Clinical trial results:
A Prospective, Single-centre, Randomised Study Evaluating the Clinical, Imaging and Immunological Depth of Remission Achieved by Very Early versus Delayed Etanercept in patients with Rheumatoid Arthritis (VEDERA)

Summary

EudraCT number	2010-023910-30
Trial protocol	GB
Global end of trial date	25 February 2019

Results information

Result version number	v1 (current)
This version publication date	16 May 2020
First version publication date	16 May 2020

Trial information

Trial identification

Sponsor protocol code	RR10/9592

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Worsley Building , Leeds, United Kingdom, LS2 9JT
Public contact	Dr Maya Buch, University of Leeds, m.buch@leeds.ac.uk
Scientific contact	Dr Maya Buch, University of Leeds, m.buch@leeds.ac.uk

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	25 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2019
Global end of trial reached?	Yes
Global end of trial date	25 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aim of the study is compare remission (absence of symptoms and signs of arthritis) achieved with very early etanercept therapy to that achieved by current standard care (methotrexate and a treat to target regimen) with or without delayed etanercept, in patients with early, untreated rheumatoid arthritis. We will compare differences in: a. the proportion of patients achieving initial remission. b. the proportion of patients who remain in sustained remission. c. the depth of remission. For example, we will look for signs of active arthritis on ultrasound scans and using sensitive MRI techniques. We will also look to see the body's immune response (in rheumatoid arthritis part of the body's defence system does not act normally and attacks its own joint tissues). We will assess if it has returned to normal using blood and urine tests and examining joint tissue (synovial biopsy tissue).

Protection of trial subjects:

The Trial was overseen by a Independent Data Monitoring committee and trial steering committee, was monitored by the Sponsor, and was conducted in accordance with GCP. Each PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol,principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2011
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	United Kingdom: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	108
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Target Patient Population
Males and females, aged between 18 and 80 years, diagnosed with rheumatoid arthritis (fulfilling new 2010 ACR/EULAR RA classification criteria, who have not yet received DMARD therapy with certain characteristics of disease

Pre-assignment

Screening details:

Patients with the following essential criteria will be recruited:
o Diagnosis of RA as per the new ACR/EULAR 2010 Classification Criteria
o Clinical evidence of synovitis (or imaging-evidence of synovitis in cases of uncertainty/subclinical disease) and DAS28-ESR>3.2.
o Presence of anti-citrullinated peptide antibody (ACPA)

Period 1

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

Blinding implementation details:

n/a

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm 1: 'Early TNFi':

Arm description:

Etanercept (subcutaneous, 50mg weekly) and MTX
combination therapy administered for a total duration of 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Etanercept (with Methotrexate combination therapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Treatment Arm 1
Etanercept was administered Subcutaneously, 50mg weekly up to week 48 unless nonresponse or intolerance

Arm title	Treatment Arm 2: 'MTX-TT (+/- Delayed TNFi)':

Arm description:

MTX monotherapy with adoption of
a 'treat to target' (TT) algorithm (standard care involving monthly disease activity assessment with escalation to combination DMARD therapy if not achieving low disease activity at, or after, 8 weeks) and step-up to ETN and MTX at 24 weeks if failing to achieve clinical remission.

Arm type	Experimental
Investigational medicinal product name	Methotrexate (with folic acid combination therapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg or 10mg tablets. Dosage regimen was Weeks 02: MTX 15 mg weekly At week 2: increase to

MTX 25 mg weekly. regimen followed fro duration of the study.

Number of subjects in period 1	Treatment Arm 1: 'Early TNFi':	Treatment Arm 2: 'MTX-TT (+/- Delayed TNFi)':
Started	60	60
Completed	60	60

Baseline characteristics

Reporting groups

Reporting group title	Main Trial Period

Reporting group description: -

Reporting group values	Main Trial Period	Total	
Number of subjects	120	120	
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	50.0		
standard deviation	± 12.8	-	
Gender categorical Units: Subjects			
Female	85	85	
Male	35	35	

End points

End points reporting groups

Reporting group title	Treatment Arm 1: 'Early TNFi':
Reporting group description:	
Etanercept (subcutaneous, 50mg weekly) and MTX combination therapy administered for a total duration of 48 weeks.	
Reporting group title	Treatment Arm 2: 'MTX-TT (+/- Delayed TNFi)':
Reporting group description:	
MTX monotherapy with adoption of a 'treat to target' (TT) algorithm (standard care involving monthly disease activity assessment with escalation to combination DMARD therapy if not achieving low disease activity at, or after, 8 weeks) and step-up to ETN and MTX at 24 weeks if failing to achieve clinical remission.	

Primary: proportion of patients with early RA that achieve clinical remission at 48 weeks, following either treatment strategy.

End point title	proportion of patients with early RA that achieve clinical remission at 48 weeks, following either treatment strategy.[1]
End point description:	
End point type	Primary
End point timeframe:	
treatment was administered up to week 48 of the study.	

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: Details of all statistical analysis can be found in the following publication: https://ard.bmj.com/content/79/4/464#DC1

End point values	Treatment Arm 1: 'Early TNFi':	Treatment Arm 2: 'MTX-TT (+/- Delayed TNFi)':		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: total no	32	23		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Number and nature of all adverse events will be assessed at every visit & documented. Serious adverse events will be
reported to the sponsor within 1 business day of the study team becoming aware of them.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: A summary of all adverse events can be found in Online supplementary table S27 in thepublication https://ard.bmj.com/content/79/4/464#DC1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2011	Sub Amendment #1 Feb 2011 Protocol changed to v3.0. Amendment to primary endpoint from DAS28-CRP to DAS28-ESR. SF-36 removed from outcome measures. Changes to cardiac MRI. Some changes to study treatments including steroids and MTX escalation. High-sensitive CRP to only be calculated when CRP is in the normal range. Changes to the main and cardiovascular PIS/ICFs & GP letter.
25 February 2011	Sub Amendment #2 Feb 2011 Protocol changed to v4.0. Urine removed from biological samples. Additional blood monitoring for MTX and sulfasalazine. Additional 3 extra study visits added for wk 36, 60 and 84 (visits now 11, from 8). Secondary objective changed from MRI remission to change in MRI synovitis. Other minor clarifications. Change to the main PIS/ICF.
01 March 2011	Sub Amendment #3 March 2011 Protocol changed to v5.1. Steroid to be given at baseline in both treatment arms. MTX dose will be escalated more rapidly in treatment arm 2. DMARD escalation to triple therapy may occur at wk 8 rather than waiting until wk 12. Changes to the main and cardiovascular PIS/ICFs i.e. storing of blood and tissue samples.
01 September 2011	Sub Amendment #4 Sept 2011 Protocol changed to v6.0. Change to some wording relating to HRUS investigations. Change to calculation of disease activity score (DAS) – added in VAS instead of patient's assessment of health. DEXA changed from hands, spine and hip to both hands, spine and hip (unilateral). Changes to the main PIS/ICF.
01 November 2011	Sub Amendment #5 Nov 2011 Protocol (only) changed to v7.0. Minor efficacy measures clarifications regarding early morning stiffness. Changes and corrