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	31.0	32.2	
standard deviation	± 9.70	± 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	1 / 140 (0.71%)	0 / 140 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Feeling cold			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 140 (0.71%)	0 / 140 (0.00%)	
occurrences (all)	1	0	
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 140 (3.57%)	7 / 140 (5.00%)	
occurrences (all)	5	8	
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 140 (0.00%)	3 / 140 (2.14%)	
occurrences (all)	0	3	
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 140 (0.71%)	0 / 140 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 140 (0.00%)	1 / 140 (0.71%)	
occurrences (all)	0	1	
Asthenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 140 (0.71%)	0 / 140 (0.00%)	
occurrences (all)	1	0	
Hunger			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 140 (0.71%)	0 / 140 (0.00%)	
occurrences (all)	1	0	

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

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

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

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

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

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

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

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