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

Summary

EudraCT number	2018-003850-25
Trial protocol	Outside EU/EEA
Global end of trial date	10 September 2019

Results information

Result version number	v1 (current)
This version publication date	15 July 2020
First version publication date	15 July 2020

Trial information

Trial identification

Sponsor protocol code	PXVX-VC-200-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03220737
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Emergent Travel Health Inc.
Sponsor organisation address	555 Twin Dolphin Drive, Suite 360 , Redwood City, California, United States, 94065
Public contact	David Cassie Scientist, Clinical Research, Emergent Travel Health Inc., +1 2042754589, dcassie@ebsi.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001490-PIP01-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2019
Global end of trial reached?	Yes
Global end of trial date	10 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) For each of Cohort 1: 12 to <18 years, Cohort 2: 6 to <12 years and Cohort 3: 2 to <6 years
Primary Immunogenicity Objectives:
- Demonstrate that the seroconversion rate at Day 11 in pediatric 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 pediatric subjects is greater than or equal to 70% with 98.3% confidence.

Primary Safety Objectives:
Objective:
- Evaluate the safety and clinical acceptability of Vaxchora vaccine in children.
- Evaluate the acceptability of Vaxchora vaccine
- Evaluate the palatability of Vaxchora vaccine

Protection of trial subjects:

Prior to any study related activities, the subjects' parent or legal guardian signed and dated an Institutional Review Board (IRB) approved informed consent form (ICF). Subjects within the older cohort 1 provided written assent. This study was conducted 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).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 3238
Worldwide total number of subjects	3238
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	361
Adolescents (12-17 years)	189
Adults (18-64 years)	2688
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study included healthy volunteers (2 - 17 years) who were not previously immunized against cholera. A total of 574 subjects were screened, of which 24 were screen failures. A total of 550 subjects randomized, of which 471 received study treatment and 433 and 62 completed the main and sub studies, respectively. Recruitment July 2017-July 2018.

Pre-assignment

Screening details:

This study included healthy volunteers (2 - 17 years) who were not previously immunized against cholera. A total of 574 subjects were screened, of which 24 were screen failures. A total of 550 subjects randomized, of which 471 received study treatment and 433 and 62 completed the main and sub studies, respectively. Recruitment July 2017-July 2018.

Period 1

Period 1 title	Main Study (Day 1 - 181)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (active, 12-17 yrs)

Arm description:

Subjects aged 12 - 17 were administered a 100 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181.

Arm type	Active comparator
Investigational medicinal product name	Vaxchora (Cholera Vaccine, live attenuated, oral)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The buffer component was dissolved in 100 mL of cold or room temperature bottled water. The active component (lyophilized V. cholerae CVD 103-HgR) was then added into the buffer solution. Mixture was stirred until a cloudy suspension was achieved. Stevia was added at the discretion of the HCP and the subject consumed the dose within 15 mins of preparation. Only one dose (1 x 10e9 cfu/dose) was administered in this study.

Arm title	Cohort 1 (placebo, 12-17 yrs)

Arm description:

Subjects aged 12 - 17 were administered a 100 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.

Arm type	Placebo
Investigational medicinal product name	0.9% Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

100 mL of cold or room temperature 0.9% saline was dispensed. Stevia was added at the discretion of the HCP and the subject consumed the dose within 15 mins of preparation. Only one dose was administered in this study.

Arm title	Cohort 2 (active, 6-11 yrs)

Arm description:

Subjects aged 6 - 11 were administered a 100 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181.

Arm type	Active comparator
Investigational medicinal product name	Vaxchora (Cholera Vaccine, live attenuated, oral)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The buffer component was dissolved in 100 mL of cold or room temperature bottled water. The active component (lyophilized V. cholerae CVD 103-HgR) was then added into the buffer solution. Mixture was stirred until a cloudy suspension was achieved. Stevia was added at the discretion of the HCP and the subject consumed the dose within 15 mins of preparation. Only one dose (1 x 10e9 cfu/dose) was administered in this study.

Arm title	Cohort 2 (placebo, 6-11 yrs)

Arm description:

Subjects aged 6 - 11 were administered a 100 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.

Arm type	Placebo
Investigational medicinal product name	0.9% Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

100 mL of cold or room temperature 0.9% saline was dispensed. Stevia was added at the discretion of the HCP and the subject consumed the dose within 15 mins of preparation. Only one dose was administered in this study.

Arm title	Cohort 3 (active, 2-5 yrs)

Arm description:

Subjects aged 2 - 5 were administered a 50 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181

Arm type	Active comparator
Investigational medicinal product name	Vaxchora (Cholera Vaccine, live attenuated, oral)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The buffer component was dissolved in 100 mL of cold or room temperature bottled water. After buffer was dissolved 50mL was discarded. The active component (lyophilized V. cholerae CVD 103-HgR) was then added into the 50 mL buffer solution. Mixture was stirred until a cloudy suspension was achieved. Stevia was added at the discretion of the HCP and the subject consumed the dose within 15 mins of preparation. Only one dose (1 x 10e9 cfu/dose) was administered in this study.

Arm title	Cohort 3 (placebo, 2-5 yrs)

Arm description:

Subjects aged 2 - 5 were administered a 50 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.

Arm type	Placebo

Investigational medicinal product name	0.9% Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

50 mL of cold or room temperature 0.9% saline was dispensed. Stevia was added at the discretion of the HCP and the subject consumed the dose within 15 mins of preparation. Only one dose was administered in this study.

Arm title	Adult bridging population

Arm description:

This arm consists of historical data from Vaxchora vaccine subjects from study PXVX-VC-200-004. The data was included in study PXVX-VC-200-006 as a comparator bridging population for the Day 11 seroconversion.

Arm type	Active comparator
Investigational medicinal product name	Vaxchora (Cholera Vaccine, live attenuated, oral)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The buffer component was dissolved in 100 mL of cold or room temperature bottled water. The active component (lyophilized V. cholerae CVD 103-HgR) was then added into the buffer solution. Mixture was stirred until a cloudy suspension was achieved. Stevia was added at the discretion of the HCP and the subject consumed the dose within 15 mins of preparation. Only one dose (1 x 109 cfu/dose) was administered in this study.

Number of subjects in period 1	Cohort 1 (active, 12-17 yrs)	Cohort 1 (placebo, 12-17 yrs)	Cohort 2 (active, 6-11 yrs)
Started	163	26	158
Day 11	162	26	155
Day 29	161	26	154
Day 91	160	26	153
Day 181	157	24	146
Completed	157	24	146
Not completed	6	2	12
Consent withdrawn by subject	4	1	4
Failed Exl 8 and randomized in error	-	-	1
Lost to follow-up	2	1	6
Protocol deviation	-	-	1

Number of subjects in period 1	Cohort 2 (placebo, 6-11 yrs)	Cohort 3 (active, 2-5 yrs)	Cohort 3 (placebo, 2-5 yrs)
Started	27	150	26
Day 11	26	144	25
Day 29	26	141	25
Day 91	26	139	25

Day 181	24	130	25
Completed	24	130	25
Not completed	3	20	1
Consent withdrawn by subject	1	4	-
Failed Exl 8 and randomized in error	-	-	-
Lost to follow-up	1	13	1
Protocol deviation	1	3	-

Number of subjects in period 1	Adult bridging population
Started	2688
Day 11	2687
Day 29	2687
Day 91	2687
Day 181	2687
Completed	2687
Not completed	1
Consent withdrawn by subject	-
Failed Exl 8 and randomized in error	-
Lost to follow-up	-
Protocol deviation	1

Period 2

Period 2 title	Long-term Sub-study (Day 181 - 730)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Arms

Arm title	Cohort 1 Long-term (active, 12-17 yrs)

Arm description:

Subjects aged 12 - 17 from the main study treatment arm had additional study visits on Day 365, 547 and 730.

Arm type	Active comparator
Investigational medicinal product name	Vaxchora (Cholera Vaccine, live attenuated, oral)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The buffer component was dissolved in 100 mL of cold or room temperature bottled water. The active component (lyophilized V. cholerae CVD 103-HgR) was then added into the buffer solution. Mixture was stirred until a cloudy suspension was achieved. Stevia was added at the discretion of the HCP and the subject consumed the dose within 15 mins of preparation. Only one dose (1 x 10e9 cfu/dose) was

administered in this study.

Number of subjects in period 2[1]	Cohort 1 Long-term (active, 12-17 yrs)
Started	73
Day 365	71
Day 547	68
Completed	62
Not completed	11
Consent withdrawn by subject	1
Subject chose to drop due to not wanting lab drawn	1
Lost to follow-up	9

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The long-term sub-study was optional for Cohort 1 subjects in the main study. A total of 73 subjects opted to continue with SVA assessments out to Day 730.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (active, 12-17 yrs)
Reporting group description:	
Subjects aged 12 - 17 were administered a 100 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Cohort 1 (placebo, 12-17 yrs)
Reporting group description:	
Subjects aged 12 - 17 were administered a 100 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Cohort 2 (active, 6-11 yrs)
Reporting group description:	
Subjects aged 6 - 11 were administered a 100 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Cohort 2 (placebo, 6-11 yrs)
Reporting group description:	
Subjects aged 6 - 11 were administered a 100 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Cohort 3 (active, 2-5 yrs)
Reporting group description:	
Subjects aged 2 - 5 were administered a 50 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181	
Reporting group title	Cohort 3 (placebo, 2-5 yrs)
Reporting group description:	
Subjects aged 2 - 5 were administered a 50 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Adult bridging population
Reporting group description:	
This arm consists of historical data from Vaxchora vaccine subjects from study PXVX-VC-200-004. The data was included in study PXVX-VC-200-006 as a comparator bridging population for the Day 11 seroconversion.	

Reporting group values	Cohort 1 (active, 12-17 yrs)	Cohort 1 (placebo, 12-17 yrs)	Cohort 2 (active, 6-11 yrs)
Number of subjects	163	26	158
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	158
Adolescents (12-17 years)	163	26	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	14.4	14.3	8.6
standard deviation	± 1.7	± 1.7	± 1.8

Gender categorical Units: Subjects			
Female	75	12	81
Male	88	14	77
Race Units: Subjects			
White	121	21	86
Black or African American	28	4	53
Multiple	13	0	15
American Indian or Alaska Native	0	1	0
Asian	1	0	4
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0

Reporting group values	Cohort 2 (placebo, 6-11 yrs)	Cohort 3 (active, 2-5 yrs)	Cohort 3 (placebo, 2-5 yrs)
Number of subjects	27	150	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	27	150	26
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	8.7	3.5	3.6
standard deviation	± 1.5	± 1.1	± 1.2
Gender categorical Units: Subjects			
Female	10	69	17
Male	17	81	9
Race Units: Subjects			
White	18	71	12
Black or African American	5	67	14
Multiple	3	11	0
American Indian or Alaska Native	1	1	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0

Reporting group values	Adult bridging population	Total	
Number of subjects	2688	3238	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	361	
Adolescents (12-17 years)	0	189	
Adults (18-64 years)	2688	2688	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	30.0		
standard deviation	± 7.8	-	
Gender categorical Units: Subjects			
Female	1482	1746	
Male	1206	1492	
Race Units: Subjects			
White	1855	2184	
Black or African American	671	842	
Multiple	50	92	
American Indian or Alaska Native	11	14	
Asian	56	61	
Native Hawaiian or Other Pacific Islander	8	8	
Other	37	37	

Subject analysis sets

Subject analysis set title	Randomized Population
Subject analysis set type	Full analysis

Subject analysis set description:

This population includes all subjects randomized into the study.

Subject analysis set title	All Ages Immunogenicity Evaluable Population (IEP)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received the study treatment, had serum titers for both Day 1 and Day 11, and had no other major deviations which could potentially affect immunogenicity

Subject analysis set title	Adult Bridging Population
Subject analysis set type	Per protocol

Subject analysis set description:

The historical data from Vaxchora vaccine subjects in study PXVX-VX-200-004 was included as a comparator bridging population for the Day 11 seroconversion in paediatrics. The IEP population was 2688 subjects and there were 2687 for the Day 11 comparison.

Reporting group values	Randomized Population	All Ages Immunogenicity Evaluable Population (IEP)	Adult Bridging Population
Number of subjects	550	399	2688
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	361	0	0
Adolescents (12-17 years)	189	0	0
Adults (18-64 years)	0	0	2688
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	9.0	9.6	30.0
standard deviation	± 4.7	± 4.6	± 7.8
Gender categorical Units: Subjects			
Female	264	188	1482
Male	286	211	1206
Race Units: Subjects			
White	329	238	1855
Black or African American	171	123	671
Multiple	42	33	50
American Indian or Alaska Native	5	1	11
Asian	3	4	56
Native Hawaiian or Other Pacific Islander	0	0	8
Other	0	0	37

End points

End points reporting groups

Reporting group title	Cohort 1 (active, 12-17 yrs)
Reporting group description:	
Subjects aged 12 - 17 were administered a 100 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Cohort 1 (placebo, 12-17 yrs)
Reporting group description:	
Subjects aged 12 - 17 were administered a 100 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Cohort 2 (active, 6-11 yrs)
Reporting group description:	
Subjects aged 6 - 11 were administered a 100 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Cohort 2 (placebo, 6-11 yrs)
Reporting group description:	
Subjects aged 6 - 11 were administered a 100 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Cohort 3 (active, 2-5 yrs)
Reporting group description:	
Subjects aged 2 - 5 were administered a 50 mL oral dose of Vaxchora vaccine on Day 1, and had study visits on Day 11, 29, 91 and 181	
Reporting group title	Cohort 3 (placebo, 2-5 yrs)
Reporting group description:	
Subjects aged 2 - 5 were administered a 50 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.	
Reporting group title	Adult bridging population
Reporting group description:	
This arm consists of historical data from Vaxchora vaccine subjects from study PXVX-VC-200-004. The data was included in study PXVX-VC-200-006 as a comparator bridging population for the Day 11 seroconversion.	
Reporting group title	Cohort 1 Long-term (active, 12-17 yrs)
Reporting group description:	
Subjects aged 12 - 17 from the main study treatment arm had additional study visits on Day 365, 547 and 730.	
Subject analysis set title	Randomized Population
Subject analysis set type	Full analysis
Subject analysis set description:	
This population includes all subjects randomized into the study.	
Subject analysis set title	All Ages Immunogenicity Evaluable Population (IEP)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects who received the study treatment, had serum titers for both Day 1 and Day 11, and had no other major deviations which could potentially affect immunogenicity	
Subject analysis set title	Adult Bridging Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The historical data from Vaxchora vaccine subjects in study PXVX-VX-200-004 was included as a comparator bridging population for the Day 11 seroconversion in paediatrics. The IEP population was 2688 subjects and there were 2687 for the Day 11 comparison.	

Primary: Seroconversion rate at Day 11 in paediatric subjects

End point title	Seroconversion rate at Day 11 in paediatric subjects[1]

End point description:

The seroconversion rate was defined as the percentage of subjects with a 4-fold or greater rise from Day 1 in Serum Vibriocidal Antibody titers (SVA) against the classical Inaba biotype of V. cholerae at Day 11 following one dose of Vaxchora vaccine. The objective was to demonstrate that the seroconversion rate at Day 11 in paediatric subjects is greater than or equal to 70% with 98.3% confidence.

End point type	Primary

End point timeframe:

Day 1 to Day 11

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is for seroconversion in paedatric subjects only. The adult bridging population, which is historical data, is included as an arm for a comparator only for the subsequent primary endpoint.

End point values	Cohort 1 (active, 12-17 yrs)	Cohort 1 (placebo, 12-17 yrs)	Cohort 2 (active, 6-11 yrs)	Cohort 2 (placebo, 6-11 yrs)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	157	23	139	24
Units: % of participants				
number (confidence interval 98.3%)				
% Seroconverted at Day 11	99.4 (95.4 to 99.9)	0 (0.0 to 14.3)	97.8 (92.5 to 99.4)	4.2 (0.7 to 20.2)

End point values	Cohort 3 (active, 2-5 yrs)	Cohort 3 (placebo, 2-5 yrs)	All Ages Immunogenicity Evaluable Population (IEP)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	103	20	399	
Units: % of participants				
number (confidence interval 98.3%)				
% Seroconverted at Day 11	98.1 (91.5 to 99.6)	0 (0.0 to 16.1)	98.5 (96.2 to 99.4)	

Statistical analyses

Statistical analysis title	Proportion of subjects seroconverted at Day 11

Statistical analysis description:

This analysis was based on the lower confidence limit and did not entail a comparative group. The requirement was for the lower limit of the 98.3% CI be at least 70%. Multiplicity adjustment due to co-primary endpoints allotted alpha=0.017 to this endpoint resulting in a 98.3% confidence interval

Comparison groups	Cohort 2 (active, 6-11 yrs) v Cohort 3 (active, 2-5 yrs) v Cohort 1 (active, 12-17 yrs)

Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	proportion
Point estimate	98.5
Confidence interval	
level	Other: 98.3 %
sides	1-sided
lower limit	0.7

Notes:

[2] - This analysis was based on the lower confidence limit and did not entail a comparative group. The requirement was for the lower limit of the 98.3% CI be at least 70%. Multiplicity adjustment due to co-primary endpoints allotted alpha=0.017 to this endpoint resulting in a 98.3% confidence interval

Primary: Non-inferiority of seroconversion rate at Day 11 in Cohort 1 (12-17 yrs) subjects relative to adult subjects aged 18 - 45 years

End point title	Non-inferiority of seroconversion rate at Day 11 in Cohort 1 (12-17 yrs) subjects relative to adult subjects aged 18 - 45 years[3]

End point description:

The seroconversion rate is defined as the percentage of subjects with a 4-fold or greater rise over baseline Day 1 Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of V. cholerae at Day 11 following one dose of Vaxchora vaccine. The objective was to demonstrate that the paediatric seroconversion rate is non-inferior to the seroconversion rate at Day 11 in adults between the ages of 18 and 45 years.

End point type	Primary

End point timeframe:

Day 1 to Day 11

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is a comparison of solely cohort 1 and the adult bridging population. Cohorts 2 and 3 are presented seperately. The placebo groups for all cohorts was not included in this non-inferiority analysis.

End point values	Cohort 1 (active, 12-17 yrs)	Adult bridging population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	2687		
Units: % of participants				
number (confidence interval 98.3%)	99.4 (95.4 to 99.9)	93.5 (92.3 to 94.6)		

Statistical analyses

Statistical analysis title	Difference in % Seroconversion at Day 11, Cohort 1

Statistical analysis description:

Non-inferiority was determined using the Newcombe method of determining the difference between two independent binomial distributions. Multiple comparison adjustment for co-primary endpoints allotted alpha=0.033 to this comparison. The lower limit of the 96.7% CI needed to be greater than -10 percentage points to prove non-inferiority

Comparison groups	Cohort 1 (active, 12-17 yrs) v Adult bridging population

Number of subjects included in analysis	2844
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	5.8
Confidence interval	
level	Other: 96.7 %
sides	2-sided
lower limit	2.4
upper limit	7.1

Notes:

[4] - Newcombe method of determining the difference between two independent binomial distributions

Primary: Non-inferiority of seroconversion rate at Day 11 in Cohort 2 (6-11 yrs) subjects relative to adult subjects aged 18 - 45 years

End point title	Non-inferiority of seroconversion rate at Day 11 in Cohort 2 (6-11 yrs) subjects relative to adult subjects aged 18 - 45 years[5]

End point description:

The seroconversion rate is defined as the percentage of subjects with a 4-fold or greater rise over baseline Day 1 Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of V. cholerae at Day 11 following one dose of Vaxchora vaccine. The objective was to demonstrate that the paediatric seroconversion rate is non-inferior to the seroconversion rate at Day 11 in adults between the ages of 18 and 45 years.

End point type	Primary

End point timeframe:

Day 1 to Day 11

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is a comparison of solely cohort 2 and the adult bridging population. Cohorts 1 and 3 are presented seperately. The placebo groups for all cohorts was not included in this non-inferiority analysis.

End point values	Cohort 2 (active, 6-11 yrs)	Adult bridging population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	2687		
Units: % of participants				
number (confidence interval 98.3%)				
% seroconverted	97.8 (92.5 to 99.4)	93.5 (92.3 to 94.6)		

Statistical analyses

Statistical analysis title	Difference in % Seroconversion at Day 11, Cohort 2

Statistical analysis description:

Non-inferiority was determined using the Newcombe method of determining the difference between two independent binomial distributions. Multiple comparison adjustment for co-primary endpoints allotted alpha=0.033 to this comparison. The lower limit of the 96.7% CI needed to be greater than -10 percentage points to prove non-inferiority

Comparison groups	Adult bridging population v Cohort 2 (active, 6-11 yrs)

Number of subjects included in analysis	2826
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Risk difference (RD)
Point estimate	4.3
Confidence interval	
level	Other: 96.7 %
sides	2-sided
lower limit	-0.3
upper limit	6.2

Notes:

[6] - Newcombe method of determining the difference between two independent binomial distributions

Primary: Non-inferiority of seroconversion rate at Day 11 in Cohort 3 (2-5 yrs) subjects relative to adult subjects aged 18 - 45 years

End point title	Non-inferiority of seroconversion rate at Day 11 in Cohort 3 (2-5 yrs) subjects relative to adult subjects aged 18 - 45 years[7]

End point description:

The seroconversion rate is defined as the percentage of subjects with a 4-fold or greater rise over baseline Day 1 Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of V. cholerae at Day 11 following one dose of Vaxchora vaccine. The objective was to demonstrate that the paediatric seroconversion rate is non-inferior to the seroconversion rate at Day 11 in adults between the ages of 18 and 45 years.

End point type	Primary

End point timeframe:

Day 1 to Day 11

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is a comparison of solely cohort 3 and the adult bridging population. Cohorts 1 and 2 are presented seperately. The placebo groups for all cohorts was not included in this non-inferiority analysis.

End point values	Cohort 3 (active, 2-5 yrs)	Adult bridging population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	2687		
Units: % of participants				
number (confidence interval 98.3%)				
% seroconverted	98.1 (91.5 to 99.6)	93.5 (92.3 to 94.6)		

Statistical analyses

Statistical analysis title	Difference in % Seroconversion at Day 11, Cohort 3

Statistical analysis description:

Non-inferiority was determined using the Newcombe method of determining the difference between two independent binomial distributions. Multiple comparison adjustment for co-primary endpoints allotted alpha=0.033 to this comparison. The lower limit of the 96.7% CI needed to be greater than -10 percentage points to prove non-inferiority

Comparison groups	Adult bridging population v Cohort 3 (active, 2-5 yrs)

Number of subjects included in analysis	2790
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Risk difference (RD)
Point estimate	4.5
Confidence interval	
level	Other: 96.7 %
sides	2-sided
lower limit	-1.1
upper limit	6.4

Notes:

[8] - Newcombe method of determining the difference between two independent binomial distributions

Secondary: Seroconversion at Day 29, 91 and 181, Cohort 1

End point title	Seroconversion at Day 29, 91 and 181, Cohort 1[9]

End point description:

The seroconversion rate is defined as the percentage of subjects with a 4-fold or greater rise over baseline Day 1 in Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of V. cholerae at Day 29, 91 and 181 following one dose of Vaxchora vaccine.

End point type	Secondary

End point timeframe:

Day 29, 91 and 181

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint result is solely for cohort 1, which had SVA values for Day 29, 91 and 181. Cohorts 2 and 3 are presented separately for Day 29, which was the last SVA result for these cohorts. The adult bridging population is not included as it was for comparison to Day 11 seroconversion only.

End point values	Cohort 1 (active, 12-17 yrs)	Cohort 1 (placebo, 12-17 yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	23		
Units: % of Participants				
number (confidence interval 95%)				
Day 29 % Seroconversion	100 (97.6 to 100)	0.0 (0.0 to 14.3)		
Day 91 % Seroconversion	85.6 (79.2 to 90.3)	0.0 (0.0 to 14.3)		
Day 181 % Seroconversion	73.5 (66.0 to 79.9)	0.0 (0.0 to 15.5)		

Statistical analyses

Statistical analysis title	Seroconversion at Day 29, 91 & 181, Cohort 1

Statistical analysis description:

Fisher’s exact test was used to compare Vaxchora vaccine to placebo on the percent of subjects who seroconverted. For Vaxchora vs placebo within each cohort at each Day on study timepoint, the p-value was the same ($p<0.0001$).

Comparison groups	Cohort 1 (placebo, 12-17 yrs) v Cohort 1 (active, 12-17 yrs)

Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Secondary: Seroconversion at Day 29, Cohort 2

End point title	Seroconversion at Day 29, Cohort 2[10]

End point description:

The seroconversion rate is defined as the percentage of subjects with a 4-fold or greater rise over baseline Day 1 in Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of V. cholerae at Day 29 following one dose of Vaxchora vaccine.

End point type	Secondary

End point timeframe:

Day 29

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint result is solely for cohort 2 at Day 29. Cohorts 1 and 3 are presented separately. The adult bridging population is not included as it was for comparison to Day 11 seroconversion only.

End point values	Cohort 2 (active, 6-11 yrs)	Cohort 2 (placebo, 6-11 yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	23		
Units: % of Participants				
number (confidence interval 95%)				
Day 29 % Seroconversion	94.9 (89.9 to 97.5)	4.3 (0.8 to 21.0)		

Statistical analyses

Statistical analysis title	Seroconversion at Day 29, Cohort 2

Statistical analysis description:

Fisher’s exact test was used to compare Vaxchora vaccine to placebo on the percent of subjects who seroconverted. For Vaxchora vs placebo within each cohort at each Day on study timepoint, the p-value was the same (p<0.0001).

Comparison groups	Cohort 2 (active, 6-11 yrs) v Cohort 2 (placebo, 6-11 yrs)
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Secondary: Seroconversion at Day 29, Cohort 3

End point title	Seroconversion at Day 29, Cohort 3[11]

End point description:

The seroconversion rate is defined as the percentage of subjects with a 4-fold or greater rise over baseline Day 1 in Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of V. cholerae at Day 29 following one dose of Vaxchora vaccine.

End point type	Secondary

End point timeframe:

Day 29

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint result is solely for cohort 3 on Day 29. Cohorts 1 and 2 are presented separately. The adult bridging population is not included as it was for comparison to Day 11 seroconversion only.

End point values	Cohort 3 (active, 2-5 yrs)	Cohort 3 (placebo, 2-5 yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	18		
Units: % of Participants				
number (confidence interval 95%)				
Day 29 % Seroconversion	93.9 (87.3 to 97.2)	0.0 (0.0 to 17.6)		

Statistical analyses

Statistical analysis title	Seroconversion at Day 29, Cohort 3

Statistical analysis description:

Fisher’s exact test was used to compare Vaxchora vaccine to placebo on the percent of subjects who seroconverted. For Vaxchora vs placebo within each cohort at each Day on study timepoint, the p-value was the same ($p<0.0001$).

Comparison groups	Cohort 3 (active, 2-5 yrs) v Cohort 3 (placebo, 2-5 yrs)
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Secondary: Seroconversion in cohort 1 at Days 365, 547 and 730

End point title	Seroconversion in cohort 1 at Days 365, 547 and 730

End point description:

The seroconversion rate is defined as the percentage of subjects with a 4-fold or greater rise over baseline Day 1 in Serum Vibriocidal Antibody (SVA) titer against the classical Inaba biotype of V. cholerae at Day 365, 547 and 730 following one dose of Vaxchora vaccine.

End point type	Secondary

End point timeframe:

Day 365, 547 and 730

End point values	Cohort 1 Long-term (active, 12-17 yrs)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: % of Participants				
number (confidence interval 95%)				
Day 365 % Seroconversion (N=70)	68.6 (57.0 to 78.2)			
Day 547 % Seroconversion (N=67)	73.1 (61.5 to 82.3)			
Day 730 % Seroconversion (N=62)	64.5 (52.1 to 75.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected for 28 days post vaccination. Serious adverse events were followed until the end of the end of the subject's participation in the study (2 years for adolescents in the long term sub-study and 6 months for all others).

Adverse event reporting additional description:

All SAEs are included in the summaries; Other Non-serious AEs collected through 28 days post vaccination and reaching a threshold of 2% are included. Solicited adverse events were collected for daily for 8 consecutive days following vaccination (Days 1-8). Events that continued past Day 8 were recorded as unsolicited adverse events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Cohort 1 (active, 12-17 yrs)

Reporting group description:

Subjects aged 12 - 17 were administered a 100 mL oral dose of Vaxchora (Cholera Vaccine, live attenuated, oral) on Day 1, and had study visits on Day 11, 29, 91 and 181.

Reporting group title	Cohort 1 (placebo, 12-17 yrs)

Reporting group description:

Subjects aged 12 - 17 were administered a 100 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.

Reporting group title	Cohort 2 (active, 6-11 yrs)

Reporting group description:

Subjects aged 6 - 11 were administered a 100 mL oral dose of Vaxchora (Cholera Vaccine, live attenuated, oral) on Day 1, and had study visits on Day 11, 29, 91 and 181

Reporting group title	Cohort 2 (placebo, 6-11 yrs)

Reporting group description:

Subjects aged 6 - 11 were administered a 100 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.

Reporting group title	Cohort 3 (active, 2-5 yrs)

Reporting group description:

Subjects aged 2 - 5 were administered a 50 mL oral dose of Vaxchora (Cholera Vaccine, live attenuated, oral) on Day 1, and had study visits on Day 11, 29, 91 and 181

Reporting group title	Cohort 3 (placebo, 2-5 yrs)

Reporting group description:

Subjects aged 2 - 5 were administered a 50 mL oral dose of placebo on Day 1, and had study visits on Day 11, 29, 91 and 181.

Serious adverse events	Cohort 1 (active, 12-17 yrs)	Cohort 1 (placebo, 12-17 yrs)	Cohort 2 (active, 6-11 yrs)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 165 (2.42%)	0 / 24 (0.00%)	0 / 157 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			

Intentional overdose			
subjects affected / exposed	1 / 165 (0.61%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 165 (0.61%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 165 (0.61%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Local Swelling			
subjects affected / exposed	1 / 165 (0.61%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2 (placebo, 6-11 yrs)	Cohort 3 (active, 2-5 yrs)	Cohort 3 (placebo, 2-5 yrs)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	1 / 26 (3.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Local Swelling			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Cohort 1 (active, 12-17 yrs)	Cohort 1 (placebo, 12-17 yrs)	Cohort 2 (active, 6-11 yrs)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	116 / 165 (70.30%)	13 / 24 (54.17%)	93 / 157 (59.24%)
Injury, poisoning and procedural complications			
Laceration - unsolicited			
subjects affected / exposed	1 / 165 (0.61%)	1 / 24 (4.17%)	0 / 157 (0.00%)
occurrences (all)	1	1	0
Joint Injury - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Arthropod bite - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache - unsolicited			
subjects affected / exposed	4 / 165 (2.42%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	4	0	0
Headache - solicited			
subjects affected / exposed	74 / 165 (44.85%)	11 / 24 (45.83%)	41 / 157 (26.11%)
occurrences (all)	191	18	77
General disorders and administration site conditions			
Fatigue - unsolicited			
subjects affected / exposed	4 / 165 (2.42%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	4	0	0
Vessel puncture site pain - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Fatigue - solicited	Additional description: Solicited as tiredness		
subjects affected / exposed	67 / 165 (40.61%)	9 / 24 (37.50%)	55 / 157 (35.03%)
occurrences (all)	170	30	123
Pyrexia - solicited	Additional description: Solicited as fever		
subjects affected / exposed	3 / 165 (1.82%)	0 / 24 (0.00%)	5 / 157 (3.18%)
occurrences (all)	4	0	6
Gastrointestinal disorders			

Loose Stool - unsolicited			
subjects affected / exposed	23 / 165 (13.94%)	5 / 24 (20.83%)	18 / 157 (11.46%)
occurrences (all)	30	6	19
Rectal tenesmus - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Vomiting - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Diarrhoea - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Nausea - solicited			
subjects affected / exposed	37 / 165 (22.42%)	6 / 24 (25.00%)	22 / 157 (14.01%)
occurrences (all)	69	16	37
Vomiting - solicited			
subjects affected / exposed	9 / 165 (5.45%)	0 / 24 (0.00%)	7 / 157 (4.46%)
occurrences (all)	14	0	12
Diarrhoea - solicited			
subjects affected / exposed	6 / 165 (3.64%)	1 / 24 (4.17%)	0 / 157 (0.00%)
occurrences (all)	7	1	0
Abdominal pain - solicited			
subjects affected / exposed	62 / 165 (37.58%)	4 / 24 (16.67%)	43 / 157 (27.39%)
occurrences (all)	130	10	83
Skin and subcutaneous tissue disorders			
Dermatitis contact - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection - unsolicited			
subjects affected / exposed	7 / 165 (4.24%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	7	0	0

Furuncle - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	1 / 24 (4.17%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Otitis media - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Ear infection - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Bronchitis - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite - unsolicited			
subjects affected / exposed	0 / 165 (0.00%)	0 / 24 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Decreased Appetite - solicited	Additional description: Solicited as lack of appetite.		
subjects affected / exposed	48 / 165 (29.09%)	3 / 24 (12.50%)	24 / 157 (15.29%)
occurrences (all)	112	8	47

Non-serious adverse events	Cohort 2 (placebo, 6-11 yrs)	Cohort 3 (active, 2-5 yrs)	Cohort 3 (placebo, 2-5 yrs)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 25 (60.00%)	74 / 146 (50.68%)	12 / 26 (46.15%)
Injury, poisoning and procedural complications			
Laceration - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Joint Injury - unsolicited			
subjects affected / exposed	1 / 25 (4.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Arthropod bite - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1

Nervous system disorders			
Headache - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Headache - solicited			
subjects affected / exposed	6 / 25 (24.00%)	13 / 146 (8.90%)	2 / 26 (7.69%)
occurrences (all)	11	18	3
General disorders and administration site conditions			
Fatigue - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	5 / 146 (3.42%)	0 / 26 (0.00%)
occurrences (all)	0	5	0
Vessel puncture site pain - unsolicited			
subjects affected / exposed	1 / 25 (4.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Fatigue - solicited	Additional description: Solicited as tiredness		
subjects affected / exposed	8 / 25 (32.00%)	45 / 146 (30.82%)	6 / 26 (23.08%)
occurrences (all)	17	108	13
Pyrexia - solicited	Additional description: Solicited as fever		
subjects affected / exposed	1 / 25 (4.00%)	3 / 146 (2.05%)	1 / 26 (3.85%)
occurrences (all)	1	4	3
Gastrointestinal disorders			
Loose Stool - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	8 / 146 (5.48%)	2 / 26 (7.69%)
occurrences (all)	0	8	2
Rectal tenesmus - unsolicited			
subjects affected / exposed	1 / 25 (4.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Vomiting - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	3 / 146 (2.05%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Diarrhoea - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Nausea - solicited			
subjects affected / exposed	4 / 25 (16.00%)	10 / 146 (6.85%)	4 / 26 (15.38%)
occurrences (all)	11	14	4

Vomiting - solicited			
subjects affected / exposed	0 / 25 (0.00%)	2 / 146 (1.37%)	3 / 26 (11.54%)
occurrences (all)	0	2	3
Diarrhoea - solicited			
subjects affected / exposed	0 / 25 (0.00%)	1 / 146 (0.68%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Abdominal pain - solicited			
subjects affected / exposed	6 / 25 (24.00%)	25 / 146 (17.12%)	4 / 26 (15.38%)
occurrences (all)	15	53	7
Skin and subcutaneous tissue disorders			
Dermatitis contact - unsolicited			
subjects affected / exposed	1 / 25 (4.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia - unsolicited			
subjects affected / exposed	1 / 25 (4.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Upper respiratory tract infection - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	6 / 146 (4.11%)	3 / 26 (11.54%)
occurrences (all)	0	6	3
Furuncle - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis - unsolicited			
subjects affected / exposed	2 / 25 (8.00%)	3 / 146 (2.05%)	0 / 26 (0.00%)
occurrences (all)	2	3	0
Otitis media - unsolicited			
subjects affected / exposed	1 / 25 (4.00%)	0 / 146 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Ear infection - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	3 / 146 (2.05%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Bronchitis - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	1 / 146 (0.68%)	1 / 26 (3.85%)
occurrences (all)	0	1	1

Metabolism and nutrition disorders			
Decreased appetite - unsolicited			
subjects affected / exposed	0 / 25 (0.00%)	3 / 146 (2.05%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Decreased Appetite - solicited	Additional description: Solicited as lack of appetite.		
subjects affected / exposed	5 / 25 (20.00%)	28 / 146 (19.18%)	3 / 26 (11.54%)
occurrences (all)	11	63	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2017	The protocol was revised to remove Canada as a location for this trial, to further define the statistical analysis, to add exclusion criteria consistent with other studies of Vaxchora vaccine and to remove a planned interim analysis.
15 November 2017	The protocol was revised 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 August 2017	Study halt 1 occurred on August 24, 2017 in response to an unrelated Grade 4 fever in one subject. The Investigator assessed the event to be non-life threatening and it did not meet any SAE criteria. The SMC was notified of this event and a temporary halt on all Day 1 vaccinations was instituted. The SMC convened with PaxVax for further review of safety information. The halt was lifted after one day, with the SMC recommending no further modifications to the study protocol. The event that triggered this temporary halt did not meet any stopping rule criteria.	25 August 2017
31 August 2017	Study halt 2 occurred on August 31, 2017 in response to 2 events of severe diarrhea in two subjects assessed as possibly related to vaccination. The events met the criteria of the study stopping rules. The SMC was notified of this event and a temporary halt on all Day 1 vaccinations was instituted. The SMC convened with PaxVax for further review of safety information. The halt was lifted after 22 days, with the SMC recommending no further modifications to the study protocol.	21 September 2017
20 October 2017	Study halt 3 occurred on October 20, 2017 in response to an event of severe fever in one subject, assessed as possibly related to vaccination, and an unrelated SAE (lower limb fracture) in another subject. These events met the criteria of the study stopping rules. The SMC was notified of these events and a temporary halt on all Day 1 vaccinations was instituted. The SMC convened with PaxVax for further review of safety information. The halt was lifted after 4 days, with the SMC recommending no further modification to the study protocol.	24 October 2017

06 November 2017	Study halt 4 occurred on November 6, 2017 in response to events of severe vomiting and diarrhea in one subject, assessed as possibly related to vaccination. These events met the criteria of the study stopping rules. The SMC was notified of these events and a temporary halt on all Day 1 vaccinations was instituted. The SMC convened with PaxVax for further review of safety information. The halt was lifted after 4 days, with the SMC recommending no further modification to the study protocol.	10 November 2017
18 January 2019	Study halt 5 occurred on January 18, 2019 in response to an event of seizure disorder and hospitalization due to worsening of seizures in one subject assessed as not related to vaccination. These events met the criteria of the study stopping rules. A de facto halt on the one remaining placebo-crossover vaccination was instituted over the subsequent weekend period. The SMC Chair was notified of this event and the halt was lifted after 20 days. No modifications to the protocol were recommended.	07 February 2019

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31769402