Clinical trial results:
A Phase 3, Randomised, Placebo-Controlled Trial of Arimoclomol in Amyotrophic Lateral Sclerosis

Summary

EudraCT number	2018-000137-13
Trial protocol	FR SE GB BE NL PL ES IT
Global end of trial date	18 December 2020

Results information

Result version number	v1 (current)
This version publication date	12 October 2024
First version publication date	12 October 2024

Trial information

Trial identification

Sponsor protocol code	ORARIALS-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03491462
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zevra Denmark A/S
Sponsor organisation address	Nordre Fasanvej 215, Frederiksberg, Denmark, 2000
Public contact	Medical Affairs, Zevra Denmark A/S, +1 8882895607, medicalaffairs@zevra.com
Scientific contact	Medical Affairs, Zevra Denmark A/S, +1 8882895607, medicalaffairs@zevra.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	05 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of chronic treatment with arimoclomol 1200 mg/day (400 mg TID) compared to placebo over 76 weeks in subjects with ALS as assessed with Combined Assessment of Function and Survival (CAFS)

Protection of trial subjects:

The IRB or IEC reviewed all appropriate trial documentation including the protocols, patient information and ICFs including amendments to these. This trial was conducted in accordance with their protocol and with the following:
• Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
• Current version of applicable ICH GCP guidelines.
• Applicable laws and regulations.

Background therapy:

Patients were allowed to have been treated with a background stable dose of riluzole. Riluzole use was a stratification factor meaning that there was a chance that patients without background riluzole therapy received placebo.

Evidence for comparator: -

Actual start date of recruitment	31 July 2018
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: 19
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 57
Country: Number of subjects enrolled	Canada: 8

Worldwide total number of subjects	245
EEA total number of subjects	175

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)	176
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening was up to 4 weeks prior to Baseline if a washout period for an investigational treatment was required and to allow for laboratory re-tests (if
required).

Period 1

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

Blinding implementation details:

ORARIALS-01 was a double-blinded trial in which arimoclomol, and placebo were visually identical and matched for taste. Neither the patient nor any of the investigator site staff or Sponsor staff (including CRO delegated staff) who were involved in the treatment or clinical evaluation and monitoring of the patients were aware of the treatment received. The packaging and labelling of the IMPs contained no evidence of their identity.

Arms

Are arms mutually exclusive?	Yes
Arm title	Drug: Arimoclomol

Arm description:

248 mg arimoclomol base (equivalent to 400 mg arimoclomol citrate) 3 times daily

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

Dosage and administration details:

Oral dosage 3 times daily for up to 76 weeks

Arm title	Drug: Placebo

Arm description:

Matching placebo 3 times daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

Matching capsules taken orally three-times daily

Number of subjects in period 1[1]	Drug: Arimoclomol	Drug: Placebo
Started	160	79
Completed	122	63
Not completed	38	16
Physician decision	3	-
Consent withdrawn by subject	22	15
Adverse event, non-fatal	11	1
Lost to follow-up	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Subjects reported at baseline include the modified Intention to Treat (mITT) population, not on concomitant Edavarone treatment (N=6) and therefore not included in analysis

Baseline characteristics

Reporting groups	
Reporting group title	Drug: Arimoclomol
Reporting group description:	
248 mg arimoclomol base (equivalent to 400 mg arimoclomol citrate) 3 times daily	
Reporting group title	Drug: Placebo
Reporting group description:	
Matching placebo 3 times daily	

Reporting group values	Drug: Arimoclomol	Drug: Placebo	Total
Number of subjects	160	79	239
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	113	60	173
From 65-84 years	47	19	66
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	58.0	56.6	
standard deviation	± 11.26	± 9.97	-
Gender categorical Units: Subjects			
Female	54	34	88
Male	106	45	151
Ethnicity Units: Subjects			
Hispanic or Latino	13	7	20
Not Hispanic or Latino	132	64	196
Unknown or Not Reported	15	8	23
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	136	66	202
More than one race	0	0	0
Unknown or Not Reported	23	11	34

Revised ALS Functional Rating Scale			
The ALSFRS-R score is based on a rating scale where 12 functions are rated on 5-point ordinal rating scales (from 0 to 4) with a maximum score of 48 (sum of all 12 items). The higher the score the better functioning.			
Units: Units on a scale			
arithmetic mean	40.6	40.2	
standard deviation	± 3.93	± 3.65	-
Percent (%) Predicted Slow Vital Capacity (SVC)			
Slow Vital Capacity (SVC) is a measure of breathing function. SVC measures the volume that can be exhaled from a full inhalation after exhaling to a maximum as slowly as possible. The percent (%) of predicted SVC is reported.			
Units: Percent (%) predicted SVC			
arithmetic mean	95.8	98.1	
standard deviation	± 15.98	± 14.78	-

Subject analysis sets

Subject analysis set title	Subject Analysis Set 1
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All participants in the modified intention-to-treat (mITT) population

Reporting group values	Subject Analysis Set 1		
Number of subjects	239		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race			
Units: Subjects			

American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Revised ALS Functional Rating Scale			
The ALSFRS-R score is based on a rating scale where 12 functions are rated on 5-point ordinal rating scales (from 0 to 4) with a maximum score of 48 (sum of all 12 items). The higher the score the better functioning.			
Units: Units on a scale arithmetic mean standard deviation	 40.5 ± 3.83		
Percent (%) Predicted Slow Vital Capacity (SVC)			
Slow Vital Capacity (SVC) is a measure of breathing function. SVC measures the volume that can be exhaled from a full inhalation after exhaling to a maximum as slowly as possible. The percent (%) of predicted SVC is reported.			
Units: Percent (%) predicted SVC arithmetic mean standard deviation	 96.5 ± 15.60		

End points

End points reporting groups

Reporting group title	Drug: Arimoclomol
Reporting group description:	
248 mg arimoclomol base (equivalent to 400 mg arimoclomol citrate) 3 times daily	
Reporting group title	Drug: Placebo
Reporting group description:	
Matching placebo 3 times daily	
Subject analysis set title	Subject Analysis Set 1
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All participants in the modified intention-to-treat (mITT) population	

Primary: Combined Assessment of Function and Survival (CAFS)

End point title	Combined Assessment of Function and Survival (CAFS)

End point description:

Combined Assessment of Function and Survival (CAFS) is a composite endpoint that includes 1) the change from baseline in revised ALS functional rating scale (ALSFRS-R) and 2) the survival endpoint (time to permanent assisted ventilation [PAV], tracheostomy or death).
On the ALSFRS-R, 12 functions are rated on 5-point ordinal rating scales (from 0 to 4) with a total score range (minimum and maximum score) of 0-48 (sum of all 12 items). The higher the score the better functioning.
For the survival endpoint, the longer time to PAV, tracheostomy, or death the better outcome.
A patient's CAFS score represents a patient's rank in the study based on comparing the patient's outcome for both the change in ALSFRS-R and the time to event (PAV, tracheostomy, or death) to the outcome for all other patients in the study in a pairwise fashion. A higher rank score (range 0-1) is considered a better outcome.

The reported values are the mean rank scores in each group for the composite endpoint.

End point type	Primary
End point timeframe:	
Over 76 Weeks	

End point values	Drug: Arimoclomol	Drug: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	79		
Units: score on a scale				
arithmetic mean (standard deviation)	0.51 (± 0.291)	0.49 (± 0.283)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Drug: Arimoclomol v Drug: Placebo

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6208
Method	Gehan's extended Wilcoxon's test

Secondary: Change from Baseline to Week 76 (or End-of-Trial) in Revised ALS Functional Rating Scale (ALSFRS-R)

End point title	Change from Baseline to Week 76 (or End-of-Trial) in Revised ALS Functional Rating Scale (ALSFRS-R)

End point description:

The ALSFRS-R score is based on a rating scale where 12 functions are rated on 5-point ordinal rating scales (from 0 to 4) with a maximum score of 48 (sum of all 12 items). The higher the score the better functioning.

End point type	Secondary

End point timeframe:

Week 76 (or end of trial)

End point values	Drug: Arimoclomol	Drug: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	79		
Units: units on a scale				
arithmetic mean (standard deviation)	-15.4 (± 8.71)	-15.0 (± 9.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 76 (or End-of-Trial) in Percent (%) Predicted Slow Vital Capacity (SVC)

End point title	Change from Baseline to Week 76 (or End-of-Trial) in Percent (%) Predicted Slow Vital Capacity (SVC)

End point description:

Slow Vital Capacity (SVC) is a measure of breathing function. SVC measures the volume that can be exhaled from a full inhalation after exhaling to a maximum as slowly as possible. The percent (%) of predicted SVC is reported.

End point type	Secondary

End point timeframe:

Week 76 (or end of trial)

End point values	Drug: Arimoclomol	Drug: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	79		
Units: percent (%) predicted SVC				
arithmetic mean (standard deviation)	-30.65 (± 26.346)	-30.38 (± 23.839)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study medication up to 76 weeks. Assessed every week.

Adverse event reporting additional description:

Safety population included all participants not on edaravone at baseline who received any amount of study medication. Analysis included all events occurring during on-treatment observation period, starting at date of first administration of study medication, until 14 days following the latest administration of study drug or last dose/end-of-trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Arimoclomol (up to 76 Weeks)
Reporting group description: -	
Reporting group title	Placebo (up to 76 Weeks)

Reporting group description: -

Serious adverse events	Arimoclomol (up to 76 Weeks)	Placebo (up to 76 Weeks)	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 160 (22.50%)	20 / 79 (25.32%)	
number of deaths (all causes)	29	18	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 160 (1.88%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Phlebitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Medical device site inflammation			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	7 / 160 (4.38%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	1 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 160 (1.25%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 160 (1.25%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 2	
Hypoxia			

subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Assisted suicide			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical observation			

subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 160 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pupils unequal			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 160 (0.63%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 160 (2.50%)	5 / 79 (6.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 3	
Respiratory tract infection			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arimoclomol (up to 76 Weeks)	Placebo (up to 76 Weeks)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 160 (93.13%)	71 / 79 (89.87%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 160 (5.63%)	2 / 79 (2.53%)	
occurrences (all)	9	2	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	33 / 160 (20.63%)	17 / 79 (21.52%)	
occurrences (all)	55	37	
Post lumbar puncture syndrome			
subjects affected / exposed	10 / 160 (6.25%)	6 / 79 (7.59%)	
occurrences (all)	10	6	
Contusion			
subjects affected / exposed	9 / 160 (5.63%)	4 / 79 (5.06%)	
occurrences (all)	9	6	
Procedural pain			
subjects affected / exposed	5 / 160 (3.13%)	4 / 79 (5.06%)	
occurrences (all)	5	5	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 160 (2.50%)	4 / 79 (5.06%)	
occurrences (all)	4	4	
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 160 (21.25%)	21 / 79 (26.58%)	
occurrences (all)	57	31	
Dizziness			
subjects affected / exposed	16 / 160 (10.00%)	4 / 79 (5.06%)	
occurrences (all)	18	4	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	15 / 160 (9.38%)	5 / 79 (6.33%)	
occurrences (all)	16	7	
Fatigue			

subjects affected / exposed	9 / 160 (5.63%)	2 / 79 (2.53%)	
occurrences (all)	10	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	33 / 160 (20.63%)	11 / 79 (13.92%)	
occurrences (all)	38	13	
Nausea			
subjects affected / exposed	27 / 160 (16.88%)	3 / 79 (3.80%)	
occurrences (all)	35	3	
Diarrhoea			
subjects affected / exposed	16 / 160 (10.00%)	8 / 79 (10.13%)	
occurrences (all)	22	11	
Dyspepsia			
subjects affected / exposed	6 / 160 (3.75%)	5 / 79 (6.33%)	
occurrences (all)	7	5	
Abdominal pain			
subjects affected / exposed	5 / 160 (3.13%)	4 / 79 (5.06%)	
occurrences (all)	6	5	
Flatulence			
subjects affected / exposed	4 / 160 (2.50%)	4 / 79 (5.06%)	
occurrences (all)	4	5	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 160 (0.63%)	5 / 79 (6.33%)	
occurrences (all)	1	5	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	7 / 160 (4.38%)	4 / 79 (5.06%)	
occurrences (all)	8	4	
Rash			
subjects affected / exposed	9 / 160 (5.63%)	2 / 79 (2.53%)	
occurrences (all)	10	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	23 / 160 (14.38%)	7 / 79 (8.86%)	
occurrences (all)	27	7	
Depression			

subjects affected / exposed	8 / 160 (5.00%)	7 / 79 (8.86%)	
occurrences (all)	8	7	
Sleep disorder			
subjects affected / exposed	3 / 160 (1.88%)	4 / 79 (5.06%)	
occurrences (all)	3	4	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	14 / 160 (8.75%)	7 / 79 (8.86%)	
occurrences (all)	15	9	
Arthralgia			
subjects affected / exposed	10 / 160 (6.25%)	5 / 79 (6.33%)	
occurrences (all)	13	5	
Musculoskeletal pain			
subjects affected / exposed	10 / 160 (6.25%)	5 / 79 (6.33%)	
occurrences (all)	12	5	
Pain in extremity			
subjects affected / exposed	11 / 160 (6.88%)	2 / 79 (2.53%)	
occurrences (all)	12	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 160 (8.75%)	15 / 79 (18.99%)	
occurrences (all)	18	23	
Pneumonia			
subjects affected / exposed	10 / 160 (6.25%)	3 / 79 (3.80%)	
occurrences (all)	17	8	
Urinary tract infection			
subjects affected / exposed	12 / 160 (7.50%)	7 / 79 (8.86%)	
occurrences (all)	14	11	
Influenza			
subjects affected / exposed	10 / 160 (6.25%)	4 / 79 (5.06%)	
occurrences (all)	11	5	
Bronchitis			
subjects affected / exposed	6 / 160 (3.75%)	5 / 79 (6.33%)	
occurrences (all)	6	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2019	protocol version 5.0 added in-clinic visits in response to an urgent safety measure that was initiated by the DMC in response to cases of increased transaminases. To monitor increased transaminases, the remote visits 4, 6, and 8 (Week 8, 16, and 32) was changed to inperson visits and a blood sample was to be taken. This was done to enable routine monitoring of patients monthly for the first 6 months of the trial, as recommended by the DMC. Furthermore, discontinuation criteria were updated according to FDA Guidance for Industry on Drug-Induced Liver Injury (DILI) in relation to the urgent safety measure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported