Clinical trial results:
CareRA2020: Effectiveness of a combination of Methotrexate and a step down glucocorticoid regimen (COBRA-Slim) for remission induction in patients with early Rheumatoid Arthritis (RA), with or without fast access to 24 weeks of Tumor Necrosis Factor (TNF) blockade in insufficient responders, a randomised, multicenter, pragmatic trial.

Summary

EudraCT number	2017-004054-41
Trial protocol	BE
Global end of trial date	01 July 2022

Results information

Result version number	v1
This version publication date	19 August 2023
First version publication date	19 August 2023

Trial information

Trial identification

Sponsor protocol code	KCE-16002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03649061
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	herestraat 49, Leuven, Belgium, 3000
Public contact	Patrick Verschueren, University Hospitals Leuven, +32 1634 25 41, patrick.verschueren@uzleuven.be
Scientific contact	Patrick Verschueren, University Hospitals Leuven, +32 1634 25 41, patrick.verschueren@uzleuven.be

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	06 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2022
Global end of trial reached?	Yes
Global end of trial date	01 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare in an early RA population with insufficient response (not achieving DAS28CRP≤3.2 within 32 weeks or DAS28CRP<2.6 at week 32) to COBRA-Slim remission induction, the long term effectiveness of accelerated access to a six-month course of anti-TNF therapy (etanercept) within a time window from week 8 up to week 32, versus further treatment adaptation according to the standard COBRA-Slim strategy.

Protection of trial subjects:

This is a pragmatic trial rooted in daily practice. Patients were started on therapy based on the remission induction principle and were followed by the treat to target principle which means treatment adapatations were done whenever patients fail to comply with low disease activity as defined in the protocol.
Patients in need for an adaptation, despite methotrexate (MTX) dose increase, during the remission induction phase of the treatment were eligible for randomisation according to the protocol.
Patients rights were protected according to GCP-ICH, Belgian legislation and GDPR.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 276
Worldwide total number of subjects	276
EEA total number of subjects	276

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)	215
From 65 to 84 years	60
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

284 participants were recruited between June 2018 and June 2020. Patients were recruited in 19 rheumatology centers in Belgium.
Patients were recruited in different type of centers: university hospitals, general hospitals and private practices.

Pre-assignment

Screening details:

Of the 284 patients screened 276 were eligible for the trial.
122 met the criteria of early insufficient reponders to the initial proposed remission-induction regimen (Cobra-Slim).
Of this last group 112 were randomised, however 2 were considered randomisation errors. 10 patients were eligible for randomisation, but were not randomised.

Period 1

Period 1 title	Remission-induction phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Remission-induction

Arm description:

All 276 patients started with a COBRA-Slim remission-induction regimen.
Patients who fail to reach low disease activity between week 8 and 32, or remission at week 32, were early insufficient responders and considered eligible for randomisation.
Of the 276 patients who entered the trial, 264 reached the end of the remission-induction phase (week 32). Of these patients, 112 were considered early insufficient responders and randomised, however 2 of them were considered randomisation-error and excluded from analysis. Subsequently 110 patients started the proposed randomised treatment regimen and were considered for analysis.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Remission-induction
Started	276
Completed	264
Not completed	12
Consent withdrawn by subject	3
Physician decision	5
logistic reasons	1
revised diagnosis	2
Lost to follow-up	1

Period 2

Period 2 title	Insufficient responders
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard COBRA-Slim

Arm description:

Addition of leflunomide 10mg per os (PO) daily to the standard COBRA-Slim remission induction regimen.

Arm type	Active comparator
Investigational medicinal product name	leflunomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg PO daily

Arm title	COBRA-Slim Bio-induction

Arm description:

Addition of etanercept 50mg Sub-cutaneous (SC) weekly for 6 months to the standard COBRA-Slim remission induction regimen.

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

Dosage and administration details:

50mg SC weekly for a period of 6 months

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the run in period for all included patients to determine which patients are considered early-insufficient responders and subsequently eligible for randomisation.

Number of subjects in period 2[2][3]	Standard COBRA-Slim	COBRA-Slim Bio-induction
Started	55	55
Completed	46	46
Not completed	9	9
Adverse event, serious fatal	1	1
Consent withdrawn by subject	2	1
Physician decision	2	4
logistic reasons	2	3
Lost to follow-up	2	-

Notes:

[2] - 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: All patients enrolled in the trial (276) started with a COBRA-Slim remission induction regimen. Patients not reaching low disease activity between w8 and w32 or remission at w32 were considered early insufficient responders.

Only early insufficient responders were randomised in the trial.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 276 patients were enrolled in the trial, 264 completed the remission induction phase.

Of these patients 122 were insufficient responders and eligible for randomisation, 142 were considered early responders and were not eligible for randomisation.

112 patients of the 122 eligible were effectively randomised, however 2 were randomisation errors, so 110 patients were analysed.

Baseline characteristics

Reporting groups	
Reporting group title	Standard COBRA-Slim
Reporting group description:	
Addition of leflunomide 10mg per os (PO) daily to the standard COBRA-Slim remission induction regimen.	
Reporting group title	COBRA-Slim Bio-induction
Reporting group description:	
Addition of etanercept 50mg Sub-cutaneous (SC) weekly for 6 months to the standard COBRA-Slim remission induction regimen.	

Reporting group values	Standard COBRA-Slim	COBRA-Slim Bio-induction	Total
Number of subjects	55	55	110
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)	43	48	91
From 65-84 years	12	7	19
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	53.4	52.5	
standard deviation	± 13.1	± 12.9	-
Gender categorical			
Units: Subjects			
Female	41	38	79
Male	14	17	31
Smoking			
Units: Subjects			
Never	22	19	41
Past	14	13	27
Current	19	23	42
RF/ACPA status			
Units: Subjects			
positive	42	41	83
negative	13	14	27
DAS28-CRP			
Disease activity score based on a 28 joint count and CRP value (mg/L)			
Units: units on a scale			
arithmetic mean	5.4	5.2	
standard deviation	± 1.1	± 1.3	-
disease duration			

Units: days			
median	7.0	7.0	
inter-quartile range (Q1-Q3)	2.5 to 20.0	2.5 to 19.5	-

End points

End points reporting groups

Reporting group title	Remission-induction
Reporting group description:	
All 276 patients started with a COBRA-Slim remission-induction regimen. Patients who fail to reach low disease activity between week 8 and 32, or remission at week 32, were early insufficient responders and considered eligible for randomisation. Of the 276 patients who entered the trial, 264 reached the end of the remission-induction phase (week 32). Of these patients, 112 were considered early insufficient responders and randomised, however 2 of them were considered randomisation-error and excluded from analysis. Subsequently 110 patients started the proposed randomised treatment regimen and were considered for analysis.	
Reporting group title	Standard COBRA-Slim
Reporting group description:	
Addition of leflunomide 10mg per os (PO) daily to the standard COBRA-Slim remission induction regimen.	
Reporting group title	COBRA-Slim Bio-induction
Reporting group description:	
Addition of etanercept 50mg Sub-cutaneous (SC) weekly for 6 months to the standard COBRA-Slim remission induction regimen.	

Primary: Area under the curve (AUC) of DAS28CRP over 104 weeks.

End point title	Area under the curve (AUC) of DAS28CRP over 104 weeks.
End point description:	
Long-term effectiveness.	
End point type	Primary
End point timeframe:	
104 weeks (Baseline (BL) until week 104)	

End point values	Standard COBRA-Slim	COBRA-Slim Bio-induction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	55		
Units: units on a scale				
arithmetic mean (standard deviation)	297.4 (± 76.1)	300.7 (± 68.9)		

Statistical analyses

Statistical analysis title	Area under the Curve (AUC) over 104 weeks
Statistical analysis description:	
To compare the two randomisation groups, a linear mixed model with DAS28-CRP as outcome (Bell et al. 2014), including random intercepts per patient, adjusted for baseline DAS28-CRP, randomisation timepoint, and RF and/or ACPA seropositivity was used. Superiority of COBRA-Slim Bio-induction compared to Standard COBRA-Slim in terms of disease control over 2 years could not be demonstrated (ß = 0.057, 95% CI (-0.178 to 0.292), p=0.632).	
Comparison groups	Standard COBRA-Slim v COBRA-Slim Bio-induction

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Proportion of insufficient responders achieving DAS28CRP remission 28 weeks after randomisation

End point title	Proportion of insufficient responders achieving DAS28CRP remission 28 weeks after randomisation

End point description:

Short-time efficacy.

End point type	Secondary

End point timeframe:

Randomisation until 28 weeks after randomisation.

End point values	Standard COBRA-Slim	COBRA-Slim Bio-induction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	55		
Units: procent	44	59		

Statistical analyses

Statistical analysis title	short time efficacy

Statistical analysis description:

To obtain this outcome, a binomial generalized linear mixed effect model for repeated measures of remission from randomisation up until 28 weeks after was carried out, adjusted for baseline DAS28-CRP, moment of randomisation, and RF and/or ACPA seropositivity. Patients in the COBRA-Slim Bio-induction group had a significantly higher odds of reaching DAS28-CRP remission during 28 weeks after randomisation compared to the Standard COBRA-Slim group (Odds ratio 2.06 (95% CI 1.20-3.56), p=0.009).

Comparison groups	Standard COBRA-Slim v COBRA-Slim Bio-induction
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Proportion of patients in remission (DAS28CRP<2.6) at week 104

End point title	Proportion of patients in remission (DAS28CRP<2.6) at week 104

End point description:

Proportion of patients achieving DAS28CRP<2.6 at the end of the trial (week 104).

End point type	Secondary

End point timeframe:

week 104

End point values	Standard COBRA-Slim	COBRA-Slim Bio-induction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	55		
Units: procent				
number (confidence interval 95%)	69 (55 to 81)	55 (40 to 68)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected over a two year period per patient (BL-week 104).

Adverse event reporting additional description:

In the CareRA2020 trial, adverse events were collected if they were related to RA, the RA treatment, or in case of an event of special interest.
All adverse events were registered by health care professionals questioning the patients at each visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Standard COBRA-Slim

Reporting group description:

addition of leflunomide to the standard COBRA-Slim remission induction regimen

Reporting group title	COBRA-Slim Bio-induction

Reporting group description:

addition of etanercept for 6 months to the standard COBRA-Slim remission induction regimen

Serious adverse events	Standard COBRA-Slim	COBRA-Slim Bio-induction	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 55 (7.27%)	5 / 55 (9.09%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric decompensation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enterococcal sepsis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard COBRA-Slim	COBRA-Slim Bio-induction	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 55 (78.18%)	47 / 55 (85.45%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 55 (0.00%)	4 / 55 (7.27%)	
occurrences (all)	0	4	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 55 (1.82%)	3 / 55 (5.45%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 55 (21.82%)	13 / 55 (23.64%)	
occurrences (all)	12	13	
Injection site erythema			
subjects affected / exposed	1 / 55 (1.82%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)	4 / 55 (7.27%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 55 (14.55%)	14 / 55 (25.45%)	
occurrences (all)	11	17	
Abdominal discomfort			
subjects affected / exposed	5 / 55 (9.09%)	6 / 55 (10.91%)	
occurrences (all)	5	6	
Diarrhoea			
subjects affected / exposed	10 / 55 (18.18%)	6 / 55 (10.91%)	
occurrences (all)	11	7	
Abdominal pain upper			
subjects affected / exposed	4 / 55 (7.27%)	4 / 55 (7.27%)	
occurrences (all)	4	5	

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 55 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
Dyspepsia			
subjects affected / exposed	3 / 55 (5.45%)	2 / 55 (3.64%)	
occurrences (all)	3	2	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	14 / 55 (25.45%)	9 / 55 (16.36%)	
occurrences (all)	18	12	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 55 (10.91%)	6 / 55 (10.91%)	
occurrences (all)	6	6	
Acne			
subjects affected / exposed	3 / 55 (5.45%)	1 / 55 (1.82%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	3 / 55 (5.45%)	1 / 55 (1.82%)	
occurrences (all)	3	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 55 (7.27%)	3 / 55 (5.45%)	
occurrences (all)	4	4	
COVID-19			
subjects affected / exposed	2 / 55 (3.64%)	6 / 55 (10.91%)	
occurrences (all)	2	6	
Bronchitis			
subjects affected / exposed	3 / 55 (5.45%)	1 / 55 (1.82%)	
occurrences (all)	4	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2019	addition of 5 extra sites to the protocol
13 May 2019	change in investigator at site 014
09 July 2019	addition of 1 extra site to the protocol
17 April 2020	to add measurements to cover COVID19 pandemic
19 August 2020	change in investigator at site005

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported