Clinical trial results:
Effects of oral Levosimendan (ODM-109) on respiratory function in patients with ALS: open label extension for patients completing study 3119002

Summary

EudraCT number	2018-004180-31
Trial protocol	BE ES DE FI AT NL IE GB FR IT
Global end of trial date	18 November 2020

Results information

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

Trial information

Trial identification

Sponsor protocol code	3119003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03948178
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Orion Corporation
Sponsor organisation address	Orionintie 1, Espoo, Finland,
Public contact	Clinical Trials Information, Orion Corporation, +358 104261, clinicaltrials@orionpharma.com
Scientific contact	Clinical Trials Information, Orion Corporation, +358 104261, clinicaltrials@orionpharma.com

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	18 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2020
Global end of trial reached?	Yes
Global end of trial date	18 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective, in addition to continuing treatment for subjects in this study, was to evaluate long-term safety of oral levosimendan in amyotrophic lateral sclerosis (ALS) patients.

Protection of trial subjects:

Adverse events were followed by sponsor and the independent data and safety monitoring board (DSMB). Specific criteria were in place for the withdrawal of patients from study treatment, including uncontrolled increased heart rate, and life threatening supraventricular or ventricular arrhytmias. The investigator could also withdraw the treatment if considered to be in the best interests of the subject. Patients were free to leave the study at any time but were also withdrawn in the event of a safety finding of clinical concern.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	United States: 61
Worldwide total number of subjects	227
EEA total number of subjects	132

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)	160
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patiens participating to REFALS study and completed 48-weeks treatment were recruited to continue with oral levosimendan for long term safety follow-up.

Pre-assignment

Screening details:

Male or female subjects with written or verbal IC obtained. Subjects who completed 48 weeks of treatment according to the REFALS study protocol. Able to swallow study treatment capsules at the time of completing 48 weeks dosing in the REFALS study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Levosimendan

Arm description:

Oral levosimendan 0.5-2 mg daily.

Arm type	Experimental
Investigational medicinal product name	levosimendan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The target maintenance dose of oral levosimendan was 2 mg/day taken as 1 mg b.i.d. Levosimendan treatment was started at 1 mg/day. The subject were to be reviewed 2 weeks after initiation of levosimendan at which time the dose was to be increased to 2 mg/day, if considered appropriate and the 1 mg/day dose was well tolerated. It was permitted to use also less frequent dosing than 1 mg once daily (e.g. 1 mg on alternate days) if levosimendan 1 mg/day was not well tolerated. The subject was to be re-assessed 2 weeks after each dose change.

Number of subjects in period 1	Levosimendan
Started	227
Completed	0
Not completed	227
Adverse event, serious fatal	5
Disease progression	30
Adverse event, non-fatal	7
Personal reason	14
Other	2
Study terminated by sponsor	164
Withdrawal of consent	2

Lost to follow-up	2
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	227	227	
Age categorical Units: Subjects			
Adults (18-64 years)	160	160	
From 65-84 years	67	67	
Gender categorical Units: Subjects			
Female	85	85	
Male	142	142	

End points

End points reporting groups

Reporting group title	Levosimendan
Reporting group description:	
Oral levosimendan 0.5-2 mg daily.	

Primary: Long term safety of oral levosimendan

End point title	Long term safety of oral levosimendan[1]
End point description:	
Number of patients with Treatment emergent adverse events (TEAE)s	
End point type	Primary
End point timeframe:	
After 48 weeks of treatment according to the REFALS study protocol until the end of study. The mean time on treatment (including dose interruptions) was 23.54 weeks.	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The primary objective, in addition to continuing treatment for subjects in REFALS study, was to evaluate long-term safety of oral levosimendan in ALS patients. Long term safety, adverse event reporting, vital signs and 12-lead ECG, was evaluated using descriptive statistics only.	

End point values	Levosimendan			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: number	161			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline, SVC (supine) at 2 weeks

End point title	Change from baseline, SVC (supine) at 2 weeks
End point description:	
End point type	Secondary
End point timeframe:	
2 and 4 weeks and 3 and 6 months after start of study treatment	

End point values	Levosimendan			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: percent				
arithmetic mean (standard deviation)	1.2 (± 7.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline, SVC (supine) at 4 weeks

End point title	Change from baseline, SVC (supine) at 4 weeks

End point description:

End point type	Secondary

End point timeframe:

2 and 4 weeks and 3 and 6 months after start of study treatment

End point values	Levosimendan			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percent				
arithmetic mean (standard deviation)	0.9 (± 9.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline, SVC (supine) at 3 months

End point title	Change from baseline, SVC (supine) at 3 months

End point description:

End point type	Secondary

End point timeframe:

2 and 4 weeks and 3 and 6 months after start of study treatment

End point values	Levosimendan			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: percent				
arithmetic mean (standard deviation)	-2.4 (± 10.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline, SVC (supine) at 6 months

End point title	Change from baseline, SVC (supine) at 6 months

End point description:

End point type	Secondary

End point timeframe:

2 and 4 weeks and 3 and 6 months after start of study treatment

End point values	Levosimendan			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percent				
arithmetic mean (standard deviation)	-3.3 (± 13.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the informed consent until the end of study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Levosimendan

Reporting group description: -

Serious adverse events	Levosimendan		
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 227 (19.38%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	19		
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
EUTHANASIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
PYREXIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
CHOKING			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DYSPNOEA			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
RESPIRATORY ARREST			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
RESPIRATORY DEPRESSION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
RESPIRATORY DISTRESS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
RESPIRATORY FAILURE			
subjects affected / exposed	11 / 227 (4.85%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 9		
RHINORRHOEA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
SUICIDE ATTEMPT			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
OXYGEN SATURATION DECREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
HUMERUS FRACTURE			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MENISCUS INJURY			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
STOMA SITE PAIN			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
WRIST FRACTURE			

subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CARDIAC ARREST			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
CARDIAC FAILURE CHRONIC			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
METASTASES TO LYMPH NODES			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
DIARRHOEA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

DYSPHAGIA				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INTESTINAL OBSTRUCTION				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LOWER GASTROINTESTINAL HAEMORRHAGE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SALIVA ALTERED				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
HAEMATURIA				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RENAL MASS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
BACK PAIN				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
CELLULITIS				

subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CYSTITIS BACTERIAL			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		
SYSTEMIC VIRAL INFECTION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
UROSEPSIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
HYPERKALAEMIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
HYPONATRAEMIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Levosimendan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	158 / 227 (69.60%)		
Vascular disorders			
AORTIC ANEURYSM			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
BLOOD PRESSURE INADEQUATELY CONTROLLED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
HAEMATOMA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
HYPERTENSION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
HYPOTENSION			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
LYMPHOEDEMA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
SUPERFICIAL VEIN PROMINENCE			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Surgical and medical procedures			
CENTRAL VENOUS CATHETER REMOVAL			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
General disorders and administration site conditions			

ASTHENIA				
subjects affected / exposed	3 / 227 (1.32%)			
occurrences (all)	3			
CHEST PAIN				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
CHILLS				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	2			
FACIAL PAIN				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
FATIGUE				
subjects affected / exposed	3 / 227 (1.32%)			
occurrences (all)	3			
GAIT DISTURBANCE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
INFLUENZA LIKE ILLNESS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
NON-CARDIAC CHEST PAIN				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
OEDEMA PERIPHERAL				
subjects affected / exposed	8 / 227 (3.52%)			
occurrences (all)	9			
PAIN				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	2			
PARADOXICAL DRUG REACTION				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
PERIPHERAL SWELLING				
subjects affected / exposed	4 / 227 (1.76%)			
occurrences (all)	4			

PYREXIA			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences (all)	5		
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
ASPIRATION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
ATELECTASIS			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
CHOKING			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
COUGH			
subjects affected / exposed	8 / 227 (3.52%)		
occurrences (all)	8		
DYSPNOEA			
subjects affected / exposed	13 / 227 (5.73%)		
occurrences (all)	13		
DYSPNOEA AT REST			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
HYPOVENTILATION			
subjects affected / exposed	6 / 227 (2.64%)		
occurrences (all)	8		
HYPOXIA			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
INCREASED BRONCHIAL SECRETION			

subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
LARYNGOSPASM			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
NASAL CONGESTION			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
OROPHARYNGEAL PAIN			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
ORTHOPNOEA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
PRODUCTIVE COUGH			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
RESPIRATORY FAILURE			
subjects affected / exposed	3 / 227 (1.32%)		
occurrences (all)	3		
RHINORRHOEA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
SLEEP APNOEA SYNDROME			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
UPPER-AIRWAY COUGH SYNDROME			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	6 / 227 (2.64%)		
occurrences (all)	6		

DEPRESSED MOOD			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DEPRESSION			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
INSOMNIA			
subjects affected / exposed	5 / 227 (2.20%)		
occurrences (all)	5		
MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
PANIC ATTACK			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	2		
PANIC REACTION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
PROCEDURAL ANXIETY			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
SLEEP DISORDER			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
TEARFULNESS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
BLOOD POTASSIUM DECREASED			

subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
BLOOD PRESSURE SYSTOLIC INCREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
HEART RATE INCREASED			
subjects affected / exposed	12 / 227 (5.29%)		
occurrences (all)	12		
OXYGEN SATURATION DECREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
PULMONARY FUNCTION TEST DECREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
TROPONIN INCREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
WEIGHT DECREASED			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
WHITE BLOOD CELL COUNT INCREASED			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
CONCUSSION			

subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
CONTUSION				
subjects affected / exposed	3 / 227 (1.32%)			
occurrences (all)	3			
EYE CONTUSION				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
FACE INJURY				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
FACIAL BONES FRACTURE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	2			
FALL				
subjects affected / exposed	23 / 227 (10.13%)			
occurrences (all)	40			
FOOT FRACTURE				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	2			
GASTROSTOMY TUBE SITE COMPLICATION				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
HEAD INJURY				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
JAW FRACTURE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
JOINT DISLOCATION				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
LIP INJURY				
subjects affected / exposed	3 / 227 (1.32%)			
occurrences (all)	3			

NASAL INJURY				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
POST LUMBAR PUNCTURE SYNDROME				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
POST-TRAUMATIC PAIN				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
RIB FRACTURE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
SKIN ABRASION				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	3			
SKIN LACERATION				
subjects affected / exposed	6 / 227 (2.64%)			
occurrences (all)	7			
STOMA SITE ERYTHEMA				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
STOMA SITE HAEMORRHAGE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
STOMA SITE PAIN				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
TOOTH FRACTURE				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	2			
WOUND				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
WRIST FRACTURE				

subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
LEFT VENTRICLE OUTFLOW TRACT OBSTRUCTION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
PALPITATIONS			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences (all)	4		
TACHYCARDIA			
subjects affected / exposed	18 / 227 (7.93%)		
occurrences (all)	20		
TACHYCARDIA PAROXYSMAL			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Nervous system disorders			
AMYOTROPHIC LATERAL SCLEROSIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
CERVICAL RADICULOPATHY			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DIZZINESS			
subjects affected / exposed	6 / 227 (2.64%)		
occurrences (all)	7		
DIZZINESS POSTURAL			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DYSGEUSIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
ENCEPHALOPATHY			

subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
HEADACHE			
subjects affected / exposed	20 / 227 (8.81%)		
occurrences (all)	28		
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
PARAESTHESIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
POST-TRAUMATIC HEADACHE			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
SCIATICA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
LUNG NEOPLASM			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
NORMOCHROMIC NORMOCYTIC ANAEMIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
SEBORRHOEIC KERATOSIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Ear and labyrinth disorders			
EAR DISCOMFORT			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
MOTION SICKNESS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
VERTIGO			

subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Eye disorders			
BLEPHARITIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
ABDOMINAL PAIN			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
ANAL INCONTINENCE			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
CONSTIPATION			
subjects affected / exposed	10 / 227 (4.41%)		
occurrences (all)	10		
DIARRHOEA			
subjects affected / exposed	8 / 227 (3.52%)		
occurrences (all)	8		
DIVERTICULUM			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DYSPEPSIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DYSPHAGIA			

subjects affected / exposed	10 / 227 (4.41%)			
occurrences (all)	10			
ENTERITIS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
GASTROOESOPHAGEAL REFLUX DISEASE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
GINGIVAL BLEEDING				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
HAEMORRHOIDS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
IRRITABLE BOWEL SYNDROME				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
NAUSEA				
subjects affected / exposed	3 / 227 (1.32%)			
occurrences (all)	3			
SALIVA ALTERED				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
SALIVARY HYPERSECRETION				
subjects affected / exposed	4 / 227 (1.76%)			
occurrences (all)	4			
TONGUE COATED				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
TOOTHACHE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
VOMITING				
subjects affected / exposed	5 / 227 (2.20%)			
occurrences (all)	5			

Skin and subcutaneous tissue disorders			
DECUBITUS ULCER			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DERMAL CYST			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DRY SKIN			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
DYSHIDROTIC ECZEMA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
ECZEMA			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
ECZEMA NUMMULAR			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
ERYTHEMA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
HYPERHIDROSIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
INGROWING NAIL			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
MILIARIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
NAIL BED INFLAMMATION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
PRURITUS			

subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all) SKIN EXFOLIATION subjects affected / exposed occurrences (all) SKIN LESION subjects affected / exposed occurrences (all) SKIN REACTION subjects affected / exposed occurrences (all)	2 / 227 (0.88%) 2 2 / 227 (0.88%) 2 1 / 227 (0.44%) 1 1 / 227 (0.44%) 1 1 / 227 (0.44%) 1		
Renal and urinary disorders INCONTINENCE subjects affected / exposed occurrences (all) MICTURITION DISORDER subjects affected / exposed occurrences (all) NEUROGENIC BLADDER subjects affected / exposed occurrences (all) POLYURIA subjects affected / exposed occurrences (all) URINARY RETENTION subjects affected / exposed occurrences (all) URINE ABNORMALITY subjects affected / exposed occurrences (all)	 1 / 227 (0.44%) 1 1 / 227 (0.44%) 1 1 / 227 (0.44%) 1 1 / 227 (0.44%) 1 2 / 227 (0.88%) 2 1 / 227 (0.44%) 1		
Musculoskeletal and connective tissue disorders			

ARTHRALGIA				
subjects affected / exposed	3 / 227 (1.32%)			
occurrences (all)	3			
ARTHRITIS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
BACK PAIN				
subjects affected / exposed	4 / 227 (1.76%)			
occurrences (all)	5			
BURSITIS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
CHONDROMALACIA				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
DUPUYTREN'S CONTRACTURE				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
JOINT SWELLING				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	2			
MOBILITY DECREASED				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
MUSCLE SPASMS				
subjects affected / exposed	6 / 227 (2.64%)			
occurrences (all)	7			
MUSCLE TWITCHING				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
MUSCULAR WEAKNESS				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	2			
MYALGIA				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	2			

NECK PAIN subjects affected / exposed occurrences (all)	3 / 227 (1.32%) 3			
PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	2 / 227 (0.88%) 2			
PAIN IN JAW subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1			
PERIARTHRITIS subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1			
TENDON PAIN subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1			
Infections and infestations BARTHOLIN'S ABSCESS subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1			
BRONCHITIS subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1			
CONJUNCTIVITIS BACTERIAL subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1			
CYSTITIS subjects affected / exposed occurrences (all)	2 / 227 (0.88%) 2			
FUNGAL SKIN INFECTION subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1			
GASTROENTERITIS subjects affected / exposed occurrences (all)	4 / 227 (1.76%) 4			
GASTROENTERITIS VIRAL				

subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
GINGIVAL ABSCESS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
HERPES ZOSTER				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
NASOPHARYNGITIS				
subjects affected / exposed	10 / 227 (4.41%)			
occurrences (all)	11			
ORAL HERPES				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
RHINITIS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
SINUSITIS				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	3			
STOMA SITE CELLULITIS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
STOMA SITE INFECTION				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences (all)	2			
TONSILLITIS				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences (all)	1			

URINARY TRACT INFECTION subjects affected / exposed occurrences (all) VULVOVAGINAL CANDIDIASIS subjects affected / exposed occurrences (all)	 9 / 227 (3.96%) 10 1 / 227 (0.44%) 1		
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all) DEHYDRATION subjects affected / exposed occurrences (all) FOLATE DEFICIENCY subjects affected / exposed occurrences (all) HYPERGLYCAEMIA subjects affected / exposed occurrences (all) HYPOKALAEMIA subjects affected / exposed occurrences (all) TYPE 2 DIABETES MELLITUS subjects affected / exposed occurrences (all)	 2 / 227 (0.88%) 2 2 / 227 (0.88%) 2 1 / 227 (0.44%) 1 1 / 227 (0.44%) 1 2 / 227 (0.88%) 2 1 / 227 (0.44%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2020	This amendment was written to describe how to perform baseline or treatment period visits remotely in case visit to the study centre was not possible due to restriction related to COVID-19 pandemic. All arrangements described in this section applied only to the extent that protocol requirements could not be met because of COVID-19 restrictions. Study centre visits had to take place to the extent possible and usual protocol requirements adopted for all subjects as soon as COVID-19 limitations permitted. SVC and weight were not assessed while these arrangements applied. During the remote visits, protocol requirements could be altered as assessments were conducted by phone interviews and for example HR values measured with automate sphygmomanometer were allowed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 August 2020	The study was terminated by the sponsor on 21 August 2020, as the efficacy endpoints of the REFALS study were not met.	-

Notes:

Limitations and caveats

None reported