



Clinical trial results:

A Phase 2 immunological bridging study assessing the non-inferiority of a new formulation of ETVAX®. A prospective double-blind, randomized study in healthy volunteers

Summary

EudraCT number	2021-001541-13
Trial protocol	SE
Global end of trial date	31 January 2023

Results information

Result version number	v1 (current)
This version publication date	28 December 2023
First version publication date	28 December 2023

Trial information

Trial identification

Sponsor protocol code	OEV-125
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05178134
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Scandinavian Biopharma Holding AB
Sponsor organisation address	Industrivägen 1, Solna, Sweden, 17148
Public contact	Scandinavian Biopharma Holding AB, Scandinavian Biopharma Holding AB, +46 (0)8 470 56 00, info@scandinavianbiopharma.se
Scientific contact	Scandinavian Biopharma Holding AB, Scandinavian Biopharma Holding AB, +46 (0)8 470 56 00, info@scandinavianbiopharma.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	20 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 October 2022
Global end of trial reached?	Yes
Global end of trial date	31 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority, in terms of immunogenicity, between the wet formulation and the newly developed partially dried formulation of selected components of ETVAX®.

Protection of trial subjects:

The study began when all of the requirements of the appropriate regulatory authorities had been fulfilled. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council on Harmonisation (ICH) - good clinical practice (GCP) guidelines.

Dosing occurred at the clinic. After each dose, subjects remained at the clinic for observation for 15 min before leaving.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2021
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	Sweden: 280
Worldwide total number of subjects	280
EEA total number of subjects	280

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)	280
From 65 to 84 years	0

85 years and over	0
-------------------	---

Subject disposition

Recruitment

Recruitment details:

The subjects were recruited through advertising on notice boards and distribution of leaflets, as well as through information posted on the study's website and social media platforms.

Pre-assignment

Screening details:

In total, 313 volunteers were screened for the study. 140 subjects were randomized into each of the two treatment groups. 139 subjects in each group received two doses of vaccine and completed the study.

Period 1

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

Blinding implementation details:

Neither the personnel directly involved in taking care of the study subjects or evaluating the results, nor the subjects themselves, were informed which of the two formulations of vaccine that was given. The two formulations had identical appearance and the same smell.

However, the person who prepared the vaccines immediately before immunization and the observer were unblinded. These persons were not directly involved in evaluation of AEs or laboratory results.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Comparator: The wet formulation of ETVAX

Arm description:

Subjects in this arm were given two oral doses of the wet formulation, administered two weeks apart.

The wet formulation consists of a liquid suspension of inactivated bacteria (ETEX 21-24) and LCTBA in one vial, freeze-dried dmLT adjuvant in a second vial, and effervescent buffer granules in a separate sachet. Prior to administration, the buffer is dissolved in 150 ml tap water, followed by the addition of the content of the vaccine vial (inactivated bacteria mixed with LCTBA) and reconstituted and diluted adjuvant dmLT from the second vial.

Arm type	Active comparator
Investigational medicinal product name	ETVAX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension, Suspension for oral suspension, Effervescent powder
Routes of administration	Oral use

Dosage and administration details:

The wet formulation consists of a liquid suspension of inactivated bacteria (ETEX 21-24) and LCTBA in one vial, freeze-dried dmLT adjuvant in a second vial, and effervescent buffer granules in a separate sachet. Prior to administration, the buffer is dissolved in 150 ml tap water, followed by the addition of the content of the vaccine vial (inactivated bacteria mixed with LCTBA) and reconstituted and diluted adjuvant dmLT from the second vial.

Etvax: Preparation of complete Wet formulation. The vaccine supplied as a liquid, is mixed with the 150 ml of sodium bicarbonate buffer solution on the day of preparation for use on dosing day. Just prior to administration 10 µg of dmLT is added by pipette (50 µl).

Arm title	Active Comparator: The partially dried formulation of ETVAX
------------------	---

Arm description:

Subjects in this arm were given two oral doses of the partially dried formulation, administered two weeks apart.

The partially dried formulation, dmLT and LCTBA are spray-dried and mixed with the buffer granules and stabilizing excipients in a sachet. Prior to administration, the content of the buffer sachet (buffer, dmLT, and LCTBA) is dissolved in 150 ml tap water, followed by the addition of a liquid suspension of inactivated bacteria (ETEX 21-24).

Arm type	Active comparator
Investigational medicinal product name	ETVAX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Effervescent powder and powder for oral suspension, Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The partially dried formulation, dmLT and LCTBA are spray-dried and mixed with the buffer granules and stabilizing excipients in a sachet. Prior to administration, the content of the buffer sachet (buffer, dmLT, and LCTBA) is dissolved in 150 ml tap water, followed by the addition of a liquid suspension of inactivated bacteria (ETEX 21-24).

Etvax: Preparation of partially dry formulation. The partially dry formulation of vaccine is prepared by adding the effervescent powder containing the dmLT and LCTBA to 150 ml of water. After mixing, the content of the vaccine vial is added to the mixture and the vaccine is administered to the volunteer within 30 minutes after adding the buffer powder to the water.

Number of subjects in period 1	Active Comparator: The wet formulation of ETVAX	Active Comparator: The partially dried formulation of ETVAX
Started	140	140
Completed	139	139
Not completed	1	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Active Comparator: The wet formulation of ETVAX
-----------------------	---

Reporting group description:

Subjects in this arm were given two oral doses of the wet formulation, administered two weeks apart.

The wet formulation consists of a liquid suspension of inactivated bacteria (ETEX 21-24) and LCTBA in one vial, freeze-dried dmLT adjuvant in a second vial, and effervescent buffer granules in a separate sachet. Prior to administration, the buffer is dissolved in 150 ml tap water, followed by the addition of the content of the vaccine vial (inactivated bacteria mixed with LCTBA) and reconstituted and diluted adjuvant dmLT from the second vial.

Reporting group title	Active Comparator: The partially dried formulation of ETVAX
-----------------------	---

Reporting group description:

Subjects in this arm were given two oral doses of the partially dried formulation, administered two weeks apart.

The partially dried formulation, dmLT and LCTBA are spray-dried and mixed with the buffer granules and stabilizing excipients in a sachet. Prior to administration, the content of the buffer sachet (buffer, dmLT, and LCTBA) is dissolved in 150 ml tap water, followed by the addition of a liquid suspension of inactivated bacteria (ETEX 21-24).

Reporting group values	Active Comparator: The wet formulation of ETVAX	Active Comparator: The partially dried formulation of ETVAX	Total
Number of subjects	140	140	280
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	31.0 ± 9.70	32.2 ± 9.54	-
Gender categorical Units: Subjects			
Female	86	87	173
Male	54	53	107

End points

End points reporting groups

Reporting group title	Active Comparator: The wet formulation of ETVAX
-----------------------	---

Reporting group description:

Subjects in this arm were given two oral doses of the wet formulation, administered two weeks apart.

The wet formulation consists of a liquid suspension of inactivated bacteria (ETEX 21-24) and LCTBA in one vial, freeze-dried dmLT adjuvant in a second vial, and effervescent buffer granules in a separate sachet. Prior to administration, the buffer is dissolved in 150 ml tap water, followed by the addition of the content of the vaccine vial (inactivated bacteria mixed with LCTBA) and reconstituted and diluted adjuvant dmLT from the second vial.

Reporting group title	Active Comparator: The partially dried formulation of ETVAX
-----------------------	---

Reporting group description:

Subjects in this arm were given two oral doses of the partially dried formulation, administered two weeks apart.

The partially dried formulation, dmLT and LCTBA are spray-dried and mixed with the buffer granules and stabilizing excipients in a sachet. Prior to administration, the content of the buffer sachet (buffer, dmLT, and LCTBA) is dissolved in 150 ml tap water, followed by the addition of a liquid suspension of inactivated bacteria (ETEX 21-24).

Primary: Vaccine response

End point title	Vaccine response
-----------------	------------------

End point description:

The primary endpoint to be measured for each patient in the study is response (yes/no) to a vaccine. A vaccine responder will be defined by a ≥ 2 -fold increase in IgA and/or IgG antibody levels against LTB in serum between post- compared to pre-immunization samples. The response rates (seroconversion rates) of IgA and/or IgG anti-LTB antibodies in serum will be derived and compared between the two treatment groups.

End point type	Primary
----------------	---------

End point timeframe:

3 weeks

End point values	Active Comparator: The wet formulation of ETVAX	Active Comparator: The partially dried formulation of ETVAX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	133		
Units: Participants	116	110		

Statistical analyses

Statistical analysis title	Statistical Analysis for Vaccine Response
----------------------------	---

Comparison groups	Active Comparator: The wet formulation of ETVAX v Active Comparator: The partially dried formulation of ETVAX
-------------------	---

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Difference in response rates
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.108
upper limit	0.069

Notes:

[1] - Non-inferiority margin was set to -15% (on an absolute scale).
The Per Protocol population was used for calculation of the primary endpoint.

