



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
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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 arrhythmias. 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 Patients were free to leave the study at any time but were also withdrawn in the event of a safety finding of clinical concern.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:

Patients 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
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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 (\pm 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
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End point description:

End point type	Secondary
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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 (\pm 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
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End point description:

End point type	Secondary
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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 (\pm 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
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End point description:

End point type	Secondary
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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 (\pm 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Levosimendan
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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 occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 227 (0.44%) 0 / 1 0 / 0		
Investigations OXYGEN SATURATION DECREASED subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 227 (0.44%) 0 / 1 0 / 0		
Injury, poisoning and procedural complications FALL subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 227 (0.88%) 0 / 2 0 / 0		
HUMERUS FRACTURE subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 227 (0.44%) 0 / 1 0 / 0		
MENISCUS INJURY subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 227 (0.44%) 0 / 1 0 / 0		
STOMA SITE PAIN subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 227 (0.88%) 0 / 2 0 / 0		
SUBDURAL HAEMATOMA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 227 (0.44%) 0 / 1 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 occurrences (all)	4 / 227 (1.76%) 5		
Immune system disorders HYPERSENSITIVITY subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1		
Respiratory, thoracic and mediastinal disorders ASPIRATION subjects affected / exposed occurrences (all) ATELECTASIS subjects affected / exposed occurrences (all) CHOKING subjects affected / exposed occurrences (all) COUGH subjects affected / exposed occurrences (all) DYSпноEA subjects affected / exposed occurrences (all) DYSпноEA AT REST subjects affected / exposed occurrences (all) DYSпноEA EXERTIONAL subjects affected / exposed occurrences (all) HYPOVENTILATION subjects affected / exposed occurrences (all) HYPOXIA subjects affected / exposed occurrences (all) INCREASED BRONCHIAL SECRETION	1 / 227 (0.44%) 1 2 / 227 (0.88%) 2 1 / 227 (0.44%) 1 8 / 227 (3.52%) 8 13 / 227 (5.73%) 13 1 / 227 (0.44%) 1 1 / 227 (0.44%) 1 6 / 227 (2.64%) 8 2 / 227 (0.88%) 2		

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	2 / 227 (0.88%)		
occurrences (all)	2		
RASH			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
SKIN EXFOLIATION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
SKIN LESION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
SKIN REACTION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Renal and urinary disorders			
INCONTINENCE			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
MICTURITION DISORDER			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
NEUROGENIC BLADDER			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
POLYURIA			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
URINARY RETENTION			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
URINE ABNORMALITY			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	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	3 / 227 (1.32%)		
occurrences (all)	3		
PAIN IN EXTREMITY			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
PAIN IN JAW			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
PERIARTHRITIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
TENDON PAIN			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Infections and infestations			
BARTHOLIN'S ABSCESS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
BRONCHITIS			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
CONJUNCTIVITIS BACTERIAL			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
CYSTITIS			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences (all)	2		
FUNGAL SKIN INFECTION			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
GASTROENTERITIS			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences (all)	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)	9 / 227 (3.96%) 10		
VULVOVAGINAL CANDIDIASIS subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1		
Metabolism and nutrition disorders			
DECREASED APPETITE subjects affected / exposed occurrences (all)	2 / 227 (0.88%) 2		
DEHYDRATION subjects affected / exposed occurrences (all)	2 / 227 (0.88%) 2		
FOLATE DEFICIENCY subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1		
HYPERGLYCAEMIA subjects affected / exposed occurrences (all)	1 / 227 (0.44%) 1		
HYPOKALAEMIA subjects affected / exposed occurrences (all)	2 / 227 (0.88%) 2		
TYPE 2 DIABETES MELLITUS subjects affected / exposed occurrences (all)	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