Clinical trial results:
Remission in rheumatoid arthritis – assessing withdrawal of disease-modifying antirheumatic drugs in a non-inferiority design (Analyses of patients who receive tumor necrosis factor inhibitor drugs (TNFi))

Summary

EudraCT number	2012-005275-14
Trial protocol	NO
Global end of trial date	23 March 2022

Results information

Result version number	v1 (current)
This version publication date	19 November 2023
First version publication date	19 November 2023

Trial information

Trial identification

Sponsor protocol code	DIA2012-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01881308
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Diakonhjemmet Hospital AS
Sponsor organisation address	Diakonveien 12, Oslo, Norway, 0370
Public contact	Principal Investigator, Diakonhjemmet Hospital AS, +47 22451500, e.a.haavardsholm@medisin.uio.no
Scientific contact	Principal Investigator, Diakonhjemmet Hospital AS, +47 22451500, e.a.haavardsholm@medisin.uio.no

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	16 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2020
Global end of trial reached?	Yes
Global end of trial date	23 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of tapering and withdrawal of TNFi on disease activity in RA patients in sustained remission.

Protection of trial subjects:

Each patient was instructed to contact the investigator immediately if they showed signs or symptoms they perceived as serious adverse events.
If the patient suspected a flare in disease activity, he or she was instructed to contact the study site immediately and they should be seen within a week.
Patients had the right to withdraw from the study at any time for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 99
Worldwide total number of subjects	99
EEA total number of subjects	99

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)	63

From 65 to 84 years	30
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Enrolment of patients took place at nine hospital-based rheumatology practices in Norway

Pre-assignment

Screening details:

Adult men and women with RA who had been in sustained remission for at least 1 year on stable TNFi medication were screened by a study investigator (physician) for inclusion into the study.

Period 1

Period 1 title	intervention (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tapering of TNFi

Arm description:

tapering of TNFi treatment.
the TNFi was reduced to half dose for 4 months, and withdrawn at the 4-month visit if the patient was still in remission.

Arm type	Experimental
Investigational medicinal product name	etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector, Solution for injection in pre-filled pen
Routes of administration	Injection

Dosage and administration details:

standard full dosage: 50 mg weekly subcutanous injection
1/2 dosage regime 25 mg weekly subcutanous injection
after 4 months discontinued intervention if still in remission.

Investigational medicinal product name	certolizumab pegol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

Standard dose: 200mg bi-weekly injection.
1/2 dosage regime: 200 mg every 4 week
Discontinuation of intervention at 4 months if still in remission.

Investigational medicinal product name	golimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

Standard dosage: 50 mg subcutanous injection every 4 weeks.
1/2 dosage regimen: 50 mg subcutanous injection every 8 weeks.
Discontinuation after 4 months if still in remission

Investigational medicinal product name	infliximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Standard full dosage: 3-5 mg/kg intravenous administration every 8 weeks
1/2 dosage regimen: 1.5-3 mg/kg intravenous administration every 8 weeks
Discontinuation at the 4 month visit if still in remission

Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

Standard full dosage: 40 mg subcutanous injection bi-weekly
1/2 dosage regimen: 40 mg subcutanous injection every 4 weeks
Discontinuation at the 4 month visit if still in remission

Arm title	Stable TNFi

Arm description:

patients randomized to continue stable TNFi treatment.

Arm type	Active comparator
Investigational medicinal product name	certolizumab pegol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

Standard dose: 200mg bi-weekly injection.

Investigational medicinal product name	etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector, Solution for injection in pre-filled pen
Routes of administration	Injection

Dosage and administration details:

standard full dosage: 50 mg weekly subcutanous injection

Investigational medicinal product name	golimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

Standard dosage: 50 mg subcutanous injection every 4 weeks.

Investigational medicinal product name	infliximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Standard full dosage: 3-5 mg/kg intravenous administration every 8 weeks

Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Injection

Dosage and administration details:

Standard full dosage: 40 mg subcutanous injection bi-weekly

Number of subjects in period 1[1]	Tapering of TNFi	Stable TNFi
Started	47	45
Completed	43	41
Not completed	4	4
patients decision	1	1
Adverse event, non-fatal	-	3
Protocol deviation	3	-

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: 7 subjects were randomised, but did not receive the allocated treatment strategy (2 subjects decided to withdraw from the study, and 5 subjects did not meet the inclusion criteria (screening failures)). These were not included in the analyses, in accordance with the protocol and the statistical analysis plan.

Baseline characteristics

Reporting groups	
Reporting group title	Tapering of TNFi
Reporting group description:	
tapering of TNFi treatment. the TNFi was reduced to half dose for 4 months, and withdrawn at the 4-month visit if the patient was still in remission.	
Reporting group title	Stable TNFi
Reporting group description:	
patients randomized to continue stable TNFi treatment.	

Reporting group values	Tapering of TNFi	Stable TNFi	Total
Number of subjects	47	45	92
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	57.6	57.4	
standard deviation	± 12.6	± 10.7	-
Gender categorical Units: Subjects			
Female	25	30	55
Male	22	15	37
Anticitrullinated peptide Units: Subjects			
Positive	36	35	71
Negative	11	10	21
Rheumatoid factor Units: Subjects			
Positive	32	28	60
Negative	15	17	32
ACR EULAR Boolean remission Units: Subjects			
Yes	38	30	68
No	9	15	24
Tumor necrosis factor inhibitor Units: Subjects			
Etanercept	20	20	40

Certoizumab pegol	14	15	29
Golimumab	1	4	5
Infliximab	9	0	9
Adalimumab	3	6	9
Co-medication with csDMARDs Units: Subjects			
Yes	42	41	83
No	5	4	9
Co-medication with methotrexate Units: Subjects			
Yes	38	38	76
No	9	7	16
Time since first swollen joint Units: year			
arithmetic mean	11.9	10.0	
standard deviation	± 6.9	± 7.2	-
Disease activity Score (DAS)			
DAS (range 0-10) includes a 44 swollen joint count, assessment of tender joints by ritchie articular index, the ESR and patients global assessment of disease activity on a VAS 0-100 mm.			
Units: score 0-10			
arithmetic mean	0.8	0.9	
standard deviation	± 0.3	± 0.4	-
Swollen joint count			
The swollen joint count is the number of swollen joints out of 44 joints assessed			
Units: 0-44			
arithmetic mean	0.0	0.0	
standard deviation	± 0.0	± 0.0	-
Tender joint count (Ritchie Articular Index)			
The tender joint count is performed by the Ritchie Articular Index assessing tenderness of 26 joint regions, the index ranges 0-3 for individual measures and the sum 0-78 overall			
Units: 0-78			
arithmetic mean	0.1	0.2	
standard deviation	± 0.2	± 0.5	-
ESR			
Erytrocyte sedimentation rate mm/hour			
Units: mm/hour			
median	7	8	
inter-quartile range (Q1-Q3)	5 to 14	5 to 15	-
CRP			
C-reactive protein			
Units: mg/dL			
median	0.1	0.1	
inter-quartile range (Q1-Q3)	0.1 to 0.3	0.1 to 0.2	-
Patient's global assessment			
self-reported overall assessment of disease activity with use of a VAS range 0-100 mm			
Units: 0-100 mm			
median	3	2	
inter-quartile range (Q1-Q3)	1 to 12	1 to 12	-
Physician's global assessment			
self-reported overall assessment of disease activity with use of a VAS range 0-100 mm			
Units: 0-100 mm			

median	0	0	
inter-quartile range (Q1-Q3)	0 to 2	0 to 2	-
PROMIS physical function			
PROMIS 20 item short form range 0-100, with scores lower than 50 indicating disability worse than average			
Units: range 0-100			
median	52.6	51.2	
inter-quartile range (Q1-Q3)	49.0 to 62.5	44.2 to 62.5	-
Total van der Heijde modified Sharp score			
This method assesses erosions in 16 of each hand and 6 joints of each foot, and joint space narrowing in 15 joints for each hand as well as six joints of each foot. This gives scores for erosions on a scale of 0-280 and joint-space narrowing on a scale of 0-168, thus the total van der Heijde Sharp score range is 0-448			
Units: range 0-448			
median	6.5	5	
inter-quartile range (Q1-Q3)	1.5 to 12	1.5 to 13.5	-
Total power Doppler SIgnal Score			
Ultrasound examination was performed using a 0-3 semiquantitative scoring system for both grey scale and power Doppler in 32 joint			
Units: range 0-96			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 0	-
Total Grey Scale Score			
Ultrasound examination was performed using a 0-3 semiquantitative scoring system for both grey scale and power Doppler in 32 joint			
Units: range 0-96			
median	1	1	
inter-quartile range (Q1-Q3)	0 to 3	0 to 3	-

Subject analysis sets

Subject analysis set title	Tapering TNFi (Per protocol set)
Subject analysis set type	Per protocol

Subject analysis set description:

all randomised patients meeting the study entry criteria and with no protocol deviations affecting the treatment efficacy

Subject analysis set title	Stable TNFi (per protocol set)
Subject analysis set type	Per protocol

Subject analysis set description:

all randomised patients meeting the study entry criteria and with no protocol deviations affecting the treatment efficacy

Reporting group values	Tapering TNFi (Per protocol set)	Stable TNFi (per protocol set)	
Number of subjects	43	41	
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	57.3	57.4	
standard deviation	± 13	± 11.2	
Gender categorical Units: Subjects			
Female	23	26	
Male	20	15	
Anticitrullinated peptide Units: Subjects			
Positive	33	33	
Negative	10	8	
Rheumatoid factor Units: Subjects			
Positive	30	25	
Negative	13	16	
ACR EULAR Boolean remission Units: Subjects			
Yes	36	27	
No	7	14	
Tumor necrosis factor inhibitor Units: Subjects			
Etanercept	19	18	
Certoizumab pegol	12	15	
Golimumab	1	4	
Infliximab	9	0	
Adalimumab	2	4	
Co-medication with csDMARDs Units: Subjects			
Yes	38	38	
No	5	3	
Co-medication with methotrexate Units: Subjects			
Yes	34	35	
No	9	6	
Time since first swollen joint Units: year			
arithmetic mean	11.7	9.4	
standard deviation	± 7.0	± 6.6	
Disease activity Score (DAS)			
DAS (range 0-10) includes a 44 swollen joint count, assessment of tender joints by ritchie articular index, the ESR and patients global assessment of disease activity on a VAS 0-100 mm.			
Units: score 0-10			
arithmetic mean	0.8	0.9	
standard deviation	± 0.3	± 0.4	
Swollen joint count			
The swollen joint count is the number of swollen joints out of 44 joints assessed			
Units: 0-44			

arithmetic mean	0.0	0.0	
standard deviation	± 0.0	± 0.0	
Tender joint count (Ritchie Articular Index)			
The tender joint count is performed by the Ritchie Articular Index assessing tenderness of 26 joint regions, the index ranges 0-3 for individual measures and the sum 0-78 overall			
Units: 0-78			
arithmetic mean	0.1	0.2	
standard deviation	± 0.3	± 0.5	
ESR			
Erytrocyte sedimentation rate mm/hour			
Units: mm/hour			
median	7.0	8	
inter-quartile range (Q1-Q3)	5 to 13	5 to 15	
CRP			
C-reactive protein			
Units: mg/dL			
median	0.1	0.1	
inter-quartile range (Q1-Q3)	0.1 to 0.3	0.1 to 0.2	
Patient's global assessment			
self-reported overall assessment of disease activity with use of a VAS range 0-100 mm			
Units: 0-100 mm			
median	3	2	
inter-quartile range (Q1-Q3)	1 to 9	1 to 12	
Physician's global assessment			
self-reported overall assessment of disease activity with use of a VAS range 0-100 mm			
Units: 0-100 mm			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 2	0 to 2	
PROMIS physical function			
PROMIS 20 item short form range 0-100, with scores lower than 50 indicating disability worse than average			
Units: range 0-100			
median	52.6	51.2	
inter-quartile range (Q1-Q3)	49.0 to 62.5	44.2 to 62.5	
Total van der Heijde modified Sharp score			
This method assesses erosions in 16 of each hand and 6 joints of each foot, and joint space narrowing in 15 joints for each hand as well as six joints of each foot. This gives scores for erosions on a scale of 0-280 and joint-space narrowing on a scale of 0-168, thus the total van der Heijde Sharp score range is 0-448			
Units: range 0-448			
median	6.5	5.0	
inter-quartile range (Q1-Q3)	1.5 to 12.5	1.5 to 13.0	
Total power Doppler SIgnal Score			
Ultrasound examination was performed using a 0-3 semiquantitative scoring system for both grey scale and power Doppler in 32 joint			
Units: range 0-96			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 0	
Total Grey Scale Score			
Ultrasound examination was performed using a 0-3 semiquantitative scoring system for both grey scale and power Doppler in 32 joint			
Units: range 0-96			
median	1	1	

inter-quartile range (Q1-Q3)	0 to 3	0 to 3	

End points

End points reporting groups

Reporting group title	Tapering of TNFi
Reporting group description:	
tapering of TNFi treatment. the TNFi was reduced to half dose for 4 months, and withdrawn at the 4-month visit if the patient was still in remission.	
Reporting group title	Stable TNFi
Reporting group description:	
patients randomized to continue stable TNFi treatment.	
Subject analysis set title	Tapering TNFi (Per protocol set)
Subject analysis set type	Per protocol
Subject analysis set description:	
all randomised patients meeting the study entry criteria and with no protocol deviations affecting the treatment efficacy	
Subject analysis set title	Stable TNFi (per protocol set)
Subject analysis set type	Per protocol
Subject analysis set description:	
all randomised patients meeting the study entry criteria and with no protocol deviations affecting the treatment efficacy	

Primary: Flare rate

End point title	Flare rate
End point description:	
Flare rate in tapered versus stable TNFi treatment. Flare was defined as a combination of DAS above cut-off for remission (1.6), a change in DAS of at least 0.6, and at least two swollen joints, or that both the treating physician and the patient agreed that a clinically significant flare had occured.	
End point type	Primary
End point timeframe:	
0-12 months	

End point values	Tapering of TNFi	Stable TNFi	Tapering TNFi (Per protocol set)	Stable TNFi (per protocol set)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	47	45	43	41
Units: flare				
yes	28	4	27	2
no	19	41	16	39

Statistical analyses

Statistical analysis title	Difference in flare rate
Statistical analysis description:	
Assess the non-inferiority of tapered TNFi therapy comapred to stable TNFi therapy.	
Comparison groups	Tapering TNFi (Per protocol set) v Stable TNFi (per protocol set)

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	57.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	42
upper limit	73.8

Secondary: Progression of radiographic joint damage

End point title	Progression of radiographic joint damage
End point description:	
Progression of radiographic joint damage was defined as a change of >=1 unit per year	
End point type	Secondary
End point timeframe:	
0-12 months	

End point values	Tapering TNFi (Per protocol set)	Stable TNFi (per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	40		
Units: van der Heijde Sharp score				
number (not applicable)				
yes	8	4		
no	34	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease activity remission (DAS)

End point title	Disease activity remission (DAS)
End point description:	
Rate of Disease activity (DAS) remission at 12 months	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Tapering TNFi (Per protocol set)	Stable TNFi (per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	40		
Units: remission				
yes	37	34		
no	42	6		

Statistical analyses

No statistical analyses for this end point

Secondary: DAS at time of flare

End point title	DAS at time of flare
End point description: Disease activity score at time of flare	
End point type	Secondary
End point timeframe: time of flare	

End point values	Tapering TNFi (Per protocol set)	Stable TNFi (per protocol set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	2		
Units: disease activity score 0-10				
median (standard error)	2.2 (± 0.8)	1.9 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 0-12 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	V21.1E

Reporting groups	
Reporting group title	Tapering of TNFi
Reporting group description: tapering of TNFi treatment. the TNFi was reduced to half dose for 4 months, and withdrawn at the 4-month visit if the patient was still in remission.	
Reporting group title	Stable TNFi
Reporting group description: patients randomized to continue stable TNFi treatment.	

Serious adverse events	Tapering of TNFi	Stable TNFi	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 47 (6.38%)	2 / 45 (4.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Falling down			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Rheumatoid vasculitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heart attack			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

atrioventricular block third degree			
subjects affected / exposed	0 / 47 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tapering of TNFi	Stable TNFi	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 47 (14.89%)	5 / 45 (11.11%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 47 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Infections and infestations			
common cold			
subjects affected / exposed	7 / 47 (14.89%)	2 / 45 (4.44%)	
occurrences (all)	7	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2017	The initial protocol required symptom duration less than 5 years; this was removed in a protocol update. The reasons included that some patients could not be included due to difficulties in determining symptom duration, and that the protocol update increased the number of patients eligible for enrolment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 January 2019	Patient recruitment was closed before the target number had been reached due to a lower inclusion rate than aticipated.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37607809