Clinical trial results:
Open-label, Non-randomised Extension Trial to Assess the Long-Term Safety and Efficacy of 1200 mg/day Arimoclomol 400 mg Three Times a Day (t.i.d.) in Subjects with Amyotrophic Lateral Sclerosis (ALS) who have Completed the ORARIALS-01 Trial

Summary

EudraCT number	2019-000374-39
Trial protocol	GB SE BE PL DE NL ES IT
Global end of trial date	11 May 2021

Results information

Result version number	v1 (current)
This version publication date	16 October 2024
First version publication date	16 October 2024

Trial information

Trial identification

Sponsor protocol code	ORARIALS-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03836716
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	11 May 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

A multicenter, non-randomized, open label trial, to assess long term safety and efficacy of Arimoclomol in subjects with Amyotrophic Lateral Sclerosis (ALS) who have completed the ORARIALS-01 trial. The planned duration of the open-label trial was 152 weeks, but the trial was terminated early as a consequence of the results of ORARIALS-01 which did not meet any of its efficacy endpoints. Therefore, the actual mean duration of open-label treatment was approximately 28 weeks (range approximately 2 to 71 weeks).

Protection of trial subjects:

Trial were 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: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	120
EEA total number of subjects	88

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)	86
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Roll-over of 120 subjects who completed the ORARIALS 01 trial (i.e., met one of the surrogate survival endpoints of tracheostomy or PAV or has completed the 76 weeks randomized treatment period).

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). Patients excluded with cilinically significant renal or hepatic disease OR clinical laboratory assessment.

Period 1

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

Blinding implementation details:

Open-label extension.

Arms

Arm title	Arimoclomol (Open-label)

Arm description:

248 mg arimoclomol base 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:

Arimoclomol 2 × 124 mg capsules were taken orally t.i.d.

Number of subjects in period 1	Arimoclomol (Open-label)
Started	120
Completed	0
Not completed	120
Adverse event, serious fatal	22
Consent withdrawn by subject	8
Adverse event, non-fatal	3
Study terminated by sponsor	87

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	120	120	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	86	86	
From 65-84 years	34	34	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	57.6		
standard deviation	± 10.30	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	84	84	

End points

End points reporting groups

Reporting group title	Arimoclomol (Open-label)
Reporting group description:	
248 mg arimoclomol base 3 times daily	

Primary: Number of Participants with Treatment-emergent Adverse Events (TEAEs) Over the Open-label Treatment Period

End point title	Number of Participants with Treatment-emergent Adverse Events (TEAEs) Over the Open-label Treatment Period[1]

End point description:

Adverse event (AE) data were collected throughout the trial until early termination. The average duration of exposure was 198.7 days (approximately 28 weeks; standard deviation 99.57 days; minimum 16 days, maximum 494 days). 58 participants (48.3%) were exposed less than 6 months; 55 participants (45.8%) were exposed 6 to less than 12 months; 7 participants (5.8%) were exposed 12 to less than 18 months. No participant was treated for 76 weeks.

Participants with on-treatment TEAEs are reported. An on-treatment TEAE is any TEAE in the on-treatment period defined as the time from first dose of IMP until 14 days since the last preceding administration of IMP (either before a temporary IMP interruption with duration >14 days or the last dose at the end of trial). A participant may have several on-treatment periods separated by interruption intervals.

End point type	Primary

End point timeframe:

From Day 1 in ORARIALS-02 to Early Termination, an average of approximately 28 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
Mild TEAEs	34			
Moderate TEAEs	44			
Severe TEAEs	15			
Treatment-related TEAEs	31			
Probably related TEAEs	9			
Possibly related TEAEs	22			
Not related TEAEs	62			
Serious TEAEs (SAEs)	21			
Treatment-related serious TEAEs	1			
TEAEs leading to IMP withdrawal	9			
TEAEs leading to IMP interruption	12			
Treatment-emergent adverse events (TEAEs)	93			

Statistical analyses

No statistical analyses for this end point

Primary: Mean and Change from Baseline in Clinical Safety Laboratory Tests - Hematology (1)

End point title	Mean and Change from Baseline in Clinical Safety Laboratory Tests - Hematology (1)[2]

End point description:

Standard hematology parameters. White blood cell differential count for basophils, eosinophils, leukocytes, lymphocytes, monocytes, and neutrophils, and platelet count.

Data only available for 2 participants at Week 76 since the trial was terminated early by the sponsor as a consequence of the results of ORARIALS-01 which did not meet any of its efficacy endpoints.

End point type	Primary

End point timeframe:

Week 76

Notes:

[2] - 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: 10^9 cells/L				
arithmetic mean (standard deviation)				
Basophils, Week 76 *Mean (Standard Deviation) | Un	0.030 (± 0.0000)			
Basophils, change from baseline to Week 76*	-0.015 (± 0.0071)			
Eosinophils, Week 76*	0.150 (± 0.0071)			
Eosinophils, change from baseline to Week 76*	-0.070 (± 0.0424)			
Leukocytes, Week 76*	9.120 (± 3.1537)			
Leukocytes, change from baseline to Week 76*	-0.565 (± 2.4395)			
Lymphocytes, Week 76*	1.445 (± 0.4738)			
Lymphocytes, change from baseline to Week 76*	-0.365 (± 0.3041)			
Monocytes, Week 76*	0.460 (± 0.1414)			
Monocytes, change from baseline to Week 76*	-0.055 (± 0.0212)			
Neutrophils, Segmented, Week 76*	7.030 (± 3.4648)			
Neutrophils, Segmented, change from baseline to We	-0.070 (± 2.8001)			
Platelets, Week 76*	334.0 (± 114.55)			
Platelets, change from baseline to Week 76*	62.5 (± 103.94)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean and Change from Baseline in Clinical Safety Laboratory Tests - Hematology (2)

End point title	Mean and Change from Baseline in Clinical Safety Laboratory Tests - Hematology (2)[3]

End point description:

Standard hematology parameters. White blood cell differential count for basophils, eosinophils, leukocytes, lymphocytes, monocytes, and neutrophils, and platelet count.

Data only available for 2 participants at Week 76 since the trial was terminated early by the sponsor as a consequence of the results of ORARIALS-01 which did not meet any of its efficacy endpoints.

End point type	Primary

End point timeframe:

Week 76

Notes:

[3] - 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: percentage of leukocytes				
arithmetic mean (standard deviation)				
Basophils/Leukocytes	0.40 (± 0.141)			
Basophils/Leukocytes, change from baseline	-0.05 (± 0.212)			
Eosinophils/Leukocytes	1.70 (± 0.424)			
Eosinophils/Leukocytes, change from baseline	-0.50 (± 0.849)			
Lymphocytes/Leukocytes	17.85 (± 11.384)			
Lymphocytes/Leukocytes, change from baseline	-0.95 (± 8.132)			
Monocytes/Leukocytes	5.05 (± 0.212)			
Monocytes/Leukocytes, change from baseline	-0.20 (± 1.556)			
Neutrophils/Leukocytes	74.95 (± 12.092)			
Neutrophils/Leukocytes, change from baseline	1.70 (± 10.607)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean and Change from Baseline in Clinical Safety Laboratory Tests- Erthrocytes

End point title	Mean and Change from Baseline in Clinical Safety Laboratory Tests- Erthrocytes[4]

End point description:

Standard hematology parameters. Percentage of leukocytes were determined for basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

Data only available for 2 participants at Week 76 since the trial was terminated early by the sponsor as a consequence of the results of ORARIALS-01 which did not meet any of its efficacy endpoints.

End point type	Primary

End point timeframe:

Week 76

Notes:

[4] - 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: 10^12 cells/L				
arithmetic mean (standard deviation)				
Erythrocytes	3.70 (± 0.000)			
Erythrocytes, change from baseline	-0.40 (± 0.707)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean and Change from Baseline in Clinical Safety Laboratory Tests - Hematocrit

End point title	Mean and Change from Baseline in Clinical Safety Laboratory Tests - Hematocrit[5]

End point description:

Standard hematology parameter.

Data only available for 2 participants at Week 76 since the trial was terminated early by the sponsor as a consequence of the results of ORARIALS-01 which did not meet any of its efficacy endpoints.

End point type	Primary

End point timeframe:

Week 76

Notes:

[5] - 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: L of cells / L of blood				
arithmetic mean (standard deviation)				
Hematocrit	0.345 (± 0.0071)			
Hematocrit, change from baseline	-0.025 (± 0.0636)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean and Change from Baseline in Clinical Safety Laboratory Tests - Hemoglobin

End point title	Mean and Change from Baseline in Clinical Safety Laboratory Tests - Hemoglobin[6]

End point description:

End point type	Primary

End point timeframe:

Week 76

Notes:

[6] - 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: g/L				
arithmetic mean (standard deviation)				
Hemoglobin	115.5 (± 3.54)			
Hemoglobin, change from baseline	-14.0 (± 21.21)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean and Change from Baseline in Clinical Safety Laboratory Tests - Cystatin C

End point title	Mean and Change from Baseline in Clinical Safety Laboratory Tests - Cystatin C[7]

End point description:

Standard clinical chemistry parameter.

Data only available for 2 participants at Week 76 since the trial was terminated early by the sponsor as a consequence of the results of ORARIALS-01 which did not meet any of its efficacy endpoints.

End point type	Primary

End point timeframe:

Week 76

Notes:

[7] - 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mg/L				
arithmetic mean (standard deviation)				
Cystatin C	1.310 (± 0.7495)			
Cystatin C, change from baseline	0.350 (± 0.6364)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with potentially clinically significant abnormalities in Clinical Safety Laboratory Tests and Vital Signs Over the Open-Label Treatment Period

End point title	Number of Participants with potentially clinically significant abnormalities in Clinical Safety Laboratory Tests and Vital Signs Over the Open-Label Treatment Period[8]

End point description:

Clinical safety laboratory data and vital signs were collected throughout the trial until early termination. The average duration of exposure was 198.7 days (approximately 28 weeks; standard deviation 99.57 days; minimum 16 days, maximum 494 days). 58 participants (48.3%) were exposed less than 6 months; 55 participants (45.8%) were exposed 6 to less than 12 months; 7 participants (5.8%) were exposed 12 to less than 18 months. No patient was treated for 76 weeks.

Safety analysis set: All enrolled patients that received at least one dose of arimoclomol.

End point type	Primary

End point timeframe:

From Day 1 in ORARIALS-02 to Early Termination, an average of approximately 28 weeks

Notes:

[8] - 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	120[9]			
Units: Participants				
number (not applicable)				

Hemoglobin (g/L) <= 95 (Females) <= 115 (Males)	10			
Hemoglobin (g/L) >= 165 (Females), >= 185 (Males)	0			
Erythrocytes (10^12/L) <= 3.5 (F), <= 3.8 (M)	16			
Erythrocytes (10^12/L) >= 6.0 (F), >= 7.0 (M)	0			
Hematocrit <= 0.32 (Females), <= 0.37 (Males)	21			
Hematocrit >= 0.5 (Females), >= 0.55 (Males)	0			
Leukocytes (10^9/L) <= 2.8	0			
Leukocytes (10^9/L) >= 16	3			
Neutrophils/Leukocytes (%) <= 20	0			
Neutrophils/Leukocytes (%) >= 85	3			
Eosinophils/Leukocytes (%) >= 10	1			
Basophils/Leukocytes (%) >= 10	0			
Lymphocytes/Leukocytes (%) <= 10	6			
Lymphocytes/Leukocytes (%) >= 75	0			
Monocytes/Leukocytes (%) >= 15	0			
Platelets (10^9/L) <= 75	0			
Platelets (10^9/L) >= 600	0			
Aspartate Aminotransferase (U/L) >= 3 x ULN	0			
Alanine Aminotransferase (U/L) >= 3 x ULN	7			
Bilirubin (umol/L) >= 34	2			
Direct Bilirubin (umol/L) >= 12	0			
Indirect Bilirubin (umol/L) >= 22	4			
Alkaline Phosphatase (U/L) >= 3 x ULN	1			
Gamma Glutamyl Transferase (U/L) >= 200	4			
Creatinine (umol/L) >= 1.5 x ULN	1			
Urea Nitrogen (mmol/L) >= 11	7			
Sodium (mmol/L) <= 125	2			
Sodium (mmol/L) >= 155	1			
Potassium (mmol/L) <= 3.0	4			
Potassium (mmol/L) >= 6.0	0			
Calcium (mmol/L) <= 1.8	0			
Calcium (mmol/L) >= 3.0	2			
Glucose (mmol/L) <= 3.9 (Fasting=No or blank)	8			
Glucose (mmol/L) >= 11.1 (Fasting=No or blank)	7			
Glucose (mmol/L) <= 3.5 (Fasting=Yes)	0			
Glucose (mmol/L) >= 7.0 (Fasting=Yes)	7			
Protein (g/L) <= 45	1			
Protein (g/L) >= 95	0			
Albumin (g/L) <= 27	2			
Cholesterol (mmol/L) >= 7.8 (Fasting=No or blank)	15			
Cholesterol (mmol/L) >= 6.2 (Fasting=Yes)	15			

Triglycerides (mmol/L) >= 5.65 (Fasting=No/blank)	6			
Triglycerides (mmol/L) >= 4.2 (Fasting=Yes)	3			
LDL Cholesterol (mmol/L) >= 5.3 (Fasting=No/blank	13			
LDL Cholesterol (mmol/L) >= 4.9 (Fasting=Yes)	7			
HDL Cholesterol (mmol/L) <= 0.8 (Fasting=No/blank	11			
HDL Cholesterol (mmol/L) <= 0.9 (Fasting=Yes)	2			
Creatine Kinase (U/L) >= 400 (F) >= 750 (M)	20			
Lactate Dehydrogenase (U/L) >= 750	0			
Pulse Rate <50 and decrease from BL>=15 beats/min	0			
PR >120 and increase from BL of >=15 beats/min	0			
Diastolic BP <=50 and decrease from BL of>=15 mmHg	1			
Diastolic BP >105 and increase from BL of>=15 mmHg	6			
Systolic BP<=90 and decrease from BL of >= 20 mmHg	3			
Systolic BP>180 and increase from BL of >= 20 mmHg	0			

Notes:

[9] - Safety analysis set: all patients enrolled that received at least 1 dose of arimoclomol

Statistical analyses

No statistical analyses for this end point

Primary: Columbia-Suicide Severity Rating Scale (C-SSRS) Over the Open-Label Treatment Period

End point title	Columbia-Suicide Severity Rating Scale (C-SSRS) Over the Open-Label Treatment Period[10]

End point description:

The C-SSRS is a detailed questionnaire assessing both suicidal behavior and suicidal ideation through a series of simple, plain-language questions administered as an interview by a qualified investigator or delegate.

Safety analysis set: All enrolled patients who received at least one dose of arimoclomol.

End point type	Primary

End point timeframe:

From Day 1 in ORARIALS-02 to Early Termination, an average of approximately 28 weeks

Notes:

[10] - 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: Early termination of trial.

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
Suicidal ideation(yes on any 1 following 5 items)	16			
Wish to be Dead	15			
Non-specific active suicidal thoughts	10			
Active Suicidal ideation w/ any methods(not Plan)	5			
Active suicidal ideation w/ some intent, w/o plan	1			
Active Suicidal ideation w/ specific Plan & Intent	0			
Suicidal Behavior (yes any 1 of following 5 item)	0			
Preparatory acts or behavior	0			
Aborted Attempt	0			
Interrupted Attempt	0			
Actual Attempt (non-fatal)	0			
Completed Suicide	0			
Suicidal ideation/Behavior(Y to any above 10 items	16			
Self-injurious Behavior without suicidal intent	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ALS Functional Rating Scale - Revised (ALSFRS-R) From Baseline to Week 76

End point title	Change in ALS Functional Rating Scale - Revised (ALSFRS-R) From Baseline to Week 76

End point description:

The ALSFRS-R is an ordinal rating scale used to determine subjects' subjective assessment of their capability and independence with 12 functional activities ('speech', 'salivation', 'swallowing', handwriting', 'cutting food and handling utensils', 'dressing and hygiene', 'turning in bed and adjusting bed clothes', 'walking', 'dyspnoea', 'orthopnoea' and 'respiratory insufficiency'). Each activity is rated on a 5-point scale (from 0 [no ability] to 4 [normal]), giving a maximal ALSFRS-R score of 48. A lower score corresponds to a lower capability and independence.

Data were not collected at Week 76 since the trial was terminated early by the sponsor as a consequence of the results of ORARIALS-01 which did not meet any of its efficacy endpoints.

End point type	Secondary

End point timeframe:

Week 76

End point values	Arimoclomol (Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: ALSFRS-R scale				
arithmetic mean (standard deviation)	()			

Notes:

[11] - Data were not collected as trial was terminated early by the sponsor as a consequence of ORARIALS-01

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE's collected throughout the trial until early termination. Average duration of exposure was 198.7 days (approximately 28 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Arimoclomol (Open-label)

Reporting group description: -

Serious adverse events	Arimoclomol (Open-label)		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 120 (17.50%)		
number of deaths (all causes)	23		
number of deaths resulting from adverse events			
Investigations			
False positive investigation result			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			

subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Ileus				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory, thoracic and mediastinal disorders				
Pneumonia aspiration				
subjects affected / exposed	3 / 120 (2.50%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Acute respiratory failure				
subjects affected / exposed	2 / 120 (1.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 120 (1.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pneumothorax			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary incontinence			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 3		
Clostridium difficile infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Corona virus infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arimoclomol (Open-label)		
Total subjects affected by non-serious adverse events subjects affected / exposed	91 / 120 (75.83%)		
Investigations Cystatin C increased subjects affected / exposed occurrences (all)	7 / 120 (5.83%) 7		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 5		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 4		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	8 / 120 (6.67%) 12		
Head injury subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 120 (5.00%) 6		
Leukocytosis subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3		
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	8 / 120 (6.67%) 8 3 / 120 (2.50%) 3 3 / 120 (2.50%) 3 4 / 120 (3.33%) 4 5 / 120 (4.17%) 6		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 4 3 / 120 (2.50%) 3		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3 3 / 120 (2.50%) 3		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Corona virus infection subjects affected / exposed occurrences (all)	7 / 120 (5.83%) 8 6 / 120 (5.00%) 6		

Fungal skin infection subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3		
Metabolism and nutrition disorders Type 2 diabetes mellitus subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 4 / 120 (3.33%) 4 4 / 120 (3.33%) 4 3 / 120 (2.50%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2019	Protocol version 3.0 added in-clinic visits in response to an urgent safety measure that was initiated by the DMC in response to cases of elevated transaminases. To monitorelevated transaminases, the remote visits 3, 5, and 7 (Week 8, 16, and 24) was to in-person 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 May 2021	As a consequence of the results of ORARIALS-01 which did not meet any of its efficacy endpoints. The planned duration was 152 weeks. After termination, the actual mean duration of treatment was approx. 28 weeks (range approx. 2 to 71 weeks).	-

Notes:

Limitations and caveats

None reported