Clinical trial results:
Exercise-induced cardiac adaptions in rheumatoid arthritis patients during interleukin-6 vs. tumor necrosis factor antibody therapy: a randomised controlled study (RABEX).

Summary

EudraCT number	2021-005287-21
Trial protocol	DK
Global end of trial date	03 August 2023

Results information

Result version number	v1 (current)
This version publication date	25 January 2025
First version publication date	25 January 2025

Trial information

Trial identification

Sponsor protocol code	Simon1234

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05215509
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Center for Aktiv Sundhed, Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark,
Public contact	Simon Jønck, Rigshospitalet, Center for Aktiv Sundhed, simon.joenck.04@regionh.dk
Scientific contact	Simon Jønck, Rigshospitalet, Center for Aktiv Sundhed, simon.joenck.04@regionh.dk

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	17 January 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 August 2023
Global end of trial reached?	Yes
Global end of trial date	03 August 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this study (RABEX) is to investigative the physiological effects of the cytokines IL-6 and TNF on the adaptive changes to exercise in patients with rheumatoid arthritis.

We will compare rheumatoid arthritis patients in treatment with either IL-6 or TNF blockage on exercise-induced cardiac adaptations as well as metabolic adaptations including oral glucose tolerance test (OGTT) and changes in adipose tissue mass.

Protection of trial subjects:

All subjects underwent standard care at out-patient clinics independent of this study. All subjects were assessed by experienced physicians at baseline. All MRI scans performed were analyzed by experts in the field.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 2022
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	Denmark: 69
Worldwide total number of subjects	69
EEA total number of subjects	69

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)	65

From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited by either 1) Direct information from a nurse at a collaborating out-patient clinic or 2) by mail

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	69
Number of subjects completed	69

Period 1

Period 1 title	Intervention (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Investigator, Monitor, Data analyst, Assessor[2]

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention (IL-6 inhibitor group)

Arm description:

Subjects in stable IL-6 inhibitor treatment randomized to supervised exercise (3 session/week for 12 weeks)

Arm type	Experimental
Investigational medicinal product name	Kevzara
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

200 mg / 2 weeks (standard dose)

Subjects in the Intervention (IL-6 inhibitor group) did not exclusively undergo treatment with Kevzara as an IL-6 inhibitor.
Kevzara was chosen as a representative for the family of drugs inhibiting IL-6.

Arm title	Intervention (TNF inhibitor group)

Arm description:

Subjects in stable TNF inhibitor treatment randomized to supervised exercise (3 session/week for 12 weeks)

Arm type	Experimental
Investigational medicinal product name	Amgevita
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg / 2 weeks (standard dose)

Subjects in the Intervention (TNF inhibitor group) did not exclusively undergo treatment with Amgevita

as an TNF inhibitor.
Amgevita was chosen as a representative for the family of drugs inhibiting TNF.

Arm title	Control (IL-6 inhibitor group)
Arm description:	
Subjects in stable IL-6 inhibitor treatment randomized to no supervised exercise (standard of care/control)	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Control (TNF inhibitor group)
Arm description:	
Subjects in stable TNF inhibitor treatment randomized to no supervised exercise (standard of care/control)	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: This was an open-label exercise intervention trial.
Subjects could not be blinded to the intervention (exercise) or control (no exercise).
Investigators and data analysts were blinded to the intervention.
[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an open-label exercise intervention trial.
Subjects could not be blinded to the intervention (exercise) or control (no exercise).
Investigators and data analysts were blinded to the intervention.

Number of subjects in period 1	Intervention (IL-6 inhibitor group)	Intervention (TNF inhibitor group)	Control (IL-6 inhibitor group)
Started	17	20	12
Completed	12	20	11
Not completed	5	0	1
Lost to follow-up	5	-	1

Number of subjects in period 1	Control (TNF inhibitor group)
Started	20
Completed	18
Not completed	2
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Intervention (IL-6 inhibitor group)
Reporting group description:	
Subjects in stable IL-6 inhibitor treatment randomized to supervised exercise (3 session/week for 12 weeks)	
Reporting group title	Intervention (TNF inhibitor group)
Reporting group description:	
Subjects in stable TNF inhibitor treatment randomized to supervised exercise (3 session/week for 12 weeks)	
Reporting group title	Control (IL-6 inhibitor group)
Reporting group description:	
Subjects in stable IL-6 inhibitor treatment randomized to no supervised exercise (standard of care/control)	
Reporting group title	Control (TNF inhibitor group)
Reporting group description:	
Subjects in stable TNF inhibitor treatment randomized to no supervised exercise (standard of care/control)	

Reporting group values	Intervention (IL-6 inhibitor group)	Intervention (TNF inhibitor group)	Control (IL-6 inhibitor group)
Number of subjects	17	20	12
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)	16	19	11
From 65-84 years	1	1	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.9	51.3	52.8
standard deviation	± 7.1	± 10.9	± 10.4
Gender categorical Units: Subjects			
Female	14	16	10
Male	3	4	2

Reporting group values	Control (TNF inhibitor group)	Total	
Number of subjects	20	69	
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)	19	65	
From 65-84 years	1	4	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	54.7		
standard deviation	± 9.5	-	
Gender categorical			
Units: Subjects			
Female	16	56	
Male	4	13	

End points

End points reporting groups

Reporting group title	Intervention (IL-6 inhibitor group)
Reporting group description:	
Subjects in stable IL-6 inhibitor treatment randomized to supervised exercise (3 session/week for 12 weeks)	
Reporting group title	Intervention (TNF inhibitor group)
Reporting group description:	
Subjects in stable TNF inhibitor treatment randomized to supervised exercise (3 session/week for 12 weeks)	
Reporting group title	Control (IL-6 inhibitor group)
Reporting group description:	
Subjects in stable IL-6 inhibitor treatment randomized to no supervised exercise (standard of care/control)	
Reporting group title	Control (TNF inhibitor group)
Reporting group description:	
Subjects in stable TNF inhibitor treatment randomized to no supervised exercise (standard of care/control)	

Primary: Change in left ventricular mass

End point title	Change in left ventricular mass
End point description:	
Measured by MRI	
End point type	Primary
End point timeframe:	
Change from baseline to follow-up (12 weeks)	

End point values	Intervention (IL-6 inhibitor group)	Intervention (TNF inhibitor group)	Control (IL-6 inhibitor group)	Control (TNF inhibitor group)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	20	12	20
Units: gram(s)				
least squares mean (confidence interval 95%)	2.7 (-0.4 to 5.8)	3.9 (1.1 to 6.8)	1.4 (-2.0 to 4.9)	0.1 (-2.9 to 3.1)

Statistical analyses

Statistical analysis title	Interaction analysis primary endpoint
Comparison groups	Intervention (IL-6 inhibitor group) v Intervention (TNF inhibitor group) v Control (IL-6 inhibitor group) v Control (TNF inhibitor group)

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39 [1]
Method	ANCOVA

Notes:

[1] - p-value for the interaction analysis between IL-6 inhibtor treatment and exercise on changes to left ventricular mass following a 12 week exercise intervention compared to TNF inhibitor treatment, relative to control

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to Follow-up (12 weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	None
Dictionary version	0

Reporting groups	
Reporting group title	Intervention (IL-6 inhibitor group)
Reporting group description: -	
Reporting group title	Intervention (TNF inhibitor group)
Reporting group description: -	
Reporting group title	Control (IL-6 inhibitor group)
Reporting group description: -	
Reporting group title	Control (TNF inhibitor group)
Reporting group description: -	

Serious adverse events	Intervention (IL-6 inhibitor group)	Intervention (TNF inhibitor group)	Control (IL-6 inhibitor group)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Control (TNF inhibitor group)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Intervention (IL-6 inhibitor group)	Intervention (TNF inhibitor group)	Control (IL-6 inhibitor group)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	18 / 20 (90.00%)	8 / 12 (66.67%)
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Other			
subjects affected / exposed	2 / 17 (11.76%)	4 / 20 (20.00%)	1 / 12 (8.33%)
occurrences (all)	2	4	1
Musculoskeletal and connective tissue disorders			
Lower extremities			
subjects affected / exposed	4 / 17 (23.53%)	3 / 20 (15.00%)	1 / 12 (8.33%)
occurrences (all)	4	3	1
Upper extremities			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Other			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Bacterial infection			
subjects affected / exposed	4 / 17 (23.53%)	2 / 20 (10.00%)	1 / 12 (8.33%)
occurrences (all)	4	2	1
Viral infection			
subjects affected / exposed	5 / 17 (29.41%)	6 / 20 (30.00%)	3 / 12 (25.00%)
occurrences (all)	5	6	3
Other			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Control (TNF inhibitor group)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 20 (90.00%)		

Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Other			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Lower extremities			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Upper extremities			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Other			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Infections and infestations			
Bacterial infection			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Other			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2021	One inclusion criteria was changed from latest Clinical Disease Activity Index <= 2.8 to Disease Activity Score-28-ESR <= 3.2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported