used for vaccine dissolution.

- Placebo (Oral Saline Solution)

The placebo for Vaxchora was provided as a normal (0.9%) oral saline solution.

Objectives

Primary immunogenicity objectives

- To demonstrate that the seroconversion rate at Day 11 in paediatric subjects is non-inferior to the seroconversion rate at Day 11 in adults between the ages of 18 and 45 years.

- To demonstrate that the seroconversion rate in paediatric subjects is greater than or equal to 70% with 98.3% confidence.

Secondary Immunogenicity objective: to evaluate the immunogenicity of Vaxchora in Cohort 1, 2 and 3.

Exploratory immunogenicity objective: to explore memory B cell response to Vaxchora vaccination at each time point in Cohort 1.

Primary safety objective: to evaluate the safety and tolerability of Vaxchora

Palatability objective: to evaluate the palatability of Vaxchora

Acceptability objective: to evaluate the acceptability of Vaxchora

Outcomes/endpoints

The purpose of the Phase 4 Study was to assess the safety, tolerability, and immunogenicity of Vaxchora in paediatric subjects (2 to <18 years of age).

Primary immunogenicity objectives

The primary immunogenicity objectives were as follows:

- To demonstrate that the seroconversion rate at Day 11 in paediatric subjects is non-inferior to the seroconversion rate at Day 11 in adults between the ages of 18 and 45 years.
- To demonstrate that the seroconversion rate in paediatric subjects is greater than or equal to 70% with 98.3% confidence.

The primary immunogenicity objectives used the following endpoint:

- Seroconversion Rate at Day 11 in each of the 3 age cohorts: The proportion of subjects achieving seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Day 11 following one dose of Vaxchora, defined as a 4-fold or greater rise over baseline Day 1 SVA titer. This was compared to the seroconversion rate for subjects aged 18 to 45 years who participated in the lot consistency study PXVX-VC-200-004 to assess non-inferiority.

Secondary Immunogenicity Objectives

The secondary immunogenicity objective was to evaluate the immunogenicity of Vaxchora in Cohort 1 using the following endpoints:

- Seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Days 29, 91, and 181 for all subjects.
- Seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Days 365, 547 and 730 for all subjects participating in the optional sub-study.

Another secondary immunogenicity objective was to evaluate the immunogenicity of Vaxchora in Cohort 2 and 3 using the following endpoint:

- Seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Day 29 following one dose of Vaxchora.

Exploratory Immunogenicity Objective

The exploratory immunogenicity objective was to explore memory B cell response to Vaxchora vaccination at each time point in Cohort 1 using the following endpoint:

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

Safety Objectives

The primary safety objective was to evaluate the safety and tolerability of Vaxchora using the following endpoints:

- Solicited Adverse Events (AE) through Day 8: abdominal pain, headache, lack of appetite, tiredness, diarrhea, nausea, vomiting and fever, by age cohort and overall.
- Unsolicited AEs through Day 29, by age cohort and overall.
- Serious Adverse Events (SAE) through Day 181, by age cohort and overall.
- For Placebo-Crossover subjects, solicited AEs were evaluated from Day 181 through Day 188; unsolicited AEs from Day 181 through Day 209; and SAEs from Day 181 through Day 365.
- For Sub-Study subjects, SAEs were evaluated through Day 730.

Palatability Objective

The primary objective was to evaluate the palatability of Vaxchora using the following endpoints:

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

Acceptability Objective

The primary objective was to evaluate the acceptability of Vaxchora using the following endpoint:

The percent of subjects in each age cohort able to complete the dosing according to protocol. This was defined as the entire volume of dose being consumed within 15 mins after reconstitution.

Sample size

Assuming that the true seroconversion rate among 12 to <18-year-olds is 92.4% or higher, the sample size of 143 evaluable vaccinees for that age cohort afforded 93.3% power to demonstrate that the seroconversion rate within the group was non-inferior to the 94% rate observed in the 2687 adult subjects assessed in the PaxVax lot-consistency trial, PXVX-VC-200-004.

This sample size allowed for up to 5% inevaluable for immunogenicity (30% inevaluable for cohort 3), and, as defined in the alpha-spending strategy, non-inferiority implied that the lower bound on the two-sided 96.7% confidence interval of the seroconversion rate among 12 to <18-year-olds was within 10 percentage points of the adult rate. Making similar assumptions about the true seroconversion rates in the other two paediatric age cohorts, and assuming that the rates in the three age cohorts were independent of one another, the overall power for demonstrating the non-inferiority of all three age cohorts was $(93.3\%)^3 = 81\%$.

To meet the other primary objective, the lower bound of the two-sided 98.3% confidence interval on the cohort-specific seroconversion rate had to equal or exceed 70%. Under the same assumptions as above –

in particular, assuming the true seroconversion rate within an age cohort was at least 92.4% – 143 evaluable vaccinees provided greater than 99.9% power to establish that the lower bound on the cohort-specific rate was at least 70%. Power was still greater than 99.9% when requiring the lower bound on all three cohorts to be 70% or greater.

The overall power of meeting both primary objectives in all three age cohorts could be approximated by multiplying the power of meeting the non-inferiority objective by the power of meeting the 70% lower bound objective: 81% x 99.9% ≈ 81%. Note that the calculations above relied on the assumption that seroconversion rate in one cohort was completely independent of the rate in another. Since that assumption was conservative, it was likely that the true power of the trial was higher than 81%. Given a total of 510 subjects receive Vaxchora, there is a 99% chance that an uncommon AE – one expected to occur in only 1% of vaccinees - would observed at least once during the trial.

Randomisation

In each cohort, subjects was randomised in a 6:1 ratio to the Active treatment group or the Placebo Crossover group. The Active treatment group received VAXCHORA on Day 1 and the Placebo Crossover group received placebo on Day 1. The Investigator confirmed and documented the eligibility of each subject immediately prior to randomisation. Subjects were considered enrolled once a randomisation number has been assigned. Users would enroll each subject by assigning and entering a Subject ID # in the Electronic Data Collection (EDC) system. The user would access the integrated randomisation function within the EDC system to randomize the subject to one of the treatment arms. Subjects were randomised at up to 30 clinical research sites. The assigned treatment appeared only on the randomisation schedule that was delivered to unblinded study personnel. Blinded study personnel printed the randomisation number for each subject from the EDC randomisation form and took it to the unblinded personnel, who matched the randomisation number to the randomisation schedule and dispense the associated treatment.

The number and percent of subjects randomized was summarized by site for each age cohort (including all ages combined), by treatment group and across treatment groups within the age cohort. The denominator for this calculation was be the total number of randomized subjects. A summary of subject disposition was provided by age cohort, treatment group and overall. This summary presented the number of subjects who completed through Day 181, who discontinued from the study early and the primary reason for discontinuing the study early. Similar summaries were provided for the placebo crossover subjects who chose to receive Vaxchora and also for subjects included in the long-term follow-up sub-study. No p-values or inferences based upon comparison of disposition in the treatments were generated. A data listing of reasons for early study discontinuation for the randomized population was provided as well as a listing of reasons for screen failure.

Blinding (masking)

The study was conducted as a double-blind study through Day 181, where neither the sponsor, the statistical team, study volunteer subjects, nor clinical site personnel (except for the unblinded staff), knew the subjects' treatment assignment. To maintain blinding, subjects were asked not to discuss the taste of the administered treatment with other study participants. Subjects, clinical site personnel, and Investigators remained blinded until a subject had completed their Day 181 visit at which point the subject was unblinded individually and their active/placebo status was recorded in the EDC

Statistical methods

Adjustment for Multiplicity and control of Type I-error rate

All the primary analyses conducted were pre-specified. For each age cohort, a two-sided 98.3% confidence interval of the Day 11 seroconversion rate was computed using the Wilson method. The lower bound of this interval had to be equal to or to exceed 70% to meet the co-primary objective of minimum seroconversion. Fisher's exact test was used to test equality of seroconversion across treatment groups.

The Day 11 seroconversion rate for vaccines in each of the cohorts was also compared to the seroconversion rate for vaccines 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% confidence interval for this difference based on Newcombe hybrid score method. The lower bound of the two-sided 96.7% confidence interval on the difference in seroconversion rates between children and adults had to be greater than -10 percentage points to meet the co-primary non-inferiority objective.

In order to ensure that the total Type I error for the study was capped at alpha = 0.05, 2/3 of the alpha was allotted to the primary immunogenicity objective of establishing noninferiority relative to the 004 Bridging Population, and 1/3 of the alpha was allotted to the primary immunogenicity objective of demonstrating that the seroconversion rate was equal to or exceeded 70%. The two primary immunogenicity objectives were evaluated independently, and within each objective, testing in the different age cohorts proceeded sequentially beginning with the data for Cohort 1, as follows:

- Non-inferiority: Analysis of non-inferiority between Cohort 1 and the 004 Bridging Population was conducted first. Analysis of non-inferiority in Cohort 2 was conducted only if the pre-specified acceptance criterion was met for Cohort 1. This strategy maintained the overall Type I error for the primary objective of noninferiority at alpha = 0.033.
- Seroconversion Rate Lower Limit (≥ 70%) Criterion: the analysis of the seroconversion rate for Cohort 1 was conducted first. Formal analysis of the acceptability of the seroconversion rate in Cohort 2 was performed only if the lower bound of the two-sided 98.3% confidence interval on the seroconversion rate in Cohort 1 met the pre-specified acceptance criterion. This strategy maintained the overall Type I error for the primary objective concerning the minimum seroconversion rate at alpha = 0.017.

As an additional sensitivity analysis, a logistic regression was performed for seroconversion. Significance of the comparison between the Bridging Population groups was assessed via the type III test of the age group effect from a logistic regression of seroconversion at Day 11 with age group, baseline titer, and gender as predictors in the model. The estimate of the adjusted difference between the groups and its confidence interval was also to be derived from this logistic model.

Missing Data, Handling of data and Transformations

A missing datum for a given study visit may be due to the fact that:

1. data were not collected for the visit or were unusable, or
2. a subject permanently discontinued from the study before reaching the assessment.

There were no plans to impute values for missing data points except for imputing missing relationship to study drug for AEs as related.

By-subject listings were presented for all randomized subjects sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, was presented in chronological order within subject. Subjects were listed according to the actual treatment received.

Baseline was defined as the Day 1 value. If the Day 1 value was missing, then the last nonmissing value prior to Day 1 was used as the baseline value.

Data that are less than the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) were imputed as follows:

- SVA assay results that were reported as less than the LLOQ were imputed as the LLOQ when calculating seroconversion rates and geometric means. For example, if the LLOQ was 20 and a result was noted as "<20", a titer of 20 was imputed.
- A value that is one unit above the limit of quantitation was used for calculation of descriptive statistics if the datum was reported in the form of "> x" (where x was considered the limit of quantitation). Values with decimal points would follow the same logic as above. The limit of quantitation was used for calculation of descriptive statistics if the datum was reported in the form of "≤ x" or "≥ x" (where x was considered the limit of quantitation).

Results

Participant flow

Of the 574 screened, a total of 550 subjects were randomised.

In Cohort 1, 197 subjects were screened for the study. Of the 197 screened, a total of 189 subjects were randomized: 26 subjects in the Placebo group and 163 in the Vaxchora group. Of the 189 enrolled and randomized, 181 (95.8%) subjects completed the main study through the Day 181 visit; 157 were to receive Vaxchora and 24 were to receive placebo. The reasons for withdrawal prior to Day 181 in Cohort 1 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 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 reasons (n=1), and withdrawal of consent (n=1). Additionally, of the 24 placebo subjects who completed the main study, 13 subjects opted for the placebo crossover study (PCO). All of these subjects completed the PCO study to Day 365.

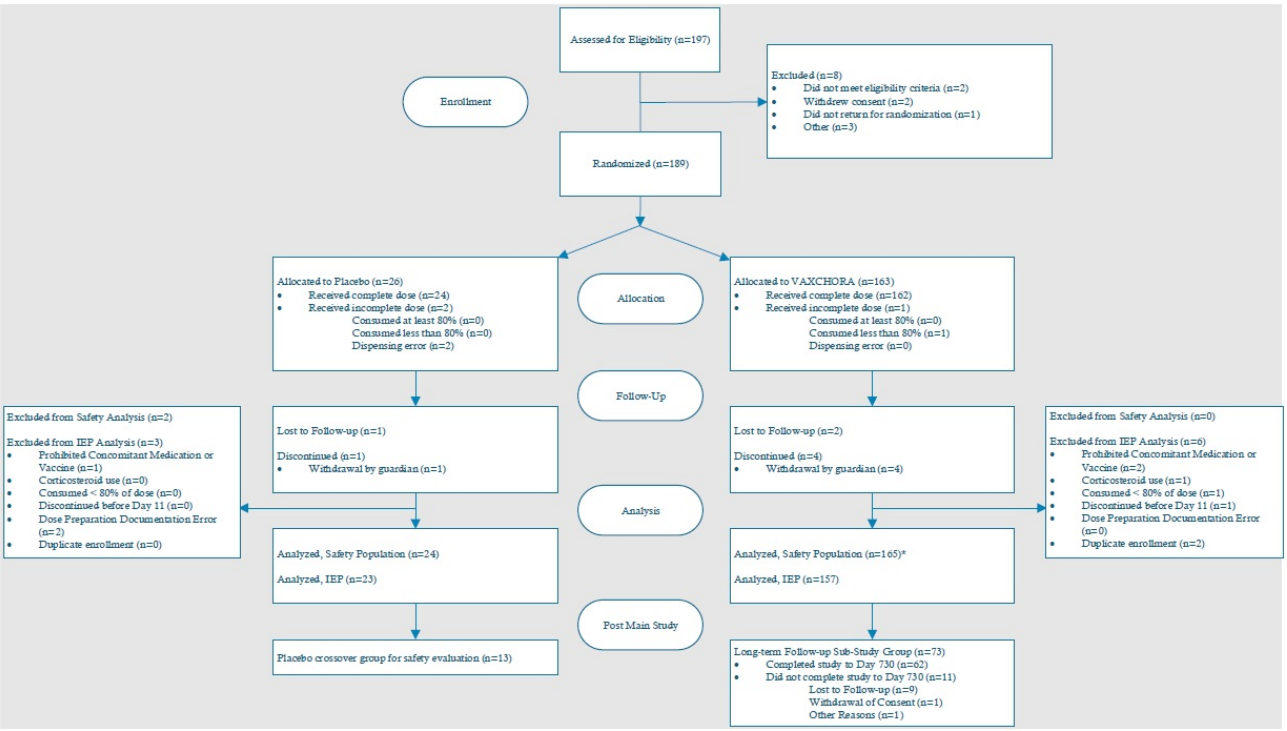

Figure 3: Disposition of subjects in cohort 1. *placebo dispensing errors were analysed with the Vaxchora safety population.

In Cohort 2, 190 subjects were screened for the study (Figure 4). Of the 190 screened, a total of 185 subjects were randomized: 27 subjects in the Placebo group and 158 in the Vaxchora group. Of the 185 enrolled and randomized, 170 (91.9%) subjects completed the main study through the Day 181 visit; 146 of whom were randomized to receive Vaxchora and 24 of whom were randomized to receive placebo. The reasons for withdrawal prior to Day 181 in Cohort 2 were: lost to follow-up (n = 7), withdrawal of consent (n = 5), non-compliance with protocol (n = 2), and other reasons (n = 1). Of the 24 who completed the main study, 11 placebo subjects opted for the PCO study. All of these subjects completed the PCO study through Day 365.

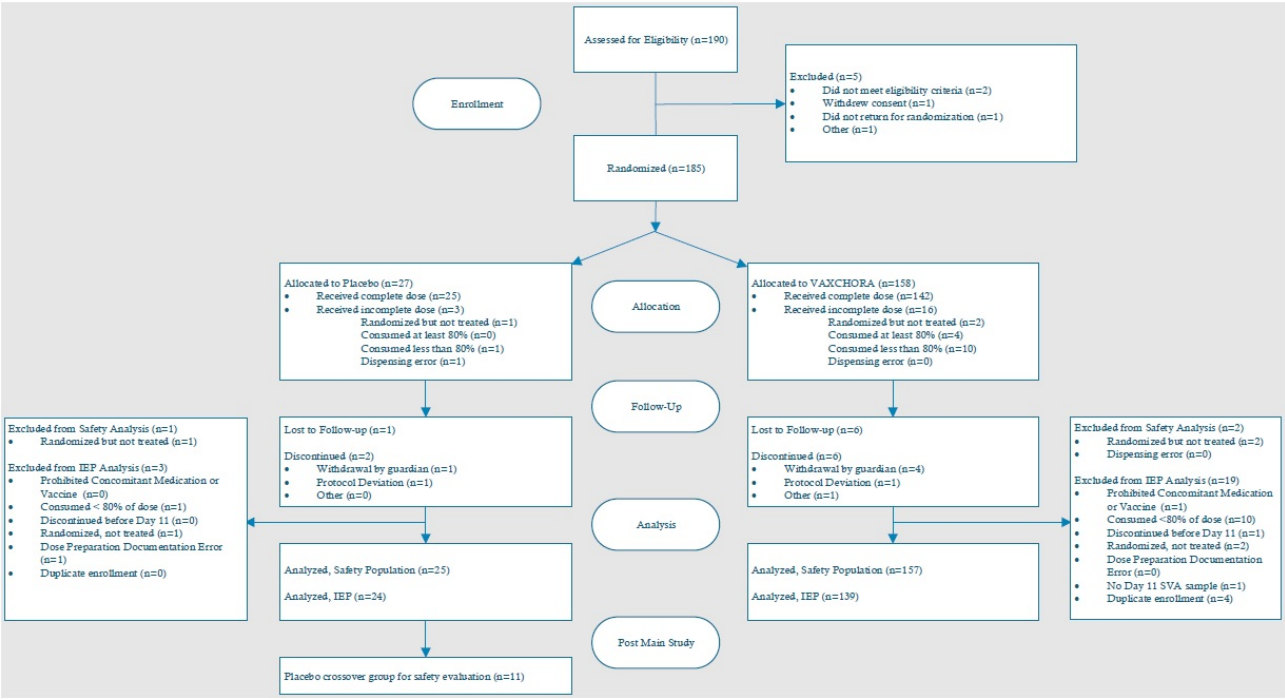

Figure 4: Disposition of subjects in cohort 2. *placebo dispensing errors were analysed with the Vaxchora safety population.

In Cohort 3, 187 subjects were screened for the study (Figure 5). Of the 187 screened, a total of 176 subjects were randomized: 26 subjects in the Placebo group and 150 in the Vaxchora group. Of the 176 enrolled and randomized, 155 (88.1%) subjects completed the main study through the Day 181 visit; 130 of whom were randomized to receive Vaxchora and 25 of whom were randomized to receive placebo. The reasons for withdrawal prior to Day 181 in Cohort 3 were: lost to follow-up (n = 14), withdrawal of consent (n = 4), and non-compliance with protocol (n = 3). Of the 25 who completed the main study, 7 placebo subjects opted for the PCO study. 5 (71.4%) of these subjects completed the PCO study through Day 365. The reasons for withdrawal prior to Day 365 were due to being lost to follow-up (n=2).

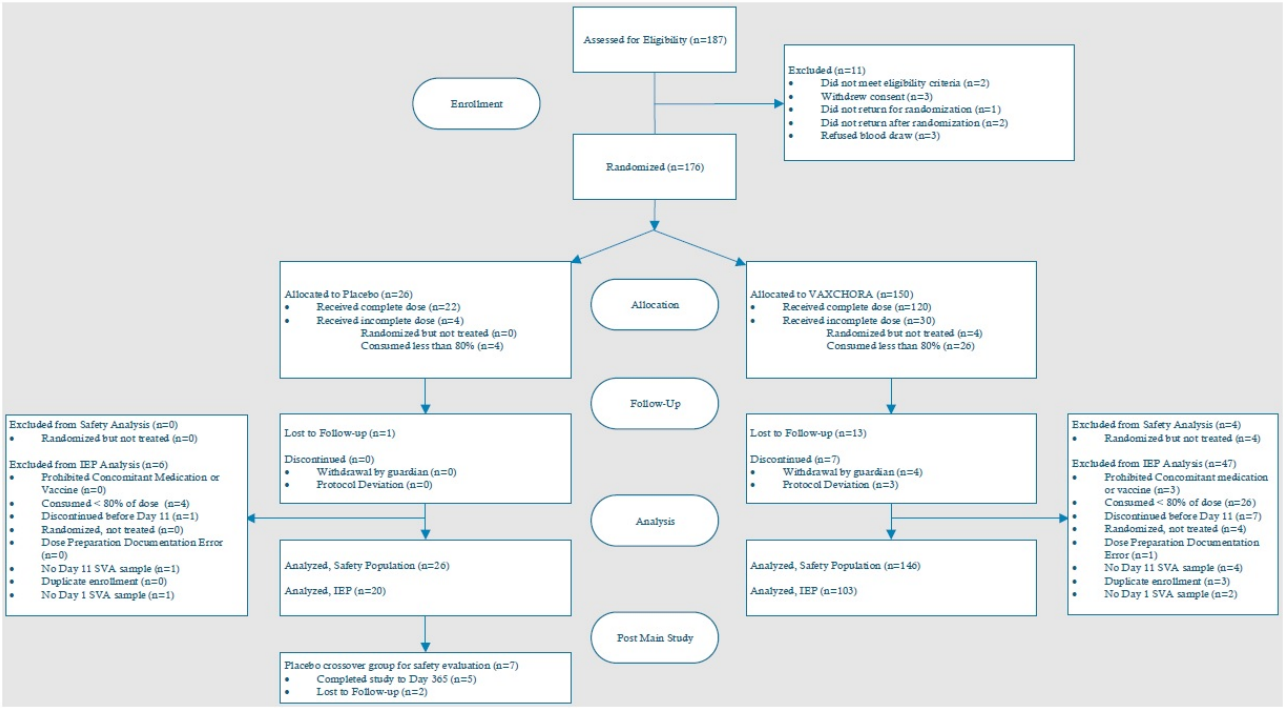

Figure 5: Disposition of subjects in Cohort 3. *placebo dispensing errors were analysed with the Vaxchora safety population.

Recruitment

Subjects in Cohorts 1, 2 and 3 were recruited and enrolled across nine study sites in the United States, although one site failed to recruit any participants.

Conduct of the study

Amendments to the clinical trial protocol

The initial protocol (Version 1.0, 25 Jan 2017) was contained in the initial Investigational New Drug. The protocol was subsequently amended twice. Amendment 1 (protocol version 2.0, 19 May 2017) removed Canada as a location for the trial and further define the statistical analysis, to add exclusion criteria consistent with other studies of Vaxchora and to remove a planned interim analysis. Amendment 2 (protocol version 3.0, 15 Nov 2017) involved revision of the protocol to increase the number of subjects in Cohort 3 (in anticipation of a high rate of inevaluable subjects), to include the collection of adverse events through 6 months post-vaccination in Placebo- Crossover subjects, and to allow for an interim analysis following completion of Cohorts 1 and 2, in order to facilitate a marketing application in Europe.

Protocol deviations

The following protocol deviations were described as exclusionary.

1. Allowed blood draw window:

- Day 1: Must be prior to vaccination
- Day 11: Must be in the period from Day 8 through Day 16 blood draws which fell outside of these windows were considered exclusionary deviations.

2. Dose of vaccine

- Must have consumed at least 80% of vaccine volume (80 mL for Cohorts 1 and 2 or 40 mL for Cohort 3). Subjects not meeting this criterion were considered to have an exclusionary PD.

3. Concomitant antibiotics or non-study concomitant vaccines

- Any antibiotic or non-study vaccine given within -14/+11 days of vaccination were decided as an exclusionary deviation on an individual antibiotic-type or vaccine-type determination.

4. Wrong treatment given/no treatment given

5. Enrollment more than once into the study

6. Inclusion/exclusion criteria violations

- Age at entry – age < 2 or ≥ 18 years
- Prohibited medications – exclusionary deviations were considered on a case-by-case basis
- Medical history conditions which could interfere with immunogenicity were decided on a case-by-case decision.

7. Other

- Other miscellaneous violations discovered during the conduct of the trial, which may have fundamentally affected the assessment of immunogenicity (i.e. immunoglobulin or high dose corticosteroid use), were decided on a case-by-case basis prior to unblinding.

Halting of the study

Throughout the duration of the study, there were five temporary study halts, none of which lasted more than 22 days. Four out of the five halts met study stopping rules.

Two halts were not considered to be related to vaccination (grade 4 unrelated fever in one subject (temporary halt 1) and worsening of seizures in one patient (temporary halt 5). The other temporary halts were associated with diarrhoea (two events in two subjects – temporary halt 2), severe fever in one subject (temporary halt 3) and severe vomiting and diarrhoea in one subject (temporary halt 4). Since one subject in the age group 2-<6 experienced potentially life-threatening fever, this subject, in this age group could have contributed to the temporary halt.

Baseline data

A summary of subject demographic and other baseline characteristics for the Randomized Population is presented in Table 8. Of the 550 randomized subjects, 52.0% of subjects were male and 48.0% were female. Of the enrolled subjects, 59.8% were White, 31.1% were Black or African American, 0.9% were Asian, 0.5% were American Indian or Alaska Native, and 7.6% had a diverse background (Multiple). The overall median age was 9.0 (range 2 to 17) years. In Cohort 3, median age was 4.0 (range 2-5) years in the Vaxchora group and 3.5 (range 2-5) years in the placebo group. Other than age (and growth associated with age), the demographic and other baseline characteristics of the treatment groups and cohorts were similar.

Table 7: Subject Demographics by Age Cohort and Treatment Group – Randomised Population

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

min = minimum, max = maximum, SD = Standard Deviation
Note: Percentages are based on the number of subjects in each treatment arm

Numbers analysed

The numbers of subjects included in the randomised population, in the mITT population, and in the immunogenicity evaluable population (IEP), by treatment group and cohort are shown in Table 9.

Table 8: Analysis populations by Age Cohort and Treatment Group

Analysis Populations n (%)	Cohort 1 (ages 12 – < 18)		Cohort 2 (ages 6 – < 12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)		Total
	VAXCHORA	Placebo	VAXCHORA	Placebo	VAXCHORA	Placebo	VAXCHORA	Placebo	
Screened	197		190		187		574		574
Randomized Population	163	26	158	27	150	26	471	79	550
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%)	543 (98.7%)
mITT Population	160 (98.2%)	26 (100.0%)	150 (94.9%)	26 (96.3%)	129 (86.0%)	24 (92.3%)	439 (93.2%)	76 (96.2%)	515 (93.6%)
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%)	466 (84.7%)

Note: Percentages are based on the number of randomized subjects in each treatment arm.
[a] Safety = Subjects who received vaccine or placebo analyzed by treatment actually received.
[b] mITT = Randomized, treated subjects, analyzed according to randomized group, who have evaluable results from both Day 1 and Day 11 assays.
[c] Immunogenicity Evaluable = Treated subjects who have evaluable results from both Day 1 and Day 11 assays, received the correct vaccine according to randomisation and have no major protocol violations that affect immunogenicity.

There were nine subjects who were randomised and had duplicate enrollment in error. This involved two participants in Cohort 1, four participants randomised to Cohort 2 and three subjects randomised to Cohort 3. These subjects were excluded from all immunogenicity populations.

Seven subjects were randomised but not vaccinated. One subject was randomized in error because the eligibility criteria were not met, six participants refused to consume the assigned treatment (three of

these subjects were in Cohort 2 and four in Cohort 3). All were excluded from all populations apart from the randomisation population.

The IEP was specified in the protocol as the set of subjects who received the correct vaccination (Vaxchora or Placebo), had evaluable results from both Day 1 and Day 11, and had no important protocol deviations classified as major, that would affect immunogenicity analysis. The mITT Population only excluded subjects who were enrolled twice, were not vaccinated, or who were missing Day 1 or Day 11 SVA results.

Study subjects were excluded from the IEP if they incurred an exclusionary PD. Such deviations were defined as factors that could alter the immunogenicity results of a subject. Failing to receive the correct treatment (or any treatment at all), discontinuing before the Day 11 visit, taking antibiotics or other prohibited concomitant medications, or failing to consume at least 80% of the study treatment were common reasons for subject exclusion from the IEP.

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 randomised 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 randomised 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 randomised 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).

These findings are summarised in Table 10.

Table 9: Exclusion of Study Subjects by Treatment Group and Cohort

Reasons for Exclusion n (%)	Cohort 1 (ages 12 – < 18)		Cohort 2 (ages 6 – < 12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)		Total (N=550)
	VAXCHORA (N=163)	Placebo (N=26)	VAXCHORA (N=158)	Placebo (N=27)	VAXCHORA (N=150)	Placebo (N=26)	VAXCHORA (N=471)	Placebo (N=79)	
Exclusions from Safety Analyses	0	0	2 (1.3%)	1 (3.7%)	4 (2.7%)	0	6 (1.3%)	1 (1.3%)	7 (1.3%)
Randomized, Not Treated	0	0	2 (1.3%)	1 (3.7%)	4 (2.7%)	0	6 (1.3%)	1 (1.3%)	7 (1.3%)
Exclusions from mITT Analysis	3 (1.8%)	0	8 (5.1%)	1 (3.7%)	21 (14.0%)	2 (7.7%)	32 (6.8%)	3 (3.8%)	35 (6.4%)
Duplicate Enrollment	2 (1.2%)	0	4 (2.5%)	0	3 (2.0%)	0	9 (1.9%)	0	9 (1.6%)
Randomized, Not Treated	0	0	2 (1.3%)	1 (3.7%)	4 (2.7%)	0	6 (1.3%)	1 (1.3%)	7 (1.3%)
Discontinued prior to Day 11	1 (0.6%)	0	1 (0.6%)	0	9 (6.0%)	1 (3.8%)	11 (2.3%)	1 (1.3%)	12 (2.2%)
No Day 1 SVA Sample	0	0	0	0	2 (1.3%)	1 (3.8%)	2 (0.4%)	1 (1.3%)	3 (0.5%)
No Day 11 SVA Sample	0	0	1 (0.6%)	0	4 (2.7%)	1 (3.8%)	5 (1.1%)	1 (1.3%)	6 (1.1%)
Exclusions from Immunogenicity Evaluable Analyses	6 (3.7%)	3 (11.5%)	19 (12.0%)	3 (11.1%)	47 (31.3%)	6 (23.1%)	72 (15.3%)	12 (15.2%)	84 (15.3%)
Consumed < 80% of Dose	1 (0.6%)	0	10 (6.3%)	1 (3.7%)	26 (17.3%)*	4 (15.4%)	37 (7.9%)	5 (6.3%)	42 (7.6%)
Duplicate Enrollment	2 (1.2%)	0	4 (2.5%)	0	3 (2.0%)	0	9 (1.9%)	0	9 (1.6%)
Prohibited Concomitant Medication or Vaccine	2 (1.2%)	1 (3.8%)	1 (0.6%)	0	3 (2.0%)	0	6 (1.3%)	1 (1.3%)	7 (1.3%)
Randomized, Not Treated	0	0	2 (1.3%)	1 (3.7%)	4 (2.7%)	0	6 (1.3%)	1 (1.3%)	7 (1.3%)
Received Incorrect Randomized Treatment	0	2 (7.7%)	0	1 (3.7%)	0	0	0	3 (3.8%)	3 (0.5%)
Discontinued Study Prior to Day 11	1 (0.6%)	0	1 (0.6%)	0	7 (4.7%)	1 (3.8%)	9 (1.9%)	1 (1.3%)	10 (1.8%)
Corticosteroid Use	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0	1 (0.2%)
No Day 1 SVA Sample	0	0	0	0	2 (1.3%)	1 (3.8%)	2 (0.4%)	1 (1.3%)	3 (0.5%)
No Day 11 SVA Sample	0	0	1 (0.6%)	0	4 (2.7%)	1 (3.8%)	5 (1.1%)	1 (1.3%)	6 (1.1%)
Dose Preparation Documentation Error	0	0	0	0	1 (0.7%)	0	1 (0.2%)	0	1 (0.2%)

mITT = Modified Intent To Treat; SVA = Serum Vibriocidal Antibody
Note: Subjects may have more than one reason for exclusion.
*Included in this count is one subject who received a full dose of vaccine, but proper reconstitution process could not be confirmed resulting in possibly 50% of the dose.

Measurement of treatment compliance:

In Cohort 1, 99.4% of Vaxchora recipients and 100% of Placebo received the complete dose for the main study. Only one (0.6%) Vaxchora recipient did not consume at least 80% of the oral solution. For the placebo crossover group on Day 181, all 13 subjects drank the complete dose. Of the subjects with acceptable dosing in Cohort 1, palatability ratings did not significantly differ among Vaxchora and Placebo recipients. Addition of PureVia Stevia Sweetener did not significantly improve subjects' opinions regarding treatment palatability.

In Cohort 2, 91.0% of Vaxchora recipients and 96.2% of Placebo recipients received the complete dose. Of note, 10 Vaxchora recipients in Cohort 2 were unable to drink at least 80% of the 100 mL solution. For the placebo crossover group on Day 181, all 11 subjects drank the complete dose. Of the subjects with unacceptable dosing in Cohort 2, palatability ratings heavily favored "Super Bad" at 80% in Vaxchora recipients and 100% in Placebo recipients. Of the subjects with acceptable dosing, palatability ratings did not significantly differ among Vaxchora and Placebo recipients. Addition of PureVia Stevia Sweetener did not significantly improve subjects' opinions regarding treatment palatability.

In Cohort 3, 79.5% of Vaxchora recipients and 73.1% of Placebo recipients received the complete dose. Of note, 26 Vaxchora recipients in Cohort 3 were either unable to drink at least 80% of the 50 mL solution (n=25) or had a likely administration error (n=1) and were excluded from the IEP. An evaluation of the seroconversion of these excluded subjects at Day 11 and Day 29 shows a high degree of variability and no clear trend in the overall relationship of dose consumed and seroconversion rate. For the placebo crossover group on Day 181, 6 of the 7 subjects (85.7%) drank the complete dose. Of the subjects with acceptable dosing, palatability ratings did not significantly differ among Vaxchora and Placebo recipients.

All but two subjects in Cohort 3 added PureVia Stevia Sweetener, so the effect of its addition on treatment palatability in this cohort cannot be assessed.

Issues with palatability possibly contributed to subjects who did not consume a complete dose of their respective randomized treatment, especially in Cohort 2 subjects. However, the palatability assessments did not differ much between the vaccine groups within each cohort. Addition of PureVia Stevia Sweetener did not significantly improve subjects' opinions regarding treatment palatability. For example, in Cohorts 1, 2 and 3, 6.9%, 22.1% and 21.5% of Vaxchora recipients gave "Super Bad" palatability scores following addition of sweetener, compared with 10.5%, 14.3% and 0% of Vaxchora recipients who did not receive sweetener. Similarly, in Cohorts 1, 2 and 3, 4.2%, 18.1% and 29.9% of Vaxchora recipients gave "Super Good" palatability scores following addition of sweetener, compared with 10.5%, 14.3% and 50% of Vaxchora recipients who did not receive sweetener. Of note is that only 2 subjects in Cohort 3 did not receive sweetener. For Cohort 3, 98.8% of the subjects received the sweetener.

Outcomes and estimation

Primary Immunogenicity Results

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 (i.e. adult Bridging Population), as shown in Table 11. The seroconversion rate was defined as the proportion of subjects achieving seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Day 11 following one dose of Vaxchora, defined as a 4-fold or greater rise over baseline Day 1 SVA titer.

Table 10: Comparison of Seroconversion Rates at Day 11 Visit by Age Group Compared to 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)
Day 11 Visit					
N analyzable	2687	157	139	103	399
N (%) Seroconverted [98.3% CI]	2513 (93.5%) [92.3%, 94.6%]	156 (99.4%) ** [95.4%, 99.9%]	136 (97.8%) * [92.5%, 99.4%]	101 (98.1%) [91.5%, 99.6%]	393 (98.5%) *** [96.2%, 99.4%]
Difference (006 Cohort minus 004 Adults)	-	5.8%	4.3%	4.5%	5.0%
96.7% CI on % Difference	-	[2.4%, 7.1%]	[-0.3%, 6.2%]	[-1.1%, 6.4%]	[2.8%, 6.4%]

CI = Confidence Interval
* $p < 0.05$ 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

According to the protocol-specified hierarchical testing procedure, for each co-primary objective, the testing of Cohort 1 subjects versus the adult Bridging Population needed to meet the acceptance criterion prior to performing the comparison for Cohort 2. Analysis of non-inferiority in Cohort 3 was only conducted if the pre-specified acceptance criteria were met for Cohorts 1 and 2.

Both co-primary objectives were met for Cohort 1. Cohort 1 was non-inferior to the adult Bridging Population with the lower limit of the difference between the groups for the required 96.7% CI greater than -10 percentage points (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 Bridging Population. For the second co-primary objective, the Cohort 1 subjects had 99.4% (98.3% CI: [95.4%,

99.9%]) of subjects seroconverting by their Day 11 visit, which surpassed the protocol-required lower limit of the 98.3% CI of 70% with seroconversion.

Both co-primary objectives were also met for Cohort 2. Cohort 2 was non-inferior to the adult Bridging Population with the lower limit of the difference between the groups for the required 96.7% CI greater than -10 percentage points (difference = +4.3%; 96.7% CI: [- 0.3%, 6.2%]). For the second co-primary objective, the Cohort 2 subjects had 97.8% (98.3% CI: [92.5%, 99.4%]) of subjects seroconverting by their Day 11 visit. This was also above the protocol required lower limit of the 98.3% CI of 70% with seroconversion.

Both co-primary objectives were also met for Cohort 3. Cohort 3 was non-inferior to the adult Bridging Population with the lower limit of the difference between the groups for the required 96.7% CI greater than -10 percentage points (difference = +4.5%; 96.7% CI: [- 1.1%, 6.4%]). For the second co-primary objective, the Cohort 3 subjects had 98.1% (98.3% CI: [91.5%, 99.6%]) of subjects seroconverting by their Day 11 visit. This was also above the protocol required lower limit of the 98.3% CI of 70% with seroconversion.

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

Secondary Immunogenicity results

A. *Seroconversion of SVA against the classical Inaba biotype of V. cholera at Day 29 for all subjects and Days 91, 181, 365, 547 and 730 for Cohort 1*

Seroconversion data (>4 fold increase in SVA titer from baseline) are shown in Table 12

Table 11: Seroconversion Rate by Treatment Group and Cohort

Seroconversion	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)	
	VAXCHORA (N=157)	Placebo (N=23)	VAXCHORA (N=139)	Placebo (N=24)	VAXCHORA (N=103)	Placebo (N=20)	VAXCHORA (N=399)	Placebo (N=67)
Day 11 Visit								
N analyzable	157	23	139	24	103	20	399	67
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%]	393 (98.5%)*** [96.8%, 99.3%]	1 (1.5%) [0.3%, 8.0%]
Day 29 Visit								
N analyzable	156	23	138	23	98	18	392	64
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%]	379 (96.7%)*** [94.4%, 98.1%]	1 (1.6%) [0.3%, 8.3%]
Day 91 Visit								
N analyzable	153	23	-	-	-	-	153	23
N (%) Seroconverted (95% CI)	131 (85.6%)*** [79.2%, 90.3%]	0 [0.0%, 14.3%]	-	-	-	-	131 (85.6%)*** [79.2%, 90.3%]	0 [0.0%, 14.3%]
Day 181 Visit								
N analyzable	151	21	-	-	-	-	151	21
N (%) Seroconverted (95% CI)	111 (73.5%)*** [66.0%, 79.9%]	0 [0.0%, 15.5%]	-	-	-	-	111 (73.5%)*** [66.0%, 79.9%]	0 [0.0%, 15.5%]
Long-Term Follow-Up Sub-Study Population [a]								
Day 365 Visit								
N analyzable	70	-	-	-	-	-	-	-
N (%) Seroconverted (95% CI)	48 (68.6%) [57.0%, 78.2%]	-	-	-	-	-	-	-
Day 547 Visit								
N analyzable	67	-	-	-	-	-	-	-
N (%) Seroconverted (95% CI)	49 (73.1%) [61.5%, 82.3%]	-	-	-	-	-	-	-
Day 730 Visit								
N analyzable	62	-	-	-	-	-	-	-
N (%) Seroconverted (95% CI)	40 (64.5%) [52.1%, 75.3%]	-	-	-	-	-	-	-

CI = Confidence Interval
[a]72 subjects from Cohort 1 opted for the long-term sub-study

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

The Day 29 seroconversion rate among Cohort 1 subjects who received Vaxchora was 100% (95% CI: [97.6%, 100%]), which was significantly higher than the seroconversion rate among Placebo recipients for the same time point (0%, 95% CI: [0.0%, 14.3%]).

The Day 29 seroconversion rate among Cohort 2 subjects who received Vaxchora was 94.9% (95% CI: [89.9%, 97.5%]), which was significantly higher than the seroconversion rate among Placebo recipients for the same time point (4.3%; (95% CI: [0.8%, 21.0%])).

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

Cohort 1 was studied further with measurements to determine duration of seroconversion rate up until day 730. The Day 91 seroconversion rate among Cohort 1 subjects who received Vaxchora was 85.6% (95% CI: [79.2%, 90.3%]), which was significantly higher than the seroconversion 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 observed for the Vaxchora group (p< 0.0001). The seroconversion rate for the long-term follow-up (n=72) at 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.

B. *Geometric mean titers (GMT) and fold increase in geometric mean titers (GMFI) of SVA against the classical Inaba biotype of V. cholera at Day 29 for all subjects and Days 91, 181, 365, 547 and 730 for Cohort 1*

The GMT of vibriocidal antibodies for Cohort 1 Vaxchora subjects at baseline, Day 11, and Day 29 post-vaccination time points is as follows (see also Table 13). GMT at baseline in Vaxchora recipients was 32.1 (95% CI: [28.1, 36.6]) and in Placebo recipients was 43.8 (95% CI: [27.5, 69.6]). Day 11 GMT in Vaxchora recipients was 8735.2 (95% CI: [7053.1, 10818.5]) and 41.2 (95% CI: [26.1, 65.1]) in Placebo recipients. Day 29 GMT was 2748.6 (95% CI: [2310.8, 3269.5]) in Vaxchora recipients and 42.5 (95% CI: [27.1, 66.7]) in Placebo recipients. All comparisons of Vaxchora to Placebo post-vaccination were significant (p< 0.0001).

In Cohort 1 the GMT at Day 91 in Vaxchora recipients was 318.6 (95% CI: [263.0, 385.8]) and in Placebo recipients was 42.5 (95% CI: [28.7, 62.9]). Day 181 GMT in Vaxchora recipients was 186.2 (95% CI: [154.3, 224.6]) and 38.7 (95% CI: [25.8, 58.0]) in Placebo recipients. All comparisons of Vaxchora to Placebo post-vaccination remained significant (p< 0.0001).

For the Cohort 1 long-term sub-study population (n=72), the retrospective Days 1, 11 and 29 GMT of vibriocidal antibodies in this subgroup did not differ significantly from the larger IEP population (n=157). Day 1 GMT was 32.4 (32.1 for IEP), Day 11 was 9035.4 (8735.2 for IEP), Day 29 was 2791.7 (2748.6 for IEP), Day 91 was 391.7 (318.6 for IEP), and Day 181 was 223.0 (186.2 for IEP). The decreasing trend continued to Days 365, 547 and 730 with GMTs of 158.4, 175.6, and 133.8, respectively.

In Cohort 2, the GMT at baseline in Vaxchora recipients was 31.5 (95% CI: [27.7, 35.8]) and in Placebo recipients was 35.6 (95% CI: [24.3, 52.3]) (Table 8). Day 11 GMT in Vaxchora recipients was 8305.0 (95% CI: [6515.6, 10585.9]) and 40.0 (95% CI: [22.7, 70.4]) in Placebo recipients. Day 29 GMT was 1951.8 (95% CI: [1554.0, 2451.5]) in Vaxchora recipients and 40.0 (95% CI: [22.1, 72.3]) in Placebo recipients. All comparisons of Vaxchora to Placebo post-vaccination were significant (p< 0.0001).

In Cohort 3 the GMT at baseline in Vaxchora recipients was 26.7 (95% CI: [23.8, 30.0]) and in Placebo recipients was 26.4 (95% CI: [19.1, 36.4]) (Table 8). Day 11 GMT in Vaxchora recipients was 4851.6 (95% CI: [3445.2, 6832.3]) and 28.3 (95% CI: [20.4, 39.1]) in Placebo recipients. The Day 29 GMT was 1013.5 (95% CI: [740.7, 1386.8]) in Vaxchora recipients and 27.2 (95% CI: [20.8, 35.7]) in Placebo recipients. All comparisons of Vaxchora to Placebo post-vaccination were significant (p<0.0001).

Table 12: Geometric Mean Titres Against Classical Inaba V. cholerae, All Time Points by Age Group and Cohort – Immunogenicity Evaluable Population.

Geometric Mean	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)	
	VAXCHORA (N=157)	Placebo (N=23)	VAXCHORA (N=139)	Placebo (N=24)	VAXCHORA (N=103)	Placebo (N=20)	VAXCHORA (N=399)	Placebo (N=67)
Day 1 Visit								
N analyzable	157	23	139	24	103	20	399	67
GMT	32.1	43.8	31.5	35.6	26.7	26.4	30.4	35.0
(95% CI)	[28.1, 36.6]	[27.5, 69.6]	[27.7, 35.8]	[24.3, 52.3]	[23.8, 30.0]	[19.1, 36.4]	[28.2, 32.8]	[27.9, 43.8]
Median	20.0	40.0	20.0	20.0	20.0	20.0	20.0	20.0
Min, Max	20, 640	20, 1280	20, 1280	20, 640	20, 320	20, 320	20, 1280	20, 1280
Day 11 Visit								
N analyzable	157	23	139	24	103	20	399	67
GMT	8735.2 ***	41.2	8305.0 ***	40.0	4851.6 ***	28.3	7347.1 ***	36.4
(95% CI)	[7053.1, 10818.5]	[26.1, 65.1]	[6515.6, 10585.9]	[22.7, 70.4]	[3445.2, 6832.3]	[20.4, 39.1]	[6352.6, 8559.8]	[28.0, 47.4]
Median	10240.0	20.0	10240.0	20.0	5120.0	20.0	10240.0	20.0
Min, Max	20, 81920	20, 1280	40, 163840	20, 5120	20, 163840	20, 320	20, 163840	20, 5120
Day 29 Visit								
N analyzable	156	23	138	23	98	18	392	64
GMT	2748.6 ***	42.5	1951.8 ***	40.0	1013.5	27.2	1898.7 ***	36.7
(95% CI)	[2310.8, 3269.5]	[27.1, 66.7]	[1554.0, 2451.5]	[22.1, 72.3]	[740.7, 1386.8]	[20.8, 35.7]	[1657.0, 2175.7]	[28.1, 48.0]
Median	2560.0	40.0	2560.0	20.0	1280.0	20.0	2560.0	20.0
Min, Max	320, 20480	20, 640	40, 40960	20, 5120	20, 40960	20, 80	40, 40960	20, 5120
Day 91 Visit								
N analyzable	153	23	-	-	-	-	153	23
GMT	318.6 ***	42.5	-	-	-	-	318.6 ***	42.5
(95% CI)	[263.0, 385.8]	[28.7, 62.9]	-	-	-	-	[263.0, 385.8]	[28.7, 62.9]
Median	320.0	40.0	-	-	-	-	320.0	40.0

Geometric Mean	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)	
	VAXCHORA (N=157)	Placebo (N=23)	VAXCHORA (N=139)	Placebo (N=24)	VAXCHORA (N=103)	Placebo (N=20)	VAXCHORA (N=399)	Placebo (N=67)
Min, Max	20, 5120	20, 640	-	-	-	-	20, 5120	20, 640
Day 181 Visit								
N analyzable	151	21	-	-	-	-	151	21
GMT	186.2 ***	38.7	-	-	-	-	186.2***	38.7
(95% CI)	[154.3, 224.6]	[25.8, 58.0]	-	-	-	-	[154.3, 224.6]	[25.8, 58.0]
Median	160.0	20.0	-	-	-	-	160.0	20.0
Min, Max	20, 5120	20, 320	-	-	-	-	20, 5120	20, 320
Long-term Follow-Up Sub-Study Population[a]								
Day 1 Visit								
N analyzable	72	-	-	-	-	-	-	-
GMT	32.4	-	-	-	-	-	-	-
(95% CI)	[26.2, 40.0]	-	-	-	-	-	-	-
Median	20.0	-	-	-	-	-	-	-
Min, Max	20, 640	-	-	-	-	-	-	-
Day 11 Visit								
N analyzable	72	-	-	-	-	-	-	-
GMT	9035.4	-	-	-	-	-	-	-
(95% CI)	[6745.3, 12103.0]	-	-	-	-	-	-	-
Median	10240.0	-	-	-	-	-	-	-
Min, Max	160, 81920	-	-	-	-	-	-	-
Day 29 Visit								
N analyzable	72	-	-	-	-	-	-	-
GMT	2791.7	-	-	-	-	-	-	-
(95% CI)	[2176.4, 3580.9]	-	-	-	-	-	-	-
Median	2560.0	-	-	-	-	-	-	-
Min, Max	320, 20480	-	-	-	-	-	-	-

Geometric Mean	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)	
	VAXCHORA (N=157)	Placebo (N=23)	VAXCHORA (N=139)	Placebo (N=24)	VAXCHORA (N=103)	Placebo (N=20)	VAXCHORA (N=399)	Placebo (N=67)
Day 91 Visit								
N analyzable	72	-	-	-	-	-	-	-
GMT	391.7	-	-	-	-	-	-	-
(95% CI)	[293.9, 522.1]	-	-	-	-	-	-	-
Median	320.0	-	-	-	-	-	-	-
Min, Max	40, 5120	-	-	-	-	-	-	-
Day 181 Visit								
N analyzable	71	-	-	-	-	-	-	-
GMT	223.0	-	-	-	-	-	-	-
(95% CI)	[166.5, 298.6]	-	-	-	-	-	-	-
Median	160.0	-	-	-	-	-	-	-
Min, Max	20, 5120	-	-	-	-	-	-	-
Day 365 Visit								
N analyzable	70	-	-	-	-	-	-	-
GMT	158.4	-	-	-	-	-	-	-
(95% CI)	[121.6, 206.4]	-	-	-	-	-	-	-
Median	160.0	-	-	-	-	-	-	-
Min, Max	20, 5120	-	-	-	-	-	-	-
Day 547 Visit								
N analyzable	67	-	-	-	-	-	-	-
GMT	175.6	-	-	-	-	-	-	-
(95% CI)	[134.1, 229.9]	-	-	-	-	-	-	-
Median	160.0	-	-	-	-	-	-	-
Min, Max	20, 2560	-	-	-	-	-	-	-
Day 730 Visit								
N analyzable	62	-	-	-	-	-	-	-

Geometric Mean	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)	
	VAXCHORA (N=157)	Placebo (N=23)	VAXCHORA (N=139)	Placebo (N=24)	VAXCHORA (N=103)	Placebo (N=20)	VAXCHORA (N=399)	Placebo (N=67)
GMT	133.8	-	-	-	-	-	-	-
(95% CI)	[101.9, 175.7]	-	-	-	-	-	-	-
Median	160.0	-	-	-	-	-	-	-
Min, Max	20, 2560	-	-	-	-	-	-	-

CI = Confidence Interval; GMT = Geometric Mean Titre; min = minimum; max = maximum
[a]72 subjects from Cohort 1 opted for the long-term sub-study. Data is presented retrospectively to Day 1 and out to Day 730 for these specific Cohort 1 subjects.

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

The geometric mean titre fold increases (GMFI) are shown in Table 14.

The GMFI of vibriocidal antibodies for Cohort 1 Vaxchora subjects was 272.3 (95% CI: [222.3, 333.6]) times baseline value at Day 11, and 85.4 (95% CI: [71.8, 101.6]) times baseline value at Day 29. For Placebo recipients, the GMFI of vibriocidal antibodies was 0.9 (95% CI: [0.8, 1.1]) times baseline value at Day 11 and 1.0 (95% CI: [0.8, 1.2]) times baseline value at Day 29. As with the GMTs, the comparisons of VAXCHORA to Placebo for mean fold increase were highly significant (p< 0.0001).

The GMFI of vibriocidal antibodies for Cohort 1 Vaxchora subjects was 9.9 (95% CI: [8.3, 11.9]) times baseline value at Day 91, and 5.8 (95% CI: [4.9, 6.8]) times baseline value at Day 181. For Placebo recipients, the GMFI of vibriocidal antibodies was 1.0 (95% CI: [0.7, 1.3]) times baseline value at Day 91 and 0.9 (95% CI: [0.8, 1.1]) times baseline value at Day 181. As with the GMTs, the comparisons of VAXCHORA to Placebo for GMFIs remained highly significant (p< 0.0001).

For the Cohort 1 long-term sub-study population (n=72), the retrospective Days 1, 11 and 29 the GMFI of vibriocidal antibodies did not differ significantly from the larger IEP population (n=157). Day 11 was

279.2 (272.3 for IEP), Day 29 was 86.3 (85.4 for IEP), Day 91 was 12.1 (9.9 for IEP), Day 181 was 6.9 (5.8 for IEP). The decreasing trend continued to Days 365, 547 and 730 with values of 4.8, 5.2, and 4.1, respectively.

The GMFI of vibriocidal antibodies for Cohort 2 Vaxchora subjects was 263.8 (95% CI: [204.1, 340.9]) times baseline value at Day 11, and 61.8 (95% CI: [49.0, 77.9]) times baseline value at Day 29 (Table 16). For Placebo recipients, the GMFI of vibriocidal antibodies was 1.1 (95% CI: [0.7, 1.9]) times baseline value at Day 11 and 1.1 (95% CI: [0.8, 1.5]) times baseline value at Day 29. As with the GMTs, the comparisons of Vaxchora to Placebo for GMFIs were significant ($p< 0.0001$) at both time points.

The GMFI of vibriocidal antibodies for Cohort 3 Vaxchora subjects was 181.6 (95% CI: [131.1, 251.6]) times baseline value at Day 11, and 37.7 (95% CI: [28.0, 50.7]) times baseline value at Day 29. For Placebo recipients, the GMFI of vibriocidal antibodies was 1.1 (95% CI: [1.0, 1.2]) times baseline value at Day 11 and 1.0 (95% CI: [0.8, 1.3]) times baseline value at Day 29. As with the GMTs, the comparisons of Vaxchora to Placebo for GMFIs were highly significant ($p< 0.0001$) at both time points.

Of the Vaxchora recipients in Cohorts 1 and 2, none had a titer level below LLOQ at Day 29. For cohort 1 and the sub-study population, there were no VAXCHORA recipients that had a titer below LLOQ, until Days 547 and 730, with 1.5% (1 subject) and 1.6% (1 subject) at each time point, respectively. Of the Vaxchora recipients in Cohort 3, 1.9% and 2.0% had titer levels below LLOQ on Days 11 and 29, respectively. For the overall study, 0.8% and 0.5% of Vaxchora recipients had a titer below LLOQ on Days 11 and 29, respectively.

Table 13: Geometric Mean Fold Increase Against Classicial Inaba V- Cholerae All Time Points by Age Group and Cohort – Immunogenicity Evaluable Population

	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)	
Fold Increase	VAXCHORA (N=157)	Placebo (N=23)	VAXCHORA (N=139)	Placebo (N=24)	VAXCHORA (N=103)	Placebo (N=20)	VAXCHORA (N=399)	Placebo (N=67)
Day 11 Visit								
N analyzable	157	23	139	24	103	20	399	67
GMFI (SD)	272.3 (3.6) ***	0.9 (1.4)	263.8 (4.6) ***	1.1 (3.3)	181.6 (5.3) ***	1.1 (1.2)	242.6 (4.4) ***	1.0 (2.1)
(95% CI)	[222.3, 333.6]	[0.8, 1.1]	[204.1, 340.9]	[0.7, 1.9]	[131.1, 251.6]	[1.0, 1.2]	[209.6, 280.7]	[0.9, 1.3]
Median	256.0	1.0	256.0	1.0	256.0	1.0	256.0	1.0
Min, Max	1.0, 4096.0	0.3, 2.0	1.0, 4096.0	0.5, 256.0	1.0, 4096.0	1.0, 2.0	1.0, 4096.0	0.3, 256.0
Day 29 Visit								
N analyzable	156	23	138	23	98	18	392	64
GMFI (SD)	85.4 (3.0) ***	1.0 (1.6)	61.8 (4.0) ***	1.1 (2.2)	37.7 (4.4) ***	1.0 (1.6)	62.1 (3.8) ***	1.0 (1.8)
(95% CI)	[71.8, 101.6]	[0.8, 1.2]	[49.0, 77.9]	[0.8, 1.5]	[28.0, 50.7]	[0.8, 1.3]	[54.4, 70.9]	[0.9, 1.2]
Median	64.0	1.0	64.0	1.0	32.0	1.0	64.0	1.0
Min, Max	8.0, 1024.0	0.3, 2.0	1.0, 1024.0	0.5, 32.0	1.0, 512.0	0.3, 2.0	1.0, 1024.0	0.3, 32.0
Day 91 Visit								
N analyzable	153	23	-	-	-	-	153	23
GMFI (SD)	9.9 (3.1) ***	1.0 (1.8)	-	-	-	-	9.9 (3.1) ***	1.0 (1.8)
(95% CI)	[8.3, 11.9]	[0.7, 1.3]	-	-	-	-	[8.3, 11.9]	[0.7, 1.3]
Median	8.0	1.0	-	-	-	-	8.0	1.0
Min, Max	1.0, 256.0	0.1, 2.0	-	-	-	-	1.0, 256.0	0.1, 2.0
Day 181 Visit								
N analyzable	151	21	-	-	-	-	151	21
GMFI (SD)	5.8 (2.9) ***	0.9 (1.5)	-	-	-	-	5.8 (2.9) ***	0.9 (1.5)
(95% CI)	[4.9, 6.8]	[0.8, 1.1]	-	-	-	-	[4.9, 6.8]	[0.8, 1.1]
Median	4.0	1.0	-	-	-	-	4.0	1.0

	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)	
Fold Increase	VAXCHORA (N=157)	Placebo (N=23)	VAXCHORA (N=139)	Placebo (N=24)	VAXCHORA (N=103)	Placebo (N=20)	VAXCHORA (N=399)	Placebo (N=67)
Min, Max	0.5, 128.0	0.3, 2.0	-	-	-	-	0.5, 128.0	0.3, 2.0
Long-term Follow-Up Sub-Study Population [a]								
Day 11 Visit								
N analyzable	72	-	-	-	-	-	-	-
GMFI (SD)	279.2 (3.2)	-	-	-	-	-	-	-
(95% CI)	[212.4, 366.9]	-	-	-	-	-	-	-
Median	256.0	-	-	-	-	-	-	-
Min, Max	8.0, 2048.0	-	-	-	-	-	-	-
Day 29 Visit								
N analyzable	72	-	-	-	-	-	-	-
GMFI (SD)	86.3 (2.8)	-	-	-	-	-	-	-
(95% CI)	[67.6, 110.1]	-	-	-	-	-	-	-
Median	96.0	-	-	-	-	-	-	-
Min, Max	8.0, 1024.0	-	-	-	-	-	-	-
Day 91 Visit								
N analyzable	72	-	-	-	-	-	-	-
GMFI (SD)	12.1 (3.1)	-	-	-	-	-	-	-
(95% CI)	[9.3, 15.8]	-	-	-	-	-	-	-
Median	16.0	-	-	-	-	-	-	-
Min, Max	2.0, 256.0	-	-	-	-	-	-	-
Day 181 Visit								
N analyzable	71	-	-	-	-	-	-	-
GMFI (SD)	6.9 (2.9)	-	-	-	-	-	-	-
(95% CI)	[5.4, 8.9]	-	-	-	-	-	-	-
Median	8.0	-	-	-	-	-	-	-
Min, Max	0.5, 128.0	-	-	-	-	-	-	-

Fold Increase	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 - <6)		Overall (ages 2 – <18)	
	VAXCHORA (N=157)	Placebo (N=23)	VAXCHORA (N=139)	Placebo (N=24)	VAXCHORA (N=103)	Placebo (N=20)	VAXCHORA (N=399)	Placebo (N=67)
Day 365 Visit								
N analyzable	70	-	-	-	-	-	-	-
GMFI (SD)	4.8 (2.7)	-	-	-	-	-	-	-
(95% CI)	[3.8, 6.1]	-	-	-	-	-	-	-
Median	4.0	-	-	-	-	-	-	-
Min, Max	0.5, 64.0	-	-	-	-	-	-	-
Day 547 Visit								
N analyzable	67	-	-	-	-	-	-	-
GMFI (SD)	5.2 (2.6)	-	-	-	-	-	-	-
(95% CI)	[4.2, 6.6]	-	-	-	-	-	-	-
Median	4.0	-	-	-	-	-	-	-
Min, Max	1.0, 64.0	-	-	-	-	-	-	-
Day 730 Visit								
N analyzable	62	-	-	-	-	-	-	-
GMFI (SD)	4.1 (2.5)	-	-	-	-	-	-	-
(95% CI)	[3.2, 5.2]	-	-	-	-	-	-	-
Median	4.0	-	-	-	-	-	-	-
Min, Max	1.0, 64.0	-	-	-	-	-	-	-

CI = Confidence Interval; min = minimum; max = maximum; SD = Standard Deviation;
[a]72 subjects from Cohort 1 opted for the long-term sub-study. Data is presented retrospectively to Day 1 and out to Day 730 for these specific Cohort 1 subjects.

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

Ancillary analyses

N/A

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14: Summary of Efficacy for trial PXVX-VC-200-006

Title: A Phase 4 Study to Assess the Safety and Immunogenicity of Vaxchora (Cholera vaccine, live, oral) in children 2 to <18 Years of Age		
Study identifier	PXVX-VC-200-006	
Design	A randomized, placebo-controlled, double-blind, single-crossover design with two treatment groups across 3 cohorts.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Day 1-29 (all cohorts);Day 1-181 (Cohort 1). Not applicable Subgroup of Cohort 1: Day 1-730
Hypothesis	Safety and Immunogenicity as well as non-inferiority with respect to seroconversion rate compared to adults in the study PXVX-VC-200-004	
Treatments groups	Cohort 1 (12-<18 years)	Randomised n=189 Vaxchora (n=163); placebo (n=26)
	Cohort 2 (6-<12 years)	Randomised n=185 Vaxchora (n=158); placebo (n=27)
	Cohort 3 (2-<6 years)	Randomised n=176 Vaxchora (n=150); placebo (n=26)

Endpoints and definitions	Co-Primary endpoint	Immunogenicity	1. seroconversion rate at Day 11 in paediatric subjects is non-inferior to the seroconversion rate at Day 11 in adults between the ages of 18 and 45 years 2. the seroconversion rate in paediatric subjects is greater than or equal to 70% with 98.3% confidence.
	Secondary endpoint	Immunogenicity	1. Seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Days 29 for all subjects. 2. Seroconversion of SVA against the classical Inaba biotype of *V. cholerae* at Days 365, 547 and 730 for all subjects participating in the optional sub-study
	Exploratory endpoint	Immune persistence	Anti–O1 lipopolysaccharide memory B cell concentration at Days 1, 91, 181 for the subjects in the active treatment group and Days 365, 547, 730 for the subjects in the active treatment group who participate in the sub-study.
Database lock	Date for database lock not provided. Includes data up to an including Day 730.		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Immunogenicity Evaluable Population (IEP) Time point: Day 11			
Descriptive statistics and estimate variability	Treatment group	Study 004 Vaxchora 18-45 years	Cohort 3 Vaxchora 2-<6 years	Overall Vaxchora 2-<18 years
	N analysable	2688	103	399
	N(%) seroconverted	2513 (93.5%)	101 (98.1%)	393 (98.5%)*
	[98.3% CI]	[92.3%, 94.6%]	[91.5%, 99.6%]	[96.2, 99.4%]
	Difference			
	(006 cohort minus 004 adults	-	4.5%	5.0%
*p<0.0001	96.7% CI on % difference	-	[-1.1%, 6.4%]	[2.8%, 6.4%]

Effect estimate per comparison	Secondary endpoint Day 29	**Comparison groups:**	**Cohort 3 2-<6 years**	**Placebo 2-<6 years**
		N analysable	98	18
		N (%) seroconverted	92 (93.2%)	0
		95% CI	[87.3%, 7.2%]	[0.0%, 7.6%]
		P-value Fisher's Exact Test of equality of seroconversion between Vaxchora and placebo	<0.0001	
	Secondary endpoint Day 29	**Comparison groups:**	**Overall (2-<18 yrs)**	**Placebo (2-<18 yrs)**
		N analysable	392	64
		N (%) seroconverted	379 (96.7%)	1 (1.6%)
		95% CI	[94.4%, 98.1%]	[0.3%, 8.3%]

		P-value Fisher's Exact Test of equality of seroconversion between Vaxchora and placebo	<0.0001		
	Secondary endpoint for long-term follow-up subgroup in Cohort 1	**Groups**	**Cohort 1 subgroup**		
		Time point	**Day 365**	**Day 547**	**Day 730**
		N analysable	70	67	62
		N (%) seroconverted	48 (68.6%)	49 (73.1%)	40 (64.5%)
		95% CI	[57.0%, 78.2%]	[61.5%, 82.3%]	[52.1%, 75.3%]
Notes	Data for the exploratory endpoint have not been provided because the data had not been analysed at the time of submission. These data will form a separate report.				

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

N/A

2.5.3. Discussion on clinical efficacy

The paediatric clinical study PXVX-VC-200-006 included subjects from 2 –<18 years of age. Vaxchora has previously been approved for persons 6 years and older. This assessment therefore focusses on the subgroup of subjects in the age range 2-<6 years in relation to the overall population aged 2-<18 years. In addition, an evaluation is made on the subgroup of participants from Cohort 1 that agreed to participate in a long-term follow-up.

Design and conduct of clinical studies

The clinical study was a blinded, randomised, placebo-controlled cross-over clinical trial.

The randomisation procedure was acceptable. To maintain blinding, subjects were asked not to discuss the taste of the administered treatment with other study participants. The integrity of the study seems not to have been jeopardized by the different instances where safety events were discussed.

Throughout the duration of the study, there were five temporary study halts, none of which lasted more than 22 days. Four out of the five halts met study stopping rules.

Handling of missing data was appropriate. There were no issued regarding the strategy used to control for Type-I error rate was adequate, although the assessment will focus on cohort 3.

The sample sizes calculation illustrate there was sufficient power to test the primary objectives. However, the protocol was revised twice to increase the number of subjects in Cohort 3 (aged 2-<6 years) to 245 subjects. The justification was that a large proportion of subjects were unable to consume the entire dose and would be ineligible for inclusion in the IEP. Despite these amendments, the sample size for Cohort 3 remained at 150 subjects of which only 103 were eligible for inclusion in the IEP, due to protocol deviations mainly relating the inability to consume the entire dose. The sample size for immunogenicity analyses is considerably reduced rendering the data less robust which is a concern.

A broader array of deviations occurred in Cohort 3 and in general with a greater frequency. Furthermore, a greater proportion in this group either missed or received an incomplete dose (Vaxchora n=34 (22.7%); placebo n=8 (30.8%). A complete dose was defined as consumption of 80% or more of the dose. Children aged 2-<6 years received this dose in a lower volume (50 mL) than older children (6-<18 years) (100 mL). The complete dose for children 2-<6 was therefore >40 mL.

The number of placebo subjects that agreed to receive Vaxchora at the end of the study was reduced compared to anticipated and the reasons for this have not been discussed in detail. The number of participants in the cross-over group that would have been eligible for inclusion in the immunogenicity evaluable population was not described. The cross-over participants were mainly followed for safety, however, immunogenicity data in these patients is requested bearing in mind the IEP population was considerably reduced due to protocol deviations.

In contrast to Cohorts 1 and 2 where the majority of participants were White and a substantial number African American, for Cohort 3, the proportion of White participants compared to Black or African American were more equivalent between the Vaxchora and placebo groups. However, in the study overall, there was a greater proportion of White participants. Few other backgrounds representative in Europe were included. The number of males and females in Cohort 3 receiving Vaxchora was balanced, however, there was a predominance of females in Cohort 3 receiving placebo compared to the other cohorts. In the study overall, the number of females and males in both the Vachora and placebo groups was balanced.

Assessment of paediatric data on clinical efficacy

This application comprises two variations. Firstly to extend the indication to include children from 2-<6 years of age by showing that the seroconversion data at day 11 post-vaccination was non-inferior to data from the adult population (aged 18-45 years) at Day 11 in the clinical study PXVX-VC-200-004. Secondly, to include immunogenicity data from the long-term follow-up of a subgroup of Cohort 1 subjects (aged 12-<18 years) up to two years of follow-up post-vaccination.

Efficacy data is based on the IEP. The IEP comprised treated subjects that had evaluable results from both Day 1 and Day 11 assays, received the correct vaccine according to randomisation and had no major protocol violations that affect immunogenicity. There was a lower number of evaluable subjects in Cohort 3 (68.7% in the Vaxchora group; 76.9% in the placebo group) compared to Cohorts 1 (96.3% Vaxchora; 88.5% placebo) and Cohort 2 (88.0% Vaxchora; 88.9% placebo). Cohort 3 (2-<6 years) was given the same dose of Vaxchora, but in a lower volume (50 mL compared to 100 mL for Cohorts 1 and 2). Despite this, 25 subjects (17.1%) were unable to drink at least 80% of the dose (40 mL). This is a concern because the vaccine is currently approved for home use. The potential for vaccination error in children 2-6 years in this setting is therefore substantial. Immunogenicity data for subjects that did not received the complete dose ($\geq$40 mL) was provided by the MAH and a recommendation has been introduced in the SmPC in the event of an incomplete dose.

SVA seroconversion corresponded to a $\geq$4 fold increase in titre from baseline. Seroconversion at Day 11 has been correlated with protection in clinical study PXVX-CV-200-003. The seroconversion rates in

children 2-<6 years of age at Day 11 as well as ages 2-<18 at Day 11 were non-inferior to the seroconversion rates in adults aged 18-45 from the PXVX-VC-200-004 study at Day 11. The primary end point was therefore met. The seroconversion rate for Cohort 3 decreased from 98.1% at Day 11 to 93.9% at Day 29 but remained above the threshold for non-inferiority.

The geometric mean titres (GMT) and the geometric mean fold increases over baseline (GMFI) at Day 11 were lower in Cohort 3 compared to Cohorts 1 and 2. This could be related to a lower immunogenicity capacity in young children and therefore may have implications for the duration of protection in this age group. In agreement with the other cohorts, the GMT and GMFI in Cohort 3 declined at Day 29 compared to Day 11. GMT and GMFI from study PXVX-VC-00-004 was provided by the MAH for comparison with. Although the titres were considerably lower for the infant/adolescent (PXVX-VC-200-006) at day 29, the GMFI was similar. Data beyond Day 29 was only available for Cohort 1.

The MAH provided immunogenicity data for a subgroup of Cohort 1 IEP (n=72) from Day 1 to Day 730 (i.e. 2 years post-vaccination). After one year (Day 365) the seroconversion rate was 68.6% (n=70) which remained relatively stable a year later (Day 730) at 64% (n=62). Regarding GMT in this subgroup, maximum GMT was achieved at Day 11 (9035.4, n=72) which declined to 2791.7 (n=72) at Day 29. However, at one year, (Day 365) the GMT was reduced to 158.4 (n=70) which remained relatively stable a year later (Day 730) at 133.8 (n=62). Regarding GMFI, this was highest at Day 11 (279.2, n=72) but after one year (Day 365) this was reduced to 4.8 (n=70) and after two years (Day 730) it was 4.1 (n=62). These later time points are at the threshold of seroconversion.

SVA were measured against Classical Inaba, homologous to the *V.cholerae* in Vaxchora. However, no analyses were carried out to determine responses to heterologous *V. cholera*, as had been done in the study of older adults PXVX-VC-200-005, where lower protection was observed against these strains compared to in adults (18-45 years of age). Since lower titres were obtained particularly to the Ogawa serotype in study PXVX-VC-200-005, it is likely that lower titres may also be observed in children 2-<18 years. It is noteworthy that the predominant *V.cholerae* biotype currently worldwide is El Tor.

SVA seroconversion in itself is not a correlate of protection, furthermore, the threshold SVA titre required to confer protection is not known. As such, the level of protection afforded by Vaxchora for Cohort 1 at one and two years post-vaccination is not known. The duration of immune memory is not known, and this data will be provided as a separate report which is requested within the next 12 months as a post-authorisation measure (LEG).

For all but two participants in Cohort 3, sweetener was added to Vaxchora. It is therefore not possible to determine whether the addition of sweetener made the vaccine more palatable for Cohort 3. In contrast, it was possible to assess the effect of adding sweetener to Vaxchora on palatability for the other cohorts. The addition of sweetener was not found to improve palatability. Nevertheless, addition of sweetener will remain optional for all age groups. Only sucrose and stevia may be used as other sweeteners and flavourings were found to be incompatible with the buffer/Vaxchora solution. Since not all vaccinees may have scales accurate to 1g, the MAH has modified the SmPC relating levels of sugar and sweetener respectively also in terms of teaspoon measurements.

Despite the addition of sweetener, 30 of the randomised subjects in Cohort 3 (2-<6 years) did not consume a complete dose defined as at least 40 mL of the 50 mL dose. The 30 subjects received from 0 to 40 ml of the 50 ml. A total of 26 participants were excluded from the IEP because they received <40 mL of the dose. For one of these subjects, this was due to a dosing error. The MAH provided seroconversion data for participants that did not receive the complete dose. Seroconversion rate was lower for those that received <50% of the full dose. The SmPC has therefore been modified request that vaccinees contact their doctor in the event of consuming <50% of the full dose. A second dose can be administered within three days of the first. This timing is necessary to avoid potential generation of SVA from the first incomplete dose which would prevent the second dose of Vaxchora from replicating and inducing an immune response.

2.5.4. Conclusions on the clinical efficacy

The SVA seroconversion rate at Day 11 post-vaccination in children 2-<6 years in the PXVX-VC-200-006 study was non-inferior to adults 18-45 years in the PXVC-VC-200-004 clinical study. The same applied to Cohorts 1 (12-<18 years) and Cohort 2 (6-<12) respectively and for the overall study group (2-<18 years). Furthermore, the lower confidence interval for seroconversion rate >70% [CI 98.3%] was observed for all individual cohorts and overall. The primary endpoint was therefore met. In agreement with other studies, the seroconversion rate was greatest at Day 11 post-vaccination. However, the GMT and GMFI was lower in Cohort 3 (2-<6 years) compared to Cohorts 1 (12-<18 years) and 2 (6-<12 years) at Day 11.

In a subgroup of subjects aged 12-<18 years, long-term follow-up immunogenicity data was provided. SVA seroconversion rates declined over time and remained stable at one year and at two years post-vaccination at 68.6% [95% CI: 57.0%, 78.2%] (n=79) and 64.5% [95% CI: 52.1%, 73.5%] (n=62) respectively.

In order to provide further data on immune memory, the MAH will submit within 12 months the results of the exploratory endpoint assessing the duration of immune memory based on B-cell data at Days 1, 91, 181 for the subjects in the active treatment group and Days 365, 547, 730 for the subjects in the active treatment group who participate in the sub-study.

2.6. Clinical safety

Introduction

Summary of safety profile

The most frequent reported adverse reactions following Vaxchora administration are tiredness (30.2%), headache (28.3%), abdominal pain (18.4%), nausea/vomiting (17.7%), and lack of appetite (15.7%).

Tabulated summary of adverse reactions

The adverse reaction frequency classification used is as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Adverse Reactions	***Frequency***
Metabolism and nutrition disorders	
Decreased appetite	Very common
Nervous system disorders	
Headache	Very common
Dizziness	Uncommon
Gastrointestinal disorders	
Abdominal pain, nausea/vomiting	Very common
Diarrhoea	Common
Flatulence, constipation, abdominal distension, dyspepsia, abnormal faeces, dry mouth, eructation	Uncommon
Skin and subcutaneous tissue disorders	
Rash	Uncommon
Musculoskeletal and connective tissue disorders	
Arthralgia	Uncommon
Chills	Rare
General disorders and administration site conditions	

Fatigue	Very common
Pyrexia	Uncommon

Paediatric population

A clinical trial was conducted in 550 children age 2 to <18 years. Based on the results of this trial the type of adverse reactions in children are expected to be similar to those in adults. Some adverse reactions were more common in children than adults, including fatigue (35.7% vs 30.2%), abdominal pain (27.8% vs 18.4%), vomiting (3.8% vs 0.2%), decreased appetite (21.4% vs 15.7%) and pyrexia (2.4% vs 0.8%).

Patient exposure

The primary Safety Objective was to evaluate the safety and tolerability of Vaxchora using the following endpoints: incidence and severity of solicited AEs through Day 8, and Days 181-188 for the PCO (placebo cross-over) group (abdominal pain, nausea, vomiting, diarrhoea, headache, fever, fatigue, tiredness, and lack of appetite); incidence and severity of unsolicited AEs through Day 29 and Days 181-209 for the PCO group; and incidence of SAEs through Day 181 (Day 730 for the long-term sub-study subjects).

The Safety Population was specified in the protocol to include all subjects who enrolled in the study and who received vaccination with Vaxchora or Placebo. There were three subjects (two from Cohort 1 and one from Cohort 2) who received Vaxchora instead of their randomized placebo assignment. These three subjects have been included in the Vaxchora Safety Population summaries. There were 9 subjects who were enrolled and received treatment twice. One of them received Vaxchora followed by placebo; all other duplicate subjects received two doses of Vaxchora.

In Cohort 1 (12 to < 18 y), 165 subjects received any amount of Vaxchora dose and 24 subjects received any amount of placebo. In Cohort 2 (6 to < 12 y), 157 subjects received any amount of Vaxchora dose and 25 subjects received any amount of placebo. In Cohort 3 (2 to < 6 y), 146 subjects received any amount of Vaxchora dose and 26 subjects received any amount of placebo. In total, 468 Vaxchora recipients and 75 Placebo recipients were included in the safety analysis.

Adverse events

The majority of subjects in all three cohorts experienced at least one AE. Within each cohort, frequencies of AEs were similar between the Vaxchora and Placebo treatment groups. Frequencies of AEs were generally higher in both treatment groups in Cohort 1 than in Cohort 2 or 3, consistent with reporting bias.

Severe or worse AEs were infrequent in all cohorts and both treatment groups. There were no deaths, treatment-related SAEs or discontinuations due to AEs in either cohort or treatment group. There were four subjects with unrelated SAEs reported in the Vaxchora recipients in Cohort 1 and one placebo subject in Cohort 3.

Solicited Adverse Events

Solicited AEs were collected from Day 1 through Day 8, and Day 181 through Day 188. They included: abdominal pain, headache, lack of appetite, tiredness, diarrhoea, nausea, vomiting, and fever (See table below).

Overall, the majority of subjects in both treatment groups reported at least one solicited AE (Vaxchora 55.1%; Placebo 50.7%). Solicited AEs were also reported by a higher proportion of subjects in Cohort 1 (Vaxchora 68.5%; Placebo 66.7%) than in Cohort 2 (Vaxchora 54.8%; Placebo 52.0%) and Cohort 3 (Vaxchora 40.4%; Placebo 34.6%).

By individual event, the most frequently reported solicited AEs in Vaxchora recipients were tiredness (35.7%), headache (27.4%), and abdominal pain (27.8%). These three events were the most frequent in Cohorts 1 and 2. For Cohort 3, tiredness, lack of appetite, and abdominal pain were the most frequent events. Fever was reported in 3/165 Vaxchora subjects in Cohort 1 (1.8%), 5/157 Vaxchora subjects in Cohort 2 (3.2%) and 3/146 Vaxchora subjects in Cohort 3 (2.1%). Diarrhea was reported in 6/165 VAXCHORA subjects in Cohort 1 (3.6%), was not reported in Cohort 2 and in 1/146 Vaxchora subjects in Cohort 3 (0.7%). Abdominal pain and lack of appetite were more frequently reported in Vaxchora recipients (27.8% and 21.4%, respectively) than in Placebo recipients (18.7% and 14.7%). Tiredness, headache, vomiting, nausea, fever, and diarrhea had similar rates between treatment groups.

By severity, Vaxchora recipients reported mostly mild (36.8%) or moderate (16.0%) solicited AEs. A total of 11 subjects (2.4%) of Vaxchora subjects reported severe or worse solicited AEs. Placebo recipients reported mostly mild (33.3%) or moderate (14.7%) solicited AEs. A total of 2 subjects (2.7%) of placebo subjects reported severe solicited AEs.

During the same time period 50.7% of Placebo recipients reported at least one solicited AE. Similar to the Vaxchora group, the most frequently reported AEs in all Placebo subjects included tiredness reported in 23/75 (30.7%) subjects, headache reported in 19/75 (25.3%) subjects, and abdominal pain or nausea reported in 14/75 (18.7%) subjects each. Again, lack of appetite, vomiting, fever, and diarrhea were each reported at lower frequencies.

Table 15. Summary of Adverse Events by Cohort and Treatment Group

Category [n (%)]	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 – <6)		Overall (ages 2 – <18)	
	VAXCHORA (N=165)	Placebo (N=24)	VAXCHORA (N=157)	Placebo (N=25)	VAXCHORA (N=146)	Placebo (N=26)	VAXCHORA (N=468)	Placebo (N=75)
Subjects with any adverse event	116 (70.3%)	16 (66.7%)	93 (59.2%)	15 (60.0%)	74 (50.7%)	12 (46.2%)	283 (60.5%)	43 (57.3%)
Severe or worse	7 (4.2%)	1 (4.2%)	5 (3.2%)	0	2 (1.4%)	1 (3.8%)	11 (2.4%)	2 (2.7%)
Subjects with any solicited adverse event through Day 8	113 (68.5%)	16 (66.7%)	86 (54.8%)	13 (52.0%)	59 (40.4%)	9 (34.6%)	258 (55.1%)	38 (50.7%)
Severe or worse	4 (2.4%)	1 (4.2%)	5 (3.2%)	0	2 (1.4%)	1 (3.8%)	11 (2.4%)	2 (2.7%)
Subjects with any unsolicited adverse event through Day 29	46 (27.9%)	7 (29.2%)	28 (17.8%)	8 (32.0%)	38 (26.0%)	6 (23.1%)	112 (23.9%)	21 (28.0%)
Severe or worse	1 (0.6%)	0	1 (0.6%)	0	0	0	2 (0.4%)	0
Subjects with any treatment-related adverse event	99 (60.0%)	12 (50.0%)	64 (40.8%)	9 (36.0%)	49 (33.6%)	9 (34.6%)	212 (45.3%)	30 (40.0%)
Severe or worse	3 (1.8%)	0	1 (0.6%)	0	1 (0.7%)	1 (3.8%)	5 (1.1%)	1 (1.3%)
Subjects with any treatment-related solicited adverse event through Day 8	95 (57.6%)	12 (50.0%)	58 (36.9%)	9 (36.0%)	44 (30.1%)	8 (30.8%)	197 (42.1%)	29 (38.7%)
Severe or worse	3 (1.8%)	0	1 (0.6%)	0	1 (0.7%)	1 (3.8%)	5 (1.1%)	1 (1.3%)
Subjects with any treatment-related unsolicited adverse event through Day 29	30 (18.2%)	5 (20.8%)	18 (11.5%)	0	14 (9.6%)	2 (7.7%)	62 (13.2%)	7 (9.3%)
Severe or worse	0	0	0	0	0	0	0	0

Subjects with any serious adverse event	4 (2.4%)	0	0	0	0	1 (3.8%)	4 (0.9%)	1 (1.3%)
Subjects with any treatment-related serious adverse event	0	0	0	0	0	0	0	0
Subjects who permanently discontinued study due to an adverse event	0	0	0	0	0	0	0	0
Subjects who died during the study	0	0	0	0	0	0	0	0

Table 16. Solicited AEs by Treatment Group, Highest Severity, and Cohort

Solicited Event [n (%)]	Cohort 1 (ages 12 – <18)		Cohort 2 (ages 6 – <12)		Cohort 3 (ages 2 – <6)		Overall (ages 2 – <18)	
	VAXCHORA (N=165)	Placebo (N=24)	VAXCHORA (N=157)	Placebo (N=25)	VAXCHORA (N=146)	Placebo (N=26)	VAXCHORA (N=468)	Placebo (N=75)
Any Event	113 (68.5%)	16 (66.7%)	86 (54.8%)	13 (52.0%)	59 (40.4%)	9 (34.6%)	258 (55.1%)	38 (50.7%)
Mild	78 (47.3%)	13 (54.2%)	59 (37.6%)	7 (28.0%)	35 (24.0%)	5 (19.2%)	172 (36.8%)	25 (33.3%)
Moderate	31 (18.8%)	2 (8.3%)	22 (14.0%)	6 (24.0%)	22 (15.1%)	3 (11.5%)	75 (16.0%)	11 (14.7%)
Severe	3 (1.8%)	1 (4.2%)	5 (3.2%)	0	1 (0.7%)	1 (3.8%)	9 (1.9%)	2 (2.7%)
Potentially Life-threatening	1 (0.6%)	0	0	0	1 (0.7%)	0	2 (0.4%)	0
Tiredness	67 (40.6%)	9 (37.5%)	55 (35.0%)	8 (32.0%)	45 (30.8%)	6 (23.1%)	167 (35.7%)	23 (30.7%)
Mild	52 (31.5%)	8 (33.3%)	35 (22.3%)	5 (20.0%)	28 (19.2%)	4 (15.4%)	115 (24.6%)	17 (22.7%)
Moderate	14 (8.5%)	0	19 (12.1%)	3 (12.0%)	17 (11.6%)	2 (7.7%)	50 (10.7%)	5 (6.7%)
Severe	0	1 (4.2%)	1 (0.6%)	0	0	0	1 (0.2%)	1 (1.3%)
Potentially Life-threatening	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0
Headache	74 (44.8%)	11 (45.8%)	41 (26.1%)	6 (24.0%)	13 (8.9%)	2 (7.7%)	128 (27.4%)	19 (25.3%)
Mild	57 (34.5%)	11 (45.8%)	30 (19.1%)	5 (20.0%)	10 (6.8%)	1 (3.8%)	97 (20.7%)	17 (22.7%)
Moderate	16 (9.7%)	0	9 (5.7%)	1 (4.0%)	3 (2.1%)	1 (3.8%)	28 (6.0%)	2 (2.7%)
Severe	1 (0.6%)	0	2 (1.3%)	0	0	0	3 (0.6%)	0
Potentially Life-threatening	0	0	0	0	0	0	0	0
Abdominal pain	62 (37.6%)	4 (16.7%)	43 (27.4%)	6 (24.0%)	25 (17.1%)	4 (15.4%)	130 (27.8%)	14 (18.7%)
Mild	47 (28.5%)	3 (12.5%)	37 (23.6%)	4 (16.0%)	21 (14.4%)	4 (15.4%)	105 (22.4%)	11 (14.7%)

Moderate	14 (8.5%)	1 (4.2%)	6 (3.8%)	2 (8.0%)	4 (2.7%)	0	24 (5.1%)	3 (4.0%)
Severe	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0
Potentially Life-threatening	0	0	0	0	0	0	0	0
Lack of appetite	48 (29.1%)	3 (12.5%)	24 (15.3%)	5 (20.0%)	28 (19.2%)	3 (11.5%)	100 (21.4%)	11 (14.7%)
Mild	39 (23.6%)	3 (12.5%)	20 (12.7%)	4 (16.0%)	18 (12.3%)	2 (7.7%)	77 (16.5%)	9 (12.0%)
Moderate	9 (5.5%)	0	3 (1.9%)	1 (4.0%)	10 (6.8%)	1 (3.8%)	22 (4.7%)	2 (2.7%)

Severe	0	0	1 (0.6%)	0	0	0	1 (0.2%)	0
Potentially Life-threatening	0	0	0	0	0	0	0	0
Nausea	37 (22.4%)	6 (25.0%)	22 (14.0%)	4 (16.0%)	10 (6.8%)	4 (15.4%)	69 (14.7%)	14 (18.7%)
Mild	28 (17.0%)	5 (20.8%)	19 (12.1%)	2 (8.0%)	9 (6.2%)	4 (15.4%)	56 (12.0%)	11 (14.7%)
Moderate	8 (4.8%)	1 (4.2%)	3 (1.9%)	2 (8.0%)	1 (0.7%)	0	12 (2.6%)	3 (4.0%)
Severe	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0
Potentially Life-threatening	0	0	0	0	0	0	0	0
Vomiting	9 (5.5%)	0	7 (4.5%)	0	2 (1.4%)	3 (11.5%)	18 (3.8%)	3 (4.0%)
Mild	5 (3.0%)	0	5 (3.2%)	0	2 (1.4%)	2 (7.7%)	12 (2.6%)	2 (2.7%)
Moderate	3 (1.8%)	0	2 (1.3%)	0	0	1 (3.8%)	5 (1.1%)	1 (1.3%)
Severe	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0
Potentially Life-threatening	0	0	0	0	0	0	0	0
Fever	3 (1.8%)	0	5 (3.2%)	1 (4.0%)	3 (2.1%)	1 (3.8%)	11 (2.4%)	2 (2.7%)
Mild	2 (1.2%)	0	0	0	1 (0.7%)	0	3 (0.6%)	0
Moderate	0	0	1 (0.6%)	1 (4.0%)	0	0	1 (0.2%)	1 (1.3%)
Severe	1 (0.6%)	0	4 (2.5%)	0	1 (0.7%)	1 (3.8%)	6 (1.3%)	1 (1.3%)
Potentially Life-threatening	0	0	0	0	1 (0.7%)	0	1 (0.2%)	0
Diarrhea	6 (3.6%)	1 (4.2%)	0	0	1 (0.7%)	1 (3.8%)	7 (1.5%)	2 (2.7%)
Mild	3 (1.8%)	0	0	0	0	1 (3.8%)	3 (0.6%)	1 (1.3%)
Moderate	0	1 (4.2%)	0	0	1 (0.7%)	0	1 (0.2%)	1 (1.3%)
Severe	3 (1.8%)	0	0	0	0	0	3 (0.6%)	0
Potentially Life-threatening	0	0	0	0	0	0	0	0

AE = Adverse Event
Source
* $p < 0.05$ from Fisher's Exact test of equality of event rate between VAXCHORA and Placebo

Solicited Adverse Events by Relationship to Study Treatment

The most common treatment-related solicited AEs among Vaxchora recipients were tiredness, abdominal pain and headache. For most subjects (n=134), related solicited AEs were mild (28.6%), 58 subjects had moderate related solicited AEs (12.4%), and 5 experienced a severe related solicited AE (1.1%).

Across all cohorts, there were 6 individual subjects who reported severe solicited AEs that were considered related to treatment. Of the related severe solicited AEs, 3 subjects reported severe diarrhoea; 3 subjects severe fever; One subject also reported severe nausea and vomiting and another subject also reported severe abdominal pain. All of these individuals were Vaxchora recipients, except for one who received placebo.

Across all cohorts, there were 7 individual subjects who reported severe solicited AEs that were considered not related to treatment. Of the unrelated severe solicited AEs, 3 subjects (reported severe headaches, 3 subjects reported severe tiredness, and 5 subjects reported severe fever. All of these individuals were Vaxchora recipients, except for one who received placebo.

Unsolicited Adverse Events

In total, 13.2% of Vaxchora recipients reported an unsolicited AE that was considered related to study treatment, while 9.3% of Placebo recipients reported an unsolicited AE that was considered related to study treatment. Loose stools were the most frequently reported treatment-related unsolicited AE among both Vaxchora and Placebo recipients. Other related unsolicited AEs reported by Vaxchora recipients included: fatigue, decreased appetite, abdominal pain, flatulence, headache, abdominal distension, cough, dermatitis diaper, diarrhea, dyspepsia, eructation, feeling cold, insomnia, irritability, myalgia, pyrexia, rash generalized, rectal tenesmus, upper respiratory tract infection, viral infection, and vomiting. All of these unsolicited AEs were reported as 'possibly related to Vaxchora.

The majority of unsolicited AEs were mild to moderate. Eleven severe (Grade 3) events were reported and included: fatigue, pyrexia, viral pharyngitis, decreased appetite, headache, lower limb fracture (reported as an SAE), acute asthma with pneumonia, hyperglycemia and influenza (reported as an SAE), intentional acetaminophen overdose (reported as an SAE), and neck swelling (reported as an SAE). Of these events, 4 occurred in a Vaxchora Subject, who reported severe fatigue, pyrexia, decreased appetite, and headache and 4 occurred in a Placebo Subject, who reported acute asthma, pneumonia, hyperglycemia and influenza. None of the Grade 3 events were considered treatment-related.

There were one potentially life-threatening (Grade 4) unsolicited events reported, an intentional acetaminophen overdose not related to treatment.

Analysis of Adverse Events by Demographic and Other Baseline Characteristics

Differences in age may have contributed to subjects' ability to communicate feeling ill. This inherent difference between the cohorts possibly contributed to a bias in reporting certain subjective solicited and unsolicited AEs, such as tiredness or lack of appetite. Cohort 1, for example, had a higher report rate of mild and moderate AEs compared to Cohort 2. The report rate in Cohort 3 was further reduced highlighting the subjects inability to communicate feeling ill.

Across all age groups, there was no difference in adverse event incidence between the males and females and Vaxchora and placebo were of similar incidence within each sex strata. Of note, the girls aged 12 to <18 had rates 20-30% higher than all the other sex by age groups. Similarly, there was no clear pattern of difference in AE rates by race (categorized as White, Black or African American and Other). The Vaxchora and placebo rates were similar within each race by age group strata and similar across races within each age cohort. Overall, the White race category was approximately 20% higher than the other

races but this is due to a higher percentage of subjects in Cohort 1 being White. Cohorts 2 and 3 had more equal distributions across the White and Black races. Therefore, the higher rates observed in Cohort 1 contributed to the apparent disparity in the overall rate for Whites.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs) were reported in five subjects. The SAEs were all considered as not related to the study drug.

There were no deaths or other significant AEs.

Laboratory findings

No paediatric data are available.

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

No paediatric data are available.

Discontinuation due to adverse events

N/A

Post marketing experience

Post marketing data from US (PAER) are available through June 2019. The reports mainly involve off-label use, suspected vaccination failure and administration errors. The first PSUR/PBRER was submitted in August 2020, covering the period 10 June 2019 to 09 June 2020. No post-marketing safety signals are currently under investigation.

2.6.1. Discussion on clinical safety

The total number of children in the safety population of 468 subjects, including 146 subjects 2 to -<6 years of age, is considered satisfactory. According to the study plan, 210 subjects were expected in cohort 3. Due to slow recruitment it was described in a study amendment how to increase the number of subjects. Instead of a higher number of subjects in cohort 3, the actual number of 146 was lower than in cohort 1 (165 subjects) and cohort 2 (157 subjects).

Safety assessment of the vaccine included evaluation of solicited AEs (abdominal pain, headache, lack of appetite, tiredness, diarrhoea, nausea, vomiting, and fever) and unsolicited AEs. Solicited AEs were monitored through day 8 and days 181-188 for the PCO (placebo cross-over) group, and unsolicited AEs through Day 29 and Days 181-209 for the PCO group. Unsolicited SAEs were monitored through Day 181 (Day 730 for the long-term sub-study subjects).

The total number of AEs (all cohorts included) in the placebo (0.9% saline) and Vaxchora recipients was similar, 60.5% in the Vaxchora arm and 57.3% in the placebo arm (solicited and unsolicited AEs).

Solicited AEs were reported by a higher proportion of subjects in Cohort 1 (Vaxchora 68.5%; Placebo 66.7%) than in Cohort 2 (Vaxchora 54.8%; Placebo 52.0%) and Cohort 3 (Vaxchora 40.4%; Placebo 34.6%). This is consistent with an age-related reporting bias, as older children have greater ability to communicate possible AEs.

By individual event, the most frequently reported solicited AEs in Vaxchora recipients (all cohorts) were tiredness (35.7%), headache (27.4%) and abdominal pain (27.8%). Abdominal pain and lack of appetite were more frequently reported in Vaxchora recipients (27.8% and 21.4%, respectively) than in Placebo recipients (18.7% and 14.7%). The other events had similar rates between treatment groups. Most solicited AEs were mild for Vaxchora and placebo recipients (36.8%, 33.3%) or moderate (16.0%, 14.7%). 2.3 % of Vaxchora recipients reported severe or worse solicited AEs (2.7% of placebo recipients).

For cohort 3 tiredness (Vaxchora 30.8%, placebo 23.1%), lack of appetite (Vaxchora 19.2%, placebo 11.5%) and abdominal pain (Vaxchora 17.1%, placebo 15.4%) were the most frequent solicited AEs.

Unsolicited AEs were reported for 23.9% and 28.0% for the Vaxchora and placebo groups (all cohorts), respectively. The corresponding numbers for unsolicited AEs considered treatment-related were 13.2 % and 9.3%. Loose stools were the most frequently reported treatment-related unsolicited AE among both Vaxchora and Placebo recipients. The majority of unsolicited AEs were mild to moderate. There were four subjects with SAEs reported in the Vaxchora recipients in Cohort 1 and one placebo subject in Cohort 3. None of the SAEs were considered treatment-related.

The safety of Vaxchora in children 2-< 6 years (cohort 3) appears to be similar to the safety profile in older children (cohort 1 and 2).

The product is intended for self-administration. As discussed when the product was first authorized, there is a considerable risk of medication error when the product is prepared and self-administered outside a health care setting. This is of concern, as in the worst case this can cause vaccine failure. Consequently, the MAH committed to prepare and submit educational material (HCP guide and patient guide) to avoid medication errors. There is an increased risk of medication errors when the dose is prepared and given to the youngest children (age 2 -<6). Half of the buffer solution should be discharged before addition of the active content which increases the risk of reconstitution errors. In addition, it may be difficult to get the child to consume a sufficient amount of the dose to achieve protection, even if sweetener is added. In the study 25 subjects (17,1%) failed to consume 80% of the vaccine in cohort 3.

The MAH is of the opinion that a new usability test for this age category is not needed. The argument is that just adding one step to the vaccine preparation process (discarding half (50%) of the buffer solution), while no new materials/equipment is needed, does not make much change to the preparation process. However, the MAH has agreed to perform a usability test for the age category 6 to 24 months as part of the PIP. The same formulation will be used, but 90% (90 mL) of the buffer solution will be discarded. Also, a dosing syringe will potentially be tested. As it is more challenging to administer an oral dose to the 6 to 24 months old children than the 2-6 years age category, the MAHs plan for usability testing is supported.

According to the MAH the accuracy of the amount of sucrose or stevia does not impact the potency of the product as long as it is controlled around the amount specified. It is not feasible to provide sweetener/sugar sachets to accompany the product, but it is proposed that the statements can be clarified further. The MAH also agrees that stevia is much sweeter than sucrose and therefore proposes to amend the statement in the SmPC and Package Leaflet as follows:

SmPC: *"…Sucrose (up to 4 g / 1 teaspoon) or stevia sweetener (no more than 1 gram / ¼ teaspoon) may then be stirred into the suspension if desired. …"*

Package Leaflet: *"…If desired, after stirring in sachet 2 for at least 30 seconds, stevia sweetener (no more than 1 gram or ¼ teaspoon) or sugar (sucrose, no more than 4 gram or 1 teaspoon) may be added, and then stirred into the suspension…"*

The new wording of the SmPC and Package Leaflet differentiating between Stevia and sucrose, Stevia being a more potent sweetener, and relating the amount of sweetener to a teaspoon are supported.

The potential use of an oral syringe to ensure that the child consumes a sufficient amount of vaccine to provide protection, has been discussed. The MAH believes that as an oral dosing device has not been used in studies in children to date it would be difficult to recommend this to parents, especially as 50 mL of solution delivered by such means may prove rather difficult to administer in a young child. The MAH is currently working on the plans for a Vaxchora study in infants (6 -24 months) under the terms of the current paediatric implementation plan (EMEA-001490-PIP01-13). The clinical team have taken onboard the comments of the EMA in association with the current paediatric indication (inclusion of 2 to < 6 year old) variation and propose to use an oral dosing device in the infant study (EBSI-VC-200-008). In this study, a 10 mL dose will be administered using an oral dosing device (design/type yet to be confirmed). Depending upon the outcome of that study Emergent will determine whether it is appropriate to recommend a dosing device in the 2 to <6 year old population.

The MAH has revised the SmPC/Package Leaflet to address the medication error issue in children age 2 to <6 years.

Based on data on seroconversion amongst subjects who consumed < 80% of the expected dose, the following text has been added to the SmPC section 4.2:

Consumption of less than a half dose may result in decreased protection. If less than half the dose is consumed, consideration may be given to repeating a full dose of Vaxchora within 72 hours.

Regarding the amount and type of sweetener than can be added for children 2 to <6 years the following text has been added to SmPC section 6.6:

Sucrose (up to 4 g / 1 teaspoon) or stevia sweetener (no more than 1 gram / ¼ teaspoon) may then be stirred into the suspension if desired. DO NOT add other sweeteners as this may reduce the effectiveness of the vaccine.

To SmPC Annex II D the following text has been added:

Health care professional Physician educational material:

There is an increased potential risk of medication errors when the vaccine is prepared and given to children 2 to < 6 years old.

The patient information pack:

Increased attention to instructions should be given when preparing and administering vaccine to children 2 to < 6 years of age.

To **Package leaflet: Information for the user section 3. How to take Vaxchora,** the following text has been added:

However for children 2 to less than 6 years old take note of Step 8 in the instructions on how to prepare the vaccine, shown below.

Also some of the text in the drawings have been revised.

2.6.1. Conclusions on clinical safety

The safety profile of Vaxchora in children 2 -< 6 years seems to be similar to that in older children (6-<18 years). Most AEs are mild or moderate. No treatment-related SAEs have been reported. The vaccine should be prepared and administered outside a healthcare setting. Medication errors is a potential risk in the RMP, and the MAH committed to prepare and distribute educational material to mitigate this risk when the product was marketed. No new safety concerns have been identified, but there is an increased risk of medication errors when the vaccine is prepared and given to the youngest children (2 -<6 years). The MAH has responded to a request to implement various measures to reduce this risk of medication errors and changed parts of the Risk Management Plan and SmPC/Package Leaflet accordingly. The educational material has also been updated.

2.6.2. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted an updated RMP version 3.0 with this application. The variation proposes to lower the approved indication for Vaxchora to include children from 2 years of age.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 is acceptable.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Medication errors
Missing information	• Use during pregnancy

Pharmacovigilance plan

There were no changes proposed in the pharmacovigilance plan.

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
Medication errors	**Routine risk minimisation measures:** • SmPC sections 4.2, 6.3, 6.4, 6.6 • PL section 2, 3, 5 • Medicinal product subject to medical prescription **Additional risk minimisation measures:** Additional risk minimisation measures will include a patient guide containing key messages and administration highlights. Also, a health care professional's guide (checklist) for assisting the provider with instructing patients will be provided.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None proposed
Missing information		
Use during pregnancy	**Routine risk minimisation measures:** • SmPC sections 4.6 • PL section 2 • Medicinal product subject to medical prescription **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** The PXVX-VC-200-PR VAXCHORA Pregnancy Registry observational study was initiated in September 2016 and is ongoing. The Applicant proposes to expand this study to the EU.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. Particularly, information with regard to consumption of less than a half dose, which may result in decreased protection has been added to the product information. The Package Leaflet has been updated accordingly.
In addition, the MAH took the opportunity to include editorial changes in the SmPC and Annex II.

Please refer to the Product Information for the complete updates approved within the current procedure.

4.1 Therapeutic indications

Vaxchora is indicated for active immunisation against disease caused by *Vibrio cholerae* serogroup O1 in adults and children aged **2** ~~6~~ years and older.

4.2 Posology and method of administration

Posology

*Adults and children aged **2** ~~6~~ years and older*

A single oral dose should be administered at least 10 days prior to potential exposure to *V. cholerae* O1.

Method of administration

[…]

Consumption of less than a half dose may result in decreased protection. If less than half the dose is consumed, consideration may be given to repeating a full dose of Vaxchora within 72 hours.

4.4 Special warnings and precautions for use

[…]

Limitations of the clinical data

Clinical trials were conducted in individuals age **2** ~~6~~ to 64 years old. Efficacy was demonstrated using human cholera challenge at 10 days or 3 months post-vaccination in adults age 18-45 years and immunobridging to other populations based on seroconversion rate. Immunogenicity data are available for **24** ~~6~~ months post-vaccination **(see section 5.1)**. There are no immunogenicity or efficacy data in individuals over 64 years of age.

[…]

4.8 Undesirable effects

[…]

Paediatric population
A clinical trial was conducted in ~~374~~**550** children age ~~6~~**2** to <18 years. Based on the results of this trial the type of adverse reactions in children are expected to be similar to those in adults. Some adverse reactions were more common in children than adults, including ~~headache (36.0% vs 28.3%),~~ fatigue (~~37.9~~ **35.7**% vs 30.2%), abdominal pain (~~32.6~~ **27.8**% vs 18.4%), vomiting (~~5.3~~ **3.8**% vs 0.2%), decreased appetite (~~22.4~~ **21.4**% vs 15.7%) and pyrexia (~~2.5~~ **2.4**% vs 0.8%).

[…]

2.8.1. User consultation

No justification for not performing a full user consultation with target patient groups on the Package Leaflet has been submitted by the MAH. However, the changes to the Package leaflet are minimal and do not require user consultation with target patient groups so the approach is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Vaxchora is a live attenuated bacterial vaccine containing the CVD 103-HgR vaccine strain of *Vibrio cholerae* serogroup O1, biotype classical, serotype Inaba. The Anatomical Therapeutic Chemical (ATC) code is J07AE02. Vaxchora is a single-dose, orally administered vaccine intended for use by individuals from non-cholera endemic areas who may be at risk of cholera infection.

The bacterium *Vibrio cholerae* is the etiological agent of cholera, an acute and potentially fatal toxigenic diarrhoeal illness. Humans are the only host for *V. cholerae*. The vibrio predominantly associated with epidemic cholera is *V. cholera* serogroup O1.

O1 vibrios contain an enterotoxin (cholera toxin) which is responsible for causing diarrhoea.

V. cholerae O1 is divided into two biotypes, Classical and El Tor. Both biotypes contain two major serotypes, Inaba and Ogawa. Worldwide, *V. cholerae* O1 El Tor is currently the predominant biotype. (Vaxchora consists of live attenuated *V. cholerae* O1 Classical biotype).

3.1.2. Available therapies

Clinical infection with cholera is often mild but can be severe and life-threatening. Cholera can be successfully treated with prompt and adequate replacement of lost fluid and electrolytes. Individuals with mild and moderate cholera can usually be treated with oral rehydration salts (ORS), pre-packaged mixtures of glucose and salts mixed with safe drinking water and orally administered.

In Europe, Australia, New Zealand, and Canada, an inactivated cholera vaccine is available for travellers (Dukoral), and therefore fulfils to some extent, the medical need for this travel vaccine in Europe. Dukoral contains inactivated V. cholerae Classical and El Tor biotypes and the Inaba and Ogawa serotypes for each biotype. In addition, recombinant cholera toxin B subunit is also included from V. cholerae O1 Classical Biotype, serotype Inaba. It is indicated for active immunisation against disease caused by V. cholerae serogroup O1 in adults and children from 2 years of age who will be visiting epidemic/endemic areas.

3.1.3. Main clinical studies

Vaxchora is currently approved for adults and children aged 6 years and above. This application seeks to extend the current indication to include children from 2 years. This is based on data from Cohort 3 in the clinical study PXVX-VC-200-006. The study was conducted using a randomised, placebo-controlled, double-blind, single crossover design with two treatment groups across 3 cohorts.

3.2. Favourable effects

Serum vibriocidal antibody (SVA) seroconversion against Classical Inaba V. cholerae was achieved in 98.1% of the immune eligible population (IEP) in the age group 2-<6 (n=103) compared to 93.5% of adults in the lot consistency trial (PXVX-VC-200-004) aged 18-45 in the immune eligible population (n=2688) at day 11. For all individual cohorts and overall, the lower confidence interval was >70% [CI

98.3%]. The primary endpoint was therefore met. Slightly lower seroconversion rates were observed for the mITT group, but these were nevertheless well above the 70% lower confidence interval, thereby supporting the findings in the IEP group.

At day 29, SVA seroconversion for children aged 2-<6 years was 93.9%. None of the placebo subjects seroconverted.

GMT is available until day 29 for children aged 2-<6 years. As for cohorts 1 and 2 (6-<18 years), the maximum GMT was achieved at Day 11. In common with cohorts 1 and 2, this titre was reduced at day 29.

For the long-term follow-up sub-study population aged group 12-<18 (n=72), SVA seroconversion rate was 100% at Days 11 and 29 and was gradually reduced over time to 64.5% at day 730 based on the number of analysable subjects (n=62). Even at one year (day 365), the seroconversion rate was 68.6% based on the number of analysable subjects (n=70). This shows that seroconversion rate falls, but may remain stable from Day 365 to Day 730.

3.3. Uncertainties and limitations about favourable effects

Sample size is lower than forecasted due to ineligibility because approximately 25 (17.1%) of the subjects in the age group 2-<6 years could not consume at least 80% of the dose (40mL), indeed the volumes consumed in such subjects ranged from 0-30 mL. This is a limitation regarding home use, where it is unclear whether children in this age group will be appropriately protected. Based on immunogenicity data for participants that did not receive the full dose, a recommendation has now been provided in the SmPC in the event of an incomplete dosing, where a second dose may be given within 3 days of the first (incomplete) dose.

GMT versus Classical Inaba V. cholerae is only available until Day 29 for age group 2 - <6 and 6-<12. The peak GMT for age groups 6-<12 and 12-<18 was higher, 1.7 and 1.8 times the value for the age group 2-<6 years respectively. It is anticipated that the GMT will be reduced over time for this age group as for the other cohorts. The GMFI was correspondingly lower for the age group 2-<6 compared to the other cohorts at both day 11 and day 29.

The duration of GMT in the long-term follow-up subgroup from Cohort 1 (12-<18 years) shows that seroconversion rate was greatest at Day 11 (9035.4; n=72) and declined to 2791.7 at Day 29 (n=72), 391.7 at Day 91 (n=72), 223 at Day 181 (n=71), 158 at Day 365 (n=70), 175.6 at Day 547 (n=67), and 133.8 at Day 730 (n=62). At day 730, the geometric mean fold increase from baseline (GMFI) was 4.1, which is just above the level defining seroconversion. Since there is no established correlate of protection, it is not clear whether this titre will provide protection. Bearing in mind that the age group 2-<6 years had lower GMT and GMFI compared to the other cohorts, it may take less time for this age group to reach a fold increase of 4.1.

The exploratory endpoint assessing the duration of immune memory based on B-cell data was not included in the dossier and will form a separate report that the MAH has committed to provide within the next 12 months (December 2021).

SVA seroconversion rates have only been determined against Classical Inaba V. Cholerae. The seroconversion rates and GMT/GMFI against biotypes El Tor Inaba, Classical Ogawa and El Tor Ogawa which are also members of the serogroup 01 are therefore not known. Data for older adults (aged 46-64), seroconversion rates as well as GMT were substantially lower against both Classical Ogawa and El Tor Ogawa biotypes. Since the GMT is low for the age group 2-<6 years, the level of protection Vaxchora can afford against these biotypes in this age group may be similarly reduced.

Protective effect against disease was determined in participants 18-45 years of age, and this was bridged to individuals aged 2-<6 years of age based on seroconversion rates. However, it is not known whether other factors may affect the efficacy of Vaxchora in these older and younger populations.

3.4. Unfavourable effects

The safety profile of Vaxchora in children 2-<6 years appears to be similar to the safety profile in older children (6-< 18 years). Solicited AEs were reported by a higher proportion of subjects in Cohort 1 (Vaxchora 68.5%; Placebo 66.7%) than in Cohort 2 (Vaxchora 54.8%; Placebo 52.0%) and Cohort 3 (Vaxchora 40.4%; Placebo 34.6%). This is consistent with an age-related bias, as older children are more able to communicate AEs. The most frequently reported solicited AEs in Vaxchora-recipients (Cohort 3) were tiredness (Vaxchora 30.8%, placebo 23.1%), lack of appetite (Vaxchora 19.2%, placebo 11.5%) and abdominal pain (Vaxchora 17.1%, placebo 15.4%). Most AEs were mild or moderate. There were no SAEs considered to be treatment-related. The vaccine is prepared and administered outside a healthcare setting, and medication errors is a potential risk in the RMP. This is of concern as this may in the worst case reduce effectiveness of the vaccine. A recommendation has been provided in the SmPC in the event of an incomplete dosing, where a second dose may be given within 3 days of the first (incomplete) dose. Accordingly, the MAH committed to prepare and distribute educational materials to mitigate this risk when the product was marketed.

3.5. Uncertainties and limitations about unfavourable effects

There is an increased risk of medication errors when the vaccine is prepared and administered to the youngest children (2 -< 6 years). Preparation requires that half of the buffer solution is discarded before the active substance is added. Spilling or inaccuracies in this context may impact the potency of the vaccine-solution. It may also be a challenge to get the child to consume sufficient of the dose to achieve protection. 25 subjects (17,1%) failed to consume 80% of the dose even when sweetener was added to increase palatability.

The MAH has responded to a request to implement various measures to reduce this risk of medication errors and changed parts of the Risk Management Plan and SmPC/Package Leaflet accordingly. The educational material has also been updated.

3.6. Effects Table

Table 17: Effects Table for Vaxchora study PXVX-VC-006

Effect	Short description	Unit	Vaxchora	Control	Uncertainties / Strength of evidence	Ref
Favourable Effects[1]						
SVA seroconversion rate	Day 11	N (%)	Cohort 3 (2-<6 years) 101 (98.1%)	Study 004 (Adults) 2513 (93.5%)	Difference 4.5% [-1.1%, 6.4%]	
SVA seroconversion rate	Day 11	N (%)	Overall (2-<18 years) 393 (98.5%)	Study 004 (Adults) 2513 (93.5%)	Difference 5.0% [2.8%, 6.4%]	
Geometric mean titre	Day 11		Cohort 3 (2-<6 years)	Placebo (2-<6 years)	*** p<0.0001	

Effect	Short description	Unit	Vaxchora	Control	Uncertainties / Strength of evidence	Ref
		N GMT (95% CI)	103 4851.6*** [3445.2,6832.3]	20 28.3 [19.1, 36.4]		
Geometric mean titre	Day 11		Overall (2-<18 years)	Placebo (2-<18 years)	*** p<0.0001	
		N GMT (95% CI)	399 7341.1**** [6352.6, 8559.8]	67 36.4 [28.0, 47.4]		
Fold increase in GMT from baseline (analysable)	Day 11	N GMFI (SD)	Cohort 3 (2-<6 years) N=103 181.6*** SD: (5.3)	Placebo (2-<6years) N=20 1.1 SD: (1.2)	*** p<0.0001	
Fold increase in GMT from baseline (analysable)	Day 11	N GMFI (SD)	Overall (2-<18 years) N=399 242.6*** SD: (4.4)	Placebo (2-<18 years) N=67 1.0 SD: (2.1)	*** p<0.0001	
Subgroup Cohort 1 LTFU SVA seroconversion rate	Day 730	N (%)	Cohort 1 (12-<18 years) 62 (64.5%)	-	[52.1%,75.3%]	
Geometric mean titre	Day 730	N GMT (95% CI)	Cohort 1 (12-18 years) 62 133.8 [101.9, 175.7]			
Fold increase GMT from baseline for subgroup Cohort 1 LTFU	Day 730	N GMFI (SD)	Cohort 1 (12-18 years) 62 4.1 (2.5)	-		
Unfavourable Effects[2]						
Cohort 3 (children 2-<6 years)						
Tiredness	Solicited AE	%	30.8	23.1		Study PXVX-VC-200-006
Headache	Solicited AE	%	8.9	7.7		
Abdominal pain	Solicited AE	%	17.1	15.4		
Lack of appetite	Solicited AE	%	19.2	11.5		
Nausea	Solicited AE	%	6.8	15.4		
Vomiting	Solicited AE	%	1.4	11.5		

Effect	Short description	Unit	Vaxchora	Control	Uncertainties / Strength of evidence	Ref
Fever	Solicited AE	%	2.1	3.8		
Diarrhea	Solicited AE	%	0.7	3.8		
Loose stool	Unsolicited AE	%	5.5	7.7		
Upper respiratory tract infection	Unsolicited AE	%	4.1	11.5		
Headache	Unsolicited AE	%	0.7	0		
Fatigue	Unsolicited AE	%	3.4	0		
Decreased appetite	Unsolicited AE	%	2.1	0		
Overall safety set (childre2-<18 years)						
Tiredness	Solicited AE	%	35.7	30.7		Study PXVX-VC-200-006
Abdominal pain	Solicited AE	%	27.8	18.7		
Headache	Solicited AE	%	27.4	25.3		
Lack of appetite	Solicited AE	%	21.4	14.7		
Nausea	Solicited AE	%	14.7	18.7		
Vomiting	Solicited AE	%	3.8	4.0		
Fever	Solicited AE	%	2.4	2.7		
Diarrhea	Solicited AE	%	1.5	2.7		
Loose stools	Unsolicited AE	%	10.5	9.3		
Upper respiratory tract infections	Unsolicited AE	%	3.2	4.0		
Fatigue	Unsolicited AE	%	2.1	0		
Decreased appetite	Unsolicited AE	%	1.5	0		
Headache	Unsolicited AE	%	1.5	0		

Abbreviations: geometric mean titre (GMT), geometric mean titre fold increase (GMFI), long-ter, follow-up (LTFU).
Notes:
[1] Favourable effects are based on the immunogenicity evaluable population (IEP)
[2]AEs were not assessed for causality

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy data was based on the IEP which corresponded to 103 of 150 randomised subjects in the Vaxchora group and 20 of 26 subjects in the placebo group, corresponding to 68.7% and 76.9% of the Vaxchora and placebo populations, respectively. SVA seroconversion rates were found to be non-inferior between the age group 2-<6 years that received Vaxchora (n=103) and adults (18-45 years, n=2687)) at Day 11 post-vaccination with a lower confidence interval above 70% [CI 98.3%]. The same was true for each individual cohort and for the age group 2-<18 overall. Seroconversion rate at Day 11 was shown to be associated with protection against moderate/severe diarrhoea in adults following challenge with Classical Inaba V. cholerae (Study PXVX-VC-200-003). Vaxchora vaccination is therefore recommended 10 days before exposure to V. cholerae. The GMT and GMFI were lower for children 2-<6 years compared to the other age groups (6-<12 and 12-<18).

For a subgroup of children in cohort 1 (12-<18years), seroconversion rate was followed for two years. After one year (day 365), the seroconversion rate had fallen to 68.6% (n=48), but corresponded to a substantial proportion of the population. This remained stable for the next year with a seroconversion rate of 65.5% (n=40) at two years (day 730). The GMT and GMFI at Day 365 was 158.4 and 4.8 (n=70) respectively. At Day 730, the GMT and GMFI were 133.8 and 4.1 (n=62) respectively. The GMFI therefore lies close to the boundary for defining seroconversion (a four-fold increase from baseline). It is not known whether these titres and fold increases measured one and two years post-vaccination will be protective. The duration of immune memory is not known, and this data will be provided as a separate report which is requested within the next 12 months.

The total number of AEs (all cohorts included, solicited and unsolicited AEs) was similar in the Vaxchora- (60,5%) and placebo-arm (57,3%). In general the vaccine was safe and well tolerated, with no additional safety concerns for the age group 2-<6 years.

There is a considerable risk of medication errors when the vaccine is prepared and administered outside a healthcare setting. Medication errors is a potential risk in the RMP, and the MAH committed to prepare and distribute educational material to mitigate this risk when the product was marketed. Preparation and ingestion of the vaccine presents additional challenges in the youngest age group (2 -<6 years). Of greatest concern is that these children may not be able to consume the whole dose. Twenty five subjects (17.1%) failed to consume 80% of the vaccine in Cohort 3. The MAH has responded to a request to implement various measures to reduce this risk of medication errors and changed parts of the Risk Management Plan and SmPC/Package Leaflet accordingly. The educational material has also been updated.

3.7.2. Balance of benefits and risks

The SVA seroconversion rate in children 2-<6 years of age was non-inferior to adults 18-45 years of age at Day 11 post-vaccination. The same applied for each Cohort and for the age group 2-<18 years overall. Seroconversion at Day 11 is associated with protection against moderate or severe diarrhoea following infection with *V. cholerae*. Vaxchora vaccination is therefore recommended to be taken 10 days before anticipated exposure to *V. cholerae*. Two years post-vaccination, the seroconversion rate was 64% which corresponds to a substantial proportion of vaccinees aged 12-<18 years. Bearing in mind that the GMT for children 2-<6 years was lower at Day 11 post-vaccination compared to children aged 12-<18 years, it can be anticipated that the duration of protection may be shorter in this age group, and consequently, the seroconversion rate at two years post-vaccination correspondingly lower.

In general the vaccine was safe and well tolerated, with no additional safety concerns for the age group 2-<6 years. The vaccine is prepared and administered outside a healthcare setting, and there is a risk of medication errors. This is of concern as this may in the worst case cause vaccine failure.

3.7.3. Additional considerations on the benefit-risk balance

There is an increased risk of medication errors in the youngest children (2 -< 6 years) compared with older children and adults. Of most concern is that the child may not be able to ingest a sufficient amount of the dose to achieve protection even if sweetener is added to the vaccine solution.

The MAH has responded to a request to implement various measures to reduce this risk of medication errors and changed parts of the Risk Management Plan and SmPC/Package Leaflet accordingly. Based on data on seroconversion amongst subjects who consumed <80% of the expected dose, the following text has been added to the SmPC section 4.2: *"Consumption of less than a half dose may result in decreased protection. If less than half the dose is consumed, consideration may be given to repeating a full dose of Vaxchora within 72 hours."*

Regarding the amount and type of sweetener than can be added for children 2 to <6 years the following text has been added to SmPC section 6.6: *"Sucrose (up to 4 g / 1 teaspoon) or stevia sweetener (no more than 1 gram / ¼ teaspoon) may then be stirred into the suspension if desired. DO NOT add other sweeteners as this may reduce the effectiveness of the vaccine."*

3.8. Conclusions

The overall B/R of Vaxchora is positive for use in children 2-<6 years of age. The extension of indication is recommended to be: "adults and children aged 2 years and older".

Further, the update of section 5.1 of the SmPC to include long-term immunogenicity in children 2 to <18 years of age is agreed.

The following measures are considered necessary to address issues related to efficacy:

- The MAH will submit within 12 months the results of the exploratory endpoint assessing the duration of immune memory based on B-cell data at Days 1, 91, 181 for the subjects in the active treatment group and Days 365, 547, 730 for the subjects in the active treatment group who participate in the sub-study. (LEG).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an	Type II	I, II, IIIA and IIIB

	approved one		

C.I.6.a (type II): Extension of the indication for the active immunisation against disease caused by Vibrio cholerae serogroup O1, from the currently approved age range "adults and children aged 6 years and older" to "adults and children aged 2 years and older" for Vaxchora. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP (version 3) is updated in line with the proposed indication.

C.I.4 (type II): Update of section 5.1 of the SmPC to include long-term immunogenicity data supporting Vaxchora effectiveness at generating a protective immune response that persists for 2 years following vaccination; based on the final results from study PXVX-VC-200-006, a randomized, double-blind, placebo-controlled trial aimed to assess the safety and immunogenicity of Vaxchora in children 2 to <18 years of age.

In addition, the MAH took the opportunity to include editorial changes in the SmPC and Annex II.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0381/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Vaxchora-H-C-003876-II-0003-G'