Secondary: Solicited Symptoms After Vaccination

End point title	Solicited Symptoms After Vaccination
End point description: Subjects who experienced solicited AEs within 6 days after first dose	
End point type	Secondary
End point timeframe: 3 weeks	

End point values	Active Comparator: The wet formulation of ETVAX	Active Comparator: The partially dried formulation of ETVAX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	140		
Units: Participants				
Abdominal pain	23	22		
Nausea	17	20		
Vomiting	3	3		
Loose stools/Diarrhea	24	33		
Fever	3	0		
No solicited symptom	70	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Solicited Symptoms After Vaccination

End point title	Solicited Symptoms After Vaccination
End point description: Subjects who experienced solicited AEs within 6 days after second dose	
End point type	Secondary

End point timeframe:

3 weeks

End point values	Active Comparator: The wet formulation of ETVAX	Active Comparator: The partially dried formulation of ETVAX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	139		
Units: Participants				
Abdominal pain	24	12		
Nausea	22	20		
Vomiting	4	5		
Loose stools/Diarrhea	27	24		
Fever	3	0		
No solicited symptom	59	78		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Collection of unsolicited AEs started with the first intervention with the study vaccine and continued until the last follow-up assessment 7 days (6-10 days) after study vaccine dose 2.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24
--------------------	----

Reporting groups

Reporting group title	The Partially Dried Formulation of ETVAX
-----------------------	--

Reporting group description:

The partially dried formulation, dmLT and LCTBA are spray-dried and mixed with the buffer granules and stabilizing excipients in a sachet. Prior to administration, the content of the buffer sachet (buffer, dmLT, and LCTBA) is dissolved in 150 ml tap water, followed by the addition of a liquid suspension of inactivated bacteria (ETEX 21-24).

Etvax: Preparation of partially dry formulation. The partially dry formulation of vaccine is prepared by adding the effervescent powder containing the dmLT and LCTBA to 150 ml of water. After mixing, the content of the vaccine vial is added to the mixture and the vaccine is administered to the volunteer within 30 minutes after adding the buffer powder to the water.

Reporting group title	The Wet Formulation of ETVAX
-----------------------	------------------------------

Reporting group description:

The wet formulation consists of a liquid suspension of inactivated bacteria (ETEX 21-24) and LCTBA in one vial, freeze-dried dmLT adjuvant in a second vial, and effervescent buffer granules in a separate sachet. Prior to administration, the buffer is dissolved in 150 ml tap water, followed by the addition of the content of the vaccine vial (inactivated bacteria mixed with LCTBA) and reconstituted and diluted adjuvant dmLT from the second vial.

Etvax: Preparation of complete Wet formulation. The vaccine supplied as a liquid, is mixed with the 150 ml of sodium bicarbonate buffer solution on the day of preparation for use on dosing day.

Just prior to administration 10 µg of dmLT is added by pipette (50 µl).

Serious adverse events	The Partially Dried Formulation of ETVAX	The Wet Formulation of ETVAX	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 140 (0.00%)	0 / 140 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	The Partially Dried Formulation of ETVAX	The Wet Formulation of ETVAX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 140 (51.43%)	89 / 140 (63.57%)	

Neoplasms benign, malignant and unspecified (incl cysts and polyps) Papilloma conjunctival alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	0 / 140 (0.00%) 0	
General disorders and administration site conditions Feeling cold alternative assessment type: Systematic subjects affected / exposed occurrences (all) Fatigue alternative assessment type: Systematic subjects affected / exposed occurrences (all) Chills alternative assessment type: Systematic subjects affected / exposed occurrences (all) Chest pain alternative assessment type: Systematic subjects affected / exposed occurrences (all) Chest discomfort alternative assessment type: Systematic subjects affected / exposed occurrences (all) Asthenia alternative assessment type: Systematic subjects affected / exposed occurrences (all) Hunger alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1 5 / 140 (3.57%) 5 0 / 140 (0.00%) 0 1 / 140 (0.71%) 1 0 / 140 (0.00%) 0 1 / 140 (0.71%) 1 0 / 140 (0.00%) 0	0 / 140 (0.00%) 0 7 / 140 (5.00%) 8 3 / 140 (2.14%) 3 0 / 140 (0.00%) 0 1 / 140 (0.71%) 1 0 / 140 (0.00%) 0 0 / 140 (0.00%) 0	

<p>Malaise</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 140 (1.43%)</p> <p>2</p>	<p>0 / 140 (0.00%)</p> <p>0</p>	
<p>Pain</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 140 (0.71%)</p> <p>1</p>	<p>1 / 140 (0.71%)</p> <p>1</p>	
<p>Pyrexia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 140 (0.00%)</p> <p>0</p>	<p>2 / 140 (1.43%)</p> <p>2</p>	
<p>Sensation of foreign body</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 140 (0.00%)</p> <p>0</p>	<p>1 / 140 (0.71%)</p> <p>1</p>	
<p>Thirst</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 140 (0.00%)</p> <p>0</p>	<p>1 / 140 (0.71%)</p> <p>1</p>	
<p>Immune system disorders</p> <p>Hypersensitivity</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Seasonal allergy</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 140 (0.71%)</p> <p>1</p> <p>1 / 140 (0.71%)</p> <p>1</p>	<p>0 / 140 (0.00%)</p> <p>0</p> <p>0 / 140 (0.00%)</p> <p>0</p>	
<p>Reproductive system and breast disorders</p> <p>Cervical polyp</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysmenorrhoea</p>	<p>0 / 140 (0.00%)</p> <p>0</p>	<p>1 / 140 (0.71%)</p> <p>1</p>	

<p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 140 (3.57%)</p> <p>5</p>	<p>13 / 140 (9.29%)</p> <p>14</p>	
<p>Premenstrual dysphoric disorder</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 140 (0.00%)</p> <p>0</p>	<p>1 / 140 (0.71%)</p> <p>1</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Nasal congestion</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry throat</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 140 (1.43%)</p> <p>2</p> <p>0 / 140 (0.00%)</p> <p>0</p> <p>3 / 140 (2.14%)</p> <p>3</p> <p>5 / 140 (3.57%)</p> <p>5</p>	<p>0 / 140 (0.00%)</p> <p>0</p> <p>1 / 140 (0.71%)</p> <p>1</p> <p>2 / 140 (1.43%)</p> <p>2</p> <p>2 / 140 (1.43%)</p> <p>2</p>	
<p>Psychiatric disorders</p> <p>Insomnia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Disorientation</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Anxiety</p> <p>alternative assessment type:</p>	<p>1 / 140 (0.71%)</p> <p>1</p> <p>0 / 140 (0.00%)</p> <p>0</p>	<p>0 / 140 (0.00%)</p> <p>0</p> <p>1 / 140 (0.71%)</p> <p>1</p>	

Systematic subjects affected / exposed occurrences (all)	2 / 140 (1.43%) 2	0 / 140 (0.00%) 0	
Injury, poisoning and procedural complications Limb injury alternative assessment type: Systematic subjects affected / exposed occurrences (all) Ligament sprain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0 1 / 140 (0.71%) 1	3 / 140 (2.14%) 3 0 / 140 (0.00%) 0	
Cardiac disorders Sinus tachycardia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	0 / 140 (0.00%) 0	
Nervous system disorders Burning sensation alternative assessment type: Systematic subjects affected / exposed occurrences (all) Dizziness alternative assessment type: Systematic subjects affected / exposed occurrences (all) Tremor alternative assessment type: Systematic subjects affected / exposed occurrences (all) Migraine alternative assessment type: Systematic subjects affected / exposed occurrences (all) Headache	1 / 140 (0.71%) 1 4 / 140 (2.86%) 4 0 / 140 (0.00%) 0 2 / 140 (1.43%) 2	0 / 140 (0.00%) 0 1 / 140 (0.71%) 1 1 / 140 (0.71%) 1 1 / 140 (0.71%) 2	

alternative assessment type: Systematic subjects affected / exposed occurrences (all)	40 / 140 (28.57%) 55	43 / 140 (30.71%) 59	
Exertional headache alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	0 / 140 (0.00%) 0	
Blood and lymphatic system disorders Lymphadenopathy alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	1 / 140 (0.71%) 1	
Ear and labyrinth disorders Cerumen impaction alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	0 / 140 (0.00%) 0	
Ear pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	0 / 140 (0.00%) 0	
Vertigo alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	1 / 140 (0.71%) 1	
Inner ear inflammation alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	1 / 140 (0.71%) 1	
Excessive cerumen production alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	2 / 140 (1.43%) 2	
Eye disorders			

<p>Eye inflammation</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 140 (0.71%)</p> <p>1</p>	<p>0 / 140 (0.00%)</p> <p>0</p>	
<p>Visual impairment</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 140 (0.71%)</p> <p>1</p>	<p>0 / 140 (0.00%)</p> <p>0</p>	
<p>Gastrointestinal disorders</p> <p>Abdominal discomfort</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal distension</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspepsia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eructation</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Faeces hard</p> <p>alternative assessment type: Systematic</p>	<p>2 / 140 (1.43%)</p> <p>3</p> <p>3 / 140 (2.14%)</p> <p>4</p> <p>0 / 140 (0.00%)</p> <p>0</p> <p>6 / 140 (4.29%)</p> <p>6</p> <p>1 / 140 (0.71%)</p> <p>1</p> <p>1 / 140 (0.71%)</p> <p>1</p>	<p>1 / 140 (0.71%)</p> <p>1</p> <p>2 / 140 (1.43%)</p> <p>2</p> <p>2 / 140 (1.43%)</p> <p>3 / 140 (2.14%)</p> <p>3</p> <p>1 / 140 (0.71%)</p> <p>1</p> <p>0 / 140 (0.00%)</p> <p>0</p>	

subjects affected / exposed	0 / 140 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	1
Flatulence		
alternative assessment type: Systematic		
subjects affected / exposed	14 / 140 (10.00%)	19 / 140 (13.57%)
occurrences (all)	18	21
Vomiting		
alternative assessment type: Systematic		
subjects affected / exposed	0 / 140 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	1
Toothache		
alternative assessment type: Systematic		
subjects affected / exposed	0 / 140 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	1
Reflux gastritis		
alternative assessment type: Systematic		
subjects affected / exposed	0 / 140 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	1
Mouth ulceration		
alternative assessment type: Systematic		
subjects affected / exposed	1 / 140 (0.71%)	0 / 140 (0.00%)
occurrences (all)	1	0
Gingival swelling		
alternative assessment type: Systematic		
subjects affected / exposed	1 / 140 (0.71%)	0 / 140 (0.00%)
occurrences (all)	1	0
Gastrooesophageal reflux disease		
alternative assessment type: Systematic		
subjects affected / exposed	1 / 140 (0.71%)	1 / 140 (0.71%)
occurrences (all)	1	2
Gastrointestinal hypermotility		
alternative assessment type: Systematic		
subjects affected / exposed	0 / 140 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	1

Gastric dilatation alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	1 / 140 (0.71%) 1	
Skin and subcutaneous tissue disorders Dermatitis atopic alternative assessment type: Systematic subjects affected / exposed occurrences (all) Cold sweat alternative assessment type: Systematic subjects affected / exposed occurrences (all) Eczema alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0 1 / 140 (0.71%) 1 0 / 140 (0.00%) 0 0 / 140 (0.00%) 0	1 / 140 (0.71%) 1 0 / 140 (0.00%) 0 1 / 140 (0.71%) 1	
Renal and urinary disorders Dysuria alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	0 / 140 (0.00%) 0	
Musculoskeletal and connective tissue disorders Neck pain alternative assessment type: Systematic subjects affected / exposed occurrences (all) Myalgia alternative assessment type: Systematic subjects affected / exposed occurrences (all) Musculoskeletal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 140 (1.43%) 2 0 / 140 (0.00%) 0 0 / 140 (0.00%) 0	0 / 140 (0.00%) 0 1 / 140 (0.71%) 1 1 / 140 (0.71%) 2	

Back pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	4 / 140 (2.86%) 5	
Arthralgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	1 / 140 (0.71%) 1	
Spondylolisthesis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	0 / 140 (0.00%) 0	
Infections and infestations COVID-19 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	1 / 140 (0.71%) 1	
Candida infection alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	1 / 140 (0.71%) 1	
Herpes simplex alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	1 / 140 (0.71%) 1	
Gastroenteritis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	1 / 140 (0.71%) 1	
Otosalpingitis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1	0 / 140 (0.00%) 0	
Ophthalmic herpes simplex alternative assessment type: Systematic			

subjects affected / exposed occurrences (all) Nasopharyngitis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 140 (0.71%) 1 11 / 140 (7.86%) 13	0 / 140 (0.00%) 0 12 / 140 (8.57%) 12	
Metabolism and nutrition disorders Appetite disorder alternative assessment type: Systematic subjects affected / exposed occurrences (all) Decreased appetite alternative assessment type: Systematic subjects affected / exposed occurrences (all) Vitamin B12 deficiency alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0 0 / 140 (0.00%) 0 1 / 140 (0.71%) 1	1 / 140 (0.71%) 1 1 / 140 (0.71%) 1 0 / 140 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2022	Protocol amendment no 3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported