Clinical trial results:
A randomized, placebo-controlled phase IIb (OEV 123) study to evaluate safety, immunogenicity, diagnostic methodology, and estimate vaccine efficacy of an oral enterotoxigenic Escherichia coli (ETEC) Vaccine (ETVAX) for prevention of clinically significant ETEC diarrhea in healthy adult travelers visiting West Africa

Summary

EudraCT number	2016-002690-35
Trial protocol	FI
Global end of trial date	15 April 2019

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	OEV 123

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03729219
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Scandinavian Biopharma Holding AB
Sponsor organisation address	Industrivägen 1, Solna, Sweden, 17148
Public contact	Björn Sjöstrand, CEO , Scandinavian Biopharma Holding AB , bjorn.sjostrand@scandinavianbiopharma.se
Scientific contact	Nils Carlin, VP Research and Development, Scandinavian Biopharma Holding AB , nils.carlin@etvax.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	27 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2019
Global end of trial reached?	Yes
Global end of trial date	15 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety:
To evaluate safety and tolerability of orally administered ETVAX vaccine in a two-dose regimen
Immunogenicity:
To evaluate Immunoglobulin A (IgA) and Immunoglobulin G (IgG) antibody responses in serum against heat labile enterotoxin B (LTB).
Diagnostic Tools:
To elucidate the agreement between culture based and non-culture based diagnostic tools for identifying ETEC, and other enteric pathogens in stool samples from subjects meeting pre-defined clinical end-points for moderate or severe Traveler's Diarrhea (TD). Culture-based diagnostics are performed on bacterial colonies isolated from stool samples and analyzed by biochemical, mass-spectrometric and immunological methods. Non-culture based methods are performed on frozen stool samples stored in eNAT tubes using a validated multiplex quantitative polymerase chain reaction (PCR) developed by Mobidiag Oy, Finland and a modified TaqMan array developed by University of Virginia (UVA) in the US.

Protection of trial subjects:

In case of an emergency or when knowledge of the treatment assignment was absolutely necessary for the medical management of the study subject, the unblinding could be performed through electronic randomization system. Authorized investigators had 24/7 access to break the code per subject in case of an emergency. Reason, initials and date of opening the code was documented. The procedure of emergency unblinding was described in detail in Safety Management Plan (SMP).

Background therapy:

All ongoing medication at the time of recruitment, including start/stop dates and indication, were recorded in the subject's medical records as well as in the appropriate section of the eCRF.

Atovaquone + proguanil (Malarone® / Rumbabor) was mandatory to take as prophylaxis for malaria. The intake of malaria prophylaxis was recorded in the subjects medical records and appropriate section of eCRF.

Evidence for comparator:

Placebo used as comparator.

Actual start date of recruitment	31 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 782
Worldwide total number of subjects	782
EEA total number of subjects	782

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	748
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were recruited among students, and personnel at the University of Helsinki and Helsinki University Hospital and among those responding to recruitment advertisements. To be eligible, the subjects had to commit to comply with the study protocol which involved vaccination, study visits, sampling and to travel to Benin.

Pre-assignment

Screening details:

Altogether, 8172 subjects contacted the study center and were prescreened over the phone. A total of 782 subjects were screened and 749 randomized into Group A and B equally, 374 in Active ETVAX group, 375 in placebo. In total, 729 subjects completed the study, and 20 discontinued during the trial. The total number of screening failures was 33.

Pre-assignment period milestones

Number of subjects started	782
Number of subjects completed	749

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 29
Reason: Number of subjects	Protocol deviation: 4

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ETVAX

Arm description:

An ETEC vaccine which contains formaldehyde or phenol inactivated recombinant E. coli strains (ETEX 21-24) overexpressing colonization factors CFA/I, CS3, CS5, and CS6 and a recombinant protein LCTBA, a chimera between E. coli heat-labile enterotoxin B subunit (LTB) and Vibrio cholerae cholera toxin B-subunit (CTB) supplemented with an adjuvant, an inactivated double mutant LT(R192G/ L211A) of wild-type E. coli heat-labile toxin (dmLT), and an effervescent powder (bicarbonate buffer) mixed with 150 ml water

Arm type	Experimental
Investigational medicinal product name	ETVAX
Investigational medicinal product code	
Other name	ETEC vaccine
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Test product:
Tetravalent ETEC vaccine with LCTBA supplemented with an adjuvant, double mutant heat labile toxin (dmLT), and an effervescent powder for oral solution (bicarbonate buffer).
The ETEC vaccine (ETVAX) contains formaldehyde or phenol inactivated recombinant E. coli strains (ETEX 21-24) overexpressing colonization factors CFA/I, CS3, CS5, and CS6 and a recombinant protein

LCTBA, a chimera between E. coli heat-labile enterotoxin B subunit (LTB) and Vibrio cholerae cholera toxin B-subunit (CTB).
An adjuvant, an inactivated double mutant LT(R192G/ L211A) of wild-type E. coli heat-labile toxin (dmLT) is administered with the vaccine

Dose:
One dose contains in total approx. 8 x 10e10 inactivated bacteria and 1 mg of recombinant protein LCTBA in a 3.3 ml vial and 10 µg of adjuvant dmLT. All of these are mixed into 150 ml of effervescent bicarbonate buffer solution (5.6 g powder mixed with 150 ml water) to neutralize gastric acid upon ingestion. Two doses were given.

Arm title	Placebo

Arm description:

Effervescent powder for oral solution (bicarbonate buffer) as control . Dose: 5.6 g/150 ml water

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Bicarbonate buffer
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Effervescent powder (bicarbonate buffer) in sachets. Dose: 5.6 g/150 ml water

Number of subjects in period 1[1]	ETVAX	Placebo
Started	374	375
Completed	363	366
Not completed	11	9
Physician decision	1	-
Consent withdrawn by subject	3	3
Adverse event, non-fatal	2	1
No reason recorded	-	1
Lost to follow-up	2	2
Protocol deviation	3	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all enrolled subject did not enter to vaccination i.e baseline period

Baseline characteristics

Reporting groups

Reporting group title	ETVAX

Reporting group description:

An ETEC vaccine which contains formaldehyde or phenol inactivated recombinant E. coli strains (ETEX 21-24) overexpressing colonization factors CFA/I, CS3, CS5, and CS6 and a recombinant protein LCTBA, a chimera between E. coli heat-labile enterotoxin B subunit (LTB) and Vibrio cholerae cholera toxin B-subunit (CTB) supplemented with an adjuvant, an inactivated double mutant LT(R192G/ L211A) of wild-type E. coli heat-labile toxin (dmLT), and an effervescent powder (bicarbonate buffer) mixed with 150 ml water

Reporting group title	Placebo

Reporting group description:

Effervescent powder for oral solution (bicarbonate buffer) as control . Dose: 5.6 g/150 ml water

Reporting group values	ETVAX	Placebo	Total
Number of subjects	374	375	749
Age categorical Units: Subjects			
Adults(18-64 years)	360	356	716
From 65 to 85 years	14	19	33
Age continuous Units: years			
arithmetic mean	46.9	45.9	
standard deviation	± 15.5	± 15.7	-
Gender categorical Units: Subjects			
Female	260	269	529
Male	114	106	220

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects that received at least one dose of the vaccine or placebo.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol population

Subject analysis set title	Post-hoc
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects having LTB IgA fold rise > 4 in active group

Subject analysis set title	Post hoc 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Post Hoc population 2 is a subset of the Per-Protocol Set (PPS) who experienced at least one Severe Traveler's diarrhea episode and in addition non-responders (i.e. less than 4-fold elevation in serum IgA

antibody levels against LTB) were excluded from the analysis (apply to ETVAX group)

Reporting group values	ITT	PPS	Post-hoc
Number of subjects	749	679	599
Age categorical Units: Subjects			
Adults(18-64 years)	716	648	
From 65 to 85 years	33	31	
Age continuous Units: years			
arithmetic mean	46.4	46.4	47.5
standard deviation	± 15.6	± 15.6	± 15.3
Gender categorical Units: Subjects			
Female	529	479	421
Male	220	200	178

Reporting group values	Post hoc 2		
Number of subjects	105		
Age categorical Units: Subjects			
Adults(18-64 years)			
From 65 to 85 years			
Age continuous Units: years			
arithmetic mean	46.1		
standard deviation	± 15.1		
Gender categorical Units: Subjects			
Female	74		
Male	31		

End points

End points reporting groups

Reporting group title	ETVAX

Reporting group description:

An ETEC vaccine which contains formaldehyde or phenol inactivated recombinant E. coli strains (ETEX 21-24) overexpressing colonization factors CFA/I, CS3, CS5, and CS6 and a recombinant protein LCTBA, a chimera between E. coli heat-labile enterotoxin B subunit (LTB) and Vibrio cholerae cholera toxin B-subunit (CTB) supplemented with an adjuvant, an inactivated double mutant LT(R192G/ L211A) of wild-type E. coli heat-labile toxin (dmLT), and an effervescent powder (bicarbonate buffer) mixed with 150 ml water

Reporting group title	Placebo

Reporting group description:

Effervescent powder for oral solution (bicarbonate buffer) as control . Dose: 5.6 g/150 ml water

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects that received at least one dose of the vaccine or placebo.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol population

Subject analysis set title	Post-hoc
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects having LTB IgA fold rise > 4 in active group

Subject analysis set title	Post hoc 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Post Hoc population 2 is a subset of the Per-Protocol Set (PPS) who experienced at least one Severe Traveler's diarrhea episode and in addition non-responders (i.e. less than 4-fold elevation in serum IgA antibody levels against LTB) were excluded from the analysis (apply to ETVAX group)

Primary: Number of Subjects Responding to Heat-labile Toxin (LTB) IgG

End point title	Number of Subjects Responding to Heat-labile Toxin (LTB) IgG

End point description:

The number of subjects having at least 2-fold rise of LTB specific IgG.

End point type	Primary

End point timeframe:

Change from baseline (just before first vaccination) to Visit 3 (5-6 days after second vaccination), an average of 20 days

End point values	ETVAX	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	370	371	741	
Units: Number of subjects	270	6	276	

Statistical analyses

Statistical analysis title	Number (%) Subjects with ≥ 2 Antibody fold rise
Comparison groups	ETVAX v Placebo
Number of subjects included in analysis	741
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Primary: Number of Subjects Responding to Heat-labile Toxin (LTB) IgA

End point title	Number of Subjects Responding to Heat-labile Toxin (LTB) IgA
End point description:	
Number of subjects with at least 2-fold rise of LTB specific IgA.	
End point type	Primary
End point timeframe:	
Change from baseline (just before first vaccination) to Visit 3 (5-6 days after second vaccination), an average of 20 days	

End point values	ETVAX	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	370	372	742	
Units: Number of subjects	301	8	309	

Statistical analyses

Statistical analysis title	Number (%) Subjects with ≥ 2 Antibody fold rise
Comparison groups	ETVAX v Placebo
Number of subjects included in analysis	742
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Secondary: Incidence rate of moderate to severe travelers´ diarrhea (TD) caused by

enterotoxigenic Escherichia coli expressing CFA/I, CS3, CS5 or CS6, and/or LT as single pathogen

End point title	Incidence rate of moderate to severe travelers´ diarrhea (TD) caused by enterotoxigenic Escherichia coli expressing CFA/I, CS3, CS5 or CS6, and/or LT as single pathogen

End point description:

Moderate Travelers´ diarrhea: 4-5 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms as vomiting, fever, bloody stool, abdominal pain, cramping, nausea, lightheadedness, feeling weak and having an impact on daily activities.
Severe Travelers´ diarrhea: ≥ 6 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms and preventing planned daily activities.
Stool sample containing an Enterotoxigenic Escherichia coli (ETEC) strain expressing CFA/I, CS3, CS5 or CS6, and/or LT as single pathogen (Vaccine Preventable Outcome), disregarding Enteropathogenic Escherichia coli (EPEC) and any other pathogens already present in at least one routine pre-travel stool sample.

End point type	Secondary

End point timeframe:

Vaccination and surveillance period until return to home country and 30 day after return.

End point values	ETVAX	Placebo	PPS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	333	346	679	
Units: Incidence of VPO	26	22	48	

Statistical analyses

Statistical analysis title	Protective efficacy

Statistical analysis description:

Protective efficacy against first episode of specified type

Comparison groups	Placebo v ETVAX
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Fisher exact
Parameter estimate	Protective efficacy
Point estimate	-23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-112
upper limit	29

Post-hoc: Incidence rate of severe travelers' diarrhea (TD) all cause (responders)

End point title	Incidence rate of severe travelers' diarrhea (TD) all cause (responders)

End point description:

Severe Travelers´ diarrhea: ≥ 16 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms as vomiting, fever, bloody stool, abdominal pain, cramping, nausea, lightheadedness, feeling weak and preventing planned daily activities.
Stool sample containing any pathogen.
The population analyzed was per protocol participants with responders to the vaccine defined as a 4-fold elevation in serum IgA antibody levels against LTB in active group.

End point type	Post-hoc

End point timeframe:

Vaccination and surveillance period until return to home country and 30 days after return.

End point values	ETVAX	Placebo	Post-hoc	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	253	346	599	
Units: Number of subjects				
Yes	10	31	41	
No	243	315	558	

Statistical analyses

Statistical analysis title	Protective efficacy

Statistical analysis description:

Protective efficacy against first episode of specified type.

Comparison groups	ETVAX v Placebo v Post-hoc
Number of subjects included in analysis	1198
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.021
Method	Fisher exact
Parameter estimate	Protective efficacy
Point estimate	56
Confidence interval	
level	95 %
sides	2-sided
lower limit	12
upper limit	78

Post-hoc: Incidence rate of moderate to severe travelers´ diarrhea (TD) caused by enterotoxigenic Escherichia coli expressing CFA/I, CS3, CS5 or CS6, and/or LT confirmed in diarrhea and all other co-pathogens acceptable except viruses (responders)

End point title	Incidence rate of moderate to severe travelers´ diarrhea (TD) caused by enterotoxigenic Escherichia coli expressing CFA/I, CS3, CS5 or CS6, and/or LT confirmed in diarrhea and all other co-pathogens acceptable except viruses (responders)

End point description:

Moderate Travelers´ diarrhea: 4-5 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms as vomiting, fever, bloody stool, abdominal pain, cramping, nausea, lightheadedness, feeling weak and having an impact on daily activities.
Severe Travelers´ diarrhea: ≥ 6 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms and preventing planned daily activities.
Stool sample (confirmed diarrhea) containing an Enterotoxigenic Escherichia coli (ETEC) strain expressing CFA/I, CS3, CS5 or CS6, and/or LT and all other co-pathogens acceptable except viruses.
The population analysed was per protocol participants with responders to the vaccine defined as a 4-fold elevation in serum IgA antibody levels against LTB in active group.

End point type	Post-hoc

End point timeframe:

Vaccination and surveillance period until return to home country and 30 days after return.

End point values	ETVAX	Placebo	Post-hoc	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	253	346	599	
Units: Number of subjects				
Yes	16	46	62	
No	237	300	537	

Statistical analyses

Statistical analysis title	Protective efficacy
Comparison groups	ETVAX v Placebo
Number of subjects included in analysis	599
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.006
Method	Fisher exact
Parameter estimate	Protective efficacy
Point estimate	52
Confidence interval	
level	95 %
sides	2-sided
lower limit	18
upper limit	72

Post-hoc: Incidence rate of moderate to severe travelers' diarrhea (TD) caused by enterotoxigenic Escherichia coli expressing CFA/I, CS3, CS5 or CS6, and/or LT confirmed in diarrhea and all other co-pathogens acceptable except virus (regardless of immune response)

End point title	Incidence rate of moderate to severe travelers' diarrhea (TD) caused by enterotoxigenic Escherichia coli expressing CFA/I, CS3, CS5 or CS6, and/or LT confirmed in diarrhea and all other co-pathogens acceptable except virus (regardless of immune response)

End point description:

Moderate travelers´ diarrhea: 4-5 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms as vomiting, fever, bloody stool, abdominal pain, cramping, nausea, lightheadedness, feeling weak and having an impact on daily activities.
Severe Travelers´ diarrhea: ≥ 6 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms and preventing planned daily activities.
Stool sample (confirmed diarrhea) containing an Enterotoxigenic Escherichia coli (ETEC) strain expressing CFA/I, CS3, CS5 or CS6, and/or LT and all other co-pathogens acceptable except viruses.

End point type	Post-hoc

End point timeframe:

Vaccination and surveillance period until return to home country and 30 days after return.

End point values	ETVAX	Placebo	PPS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	333	346	679	
Units: Number of subjects	26	46	72	

Statistical analyses

Statistical analysis title	Protective efficacy
Comparison groups	ETVAX v Placebo
Number of subjects included in analysis	679
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.024
Method	Fisher exact
Parameter estimate	Protective efficacy
Point estimate	41
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	63

Post-hoc: Incidence rate of severe travelers´ diarrhea (TD) all cause (regardless of immune response)

End point title	Incidence rate of severe travelers´ diarrhea (TD) all cause (regardless of immune response)

End point description:

Severe Travelers´ diarrhea: ≥ 16 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms as vomiting, fever, bloody stool, abdominal pain, cramping, nausea, lightheadedness, feeling weak and preventing planned daily activities.
Stool sample containing any pathogen.

Regardless of immune response

End point type	Post-hoc

End point timeframe:

Vaccination and surveillance period until return to home country and 30 days after return.

End point values	ETVAX	Placebo	PPS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	333	346	679	
Units: Number of subjects	17	31	48	

Statistical analyses

Statistical analysis title	Protective efficacy
Comparison groups	ETVAX v Placebo
Number of subjects included in analysis	679
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.053
Method	Fisher exact
Parameter estimate	Protective efficacy
Point estimate	43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	68

Post-hoc: Proportion of subjects who used anti-diarrheal medications or antibiotics during Severe Traveler's diarrhea episode

End point title	Proportion of subjects who used anti-diarrheal medications or antibiotics during Severe Traveler's diarrhea episode

End point description:

The population analysed was the Post Hoc population 2 (subset of the Per-Protocol Set (PPS) who experienced at least one Severe Traveler's diarrhea episode, non-responders (i.e. less than 4-fold elevation in serum IgA antibody levels against LTB) were excluded (apply to ETVAX group).

Severe Travelers´ diarrhea as defined as follows : ≥ 6 unformed/liquid stools in a 24-hour period associated with one or more of other symptoms and preventing planned daily activities. Antibiotics were specified by ATC codes J01 and J04, and anti-diarrheal medications by ATC codes A07B, A07C, A07D, A07F, and A07X.

End point type	Post-hoc

End point timeframe:

Vaccination and surveillance period until return to home country and 30 days after return.

End point values	ETVAX	Placebo	Post hoc 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	44	61	105	
Units: Number of subjects				
No medication	28	24	52	
Medication	16	37	53	

Statistical analyses

Statistical analysis title	Proportion of subjects
Statistical analysis description: Proportion of subjects who used anti-diarrheal medications or antibiotics during Severe TD	
Comparison groups	ETVAX v Placebo
Number of subjects included in analysis	105
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.018
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.374
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.154
upper limit	0.887

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period for this study began after receiving the first dose of IMP and ended the day the subject travelled to Benin or at the withdrawal of the subject. On-going AEs at the end of the study period were followed until resolution.

Adverse event reporting additional description:

AEs and SAEs reported here were collected also during the surveillance period. None of the SAEs were not reported during the vaccine attributable period , but thereafter.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	ETVAX

Reporting group description:

The adverse event reporting period for this study began after receiving the first dose of IMP and ended the day the subject travelled to Benin or at the withdrawal of the subject. On-going AEs at the end of the study period were followed until resolution or until the whole follow-up period back in Finland (30 days), whichever came first.

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	ETVAX	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 374 (4.55%)	24 / 375 (6.40%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	1 / 374 (0.27%)	0 / 375 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Stress cardiomyopathy			

subjects affected / exposed	1 / 374 (0.27%)	0 / 375 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 374 (0.27%)	4 / 375 (1.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 374 (0.27%)	0 / 375 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 374 (0.27%)	0 / 375 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	4 / 374 (1.07%)	4 / 375 (1.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 374 (0.27%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 374 (0.80%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 374 (0.53%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 374 (0.27%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			
subjects affected / exposed	1 / 374 (0.27%)	3 / 375 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shigella infection			

subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	ETVAX	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	289 / 374 (77.27%)	284 / 375 (75.73%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 374 (3.48%)	10 / 375 (2.67%)	
occurrences (all)	17	12	
Headache			
subjects affected / exposed	71 / 374 (18.98%)	87 / 375 (23.20%)	
occurrences (all)	96	126	
Migraine			
subjects affected / exposed	6 / 374 (1.60%)	10 / 375 (2.67%)	
occurrences (all)	8	15	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	25 / 374 (6.68%)	21 / 375 (5.60%)	
occurrences (all)	25	23	
Pyrexia			
subjects affected / exposed	22 / 374 (5.88%)	22 / 375 (5.87%)	
occurrences (all)	24	24	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	7 / 374 (1.87%)	2 / 375 (0.53%)	
occurrences (all)	9	2	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	9 / 374 (2.41%)	7 / 375 (1.87%)	
occurrences (all)	11	10	
Abdominal distension			
subjects affected / exposed	6 / 374 (1.60%)	7 / 375 (1.87%)	
occurrences (all)	9	7	
Abdominal pain upper			
subjects affected / exposed	90 / 374 (24.06%)	77 / 375 (20.53%)	
occurrences (all)	122	109	
Constipation			
subjects affected / exposed	5 / 374 (1.34%)	6 / 375 (1.60%)	
occurrences (all)	6	8	
Diarrhoea			
subjects affected / exposed	109 / 374 (29.14%)	103 / 375 (27.47%)	
occurrences (all)	150	150	
Dyspepsia			
subjects affected / exposed	8 / 374 (2.14%)	9 / 375 (2.40%)	
occurrences (all)	11	10	
Eructation			
subjects affected / exposed	11 / 374 (2.94%)	9 / 375 (2.40%)	
occurrences (all)	13	12	
Flatulence			
subjects affected / exposed	26 / 374 (6.95%)	18 / 375 (4.80%)	
occurrences (all)	32	25	
Nausea			
subjects affected / exposed	80 / 374 (21.39%)	66 / 375 (17.60%)	
occurrences (all)	110	86	
Vomiting			
subjects affected / exposed	16 / 374 (4.28%)	9 / 375 (2.40%)	
occurrences (all)	18	9	
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	7 / 374 (1.87%)	10 / 375 (2.67%)	
occurrences (all)	9	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 374 (2.94%)	7 / 375 (1.87%)	
occurrences (all)	11	7	
Nasal congestion			
subjects affected / exposed	4 / 374 (1.07%)	9 / 375 (2.40%)	
occurrences (all)	4	9	
Oropharyngeal pain			
subjects affected / exposed	21 / 374 (5.61%)	24 / 375 (6.40%)	
occurrences (all)	22	24	
Rhinorrhoea			
subjects affected / exposed	15 / 374 (4.01%)	12 / 375 (3.20%)	
occurrences (all)	16	12	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 374 (1.34%)	5 / 375 (1.33%)	
occurrences (all)	5	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 374 (4.28%)	9 / 375 (2.40%)	
occurrences (all)	16	18	
Back pain			
subjects affected / exposed	16 / 374 (4.28%)	10 / 375 (2.67%)	
occurrences (all)	16	13	
Musculoskeletal pain			
subjects affected / exposed	6 / 374 (1.60%)	5 / 375 (1.33%)	
occurrences (all)	6	7	
Myalgia			
subjects affected / exposed	15 / 374 (4.01%)	7 / 375 (1.87%)	
occurrences (all)	21	8	
Neck pain			
subjects affected / exposed	2 / 374 (0.53%)	7 / 375 (1.87%)	
occurrences (all)	2	8	

Pain in extremity			
subjects affected / exposed	7 / 374 (1.87%)	5 / 375 (1.33%)	
occurrences (all)	8	5	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	4 / 374 (1.07%)	4 / 375 (1.07%)	
occurrences (all)	4	4	
Influenza			
subjects affected / exposed	30 / 374 (8.02%)	21 / 375 (5.60%)	
occurrences (all)	32	24	
Nasopharyngitis			
subjects affected / exposed	12 / 374 (3.21%)	11 / 375 (2.93%)	
occurrences (all)	12	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2017	Amendment 1; Protocol Version 2.0 and respective updates of ICF
22 May 2017	Amendment 2; Protocol version 3.0 and respective updates of ICFs
24 July 2017	Amendment 3; Protocol Version 4.1 and respective updates of ICF and approval for subject questionnaires
18 September 2017	Amendment 4; protocol version 5.0 and respective updates in ICF and subject materials
23 May 2018	Amendment 5; Protocol version 6.0 and respective updates in ICF and study documents

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported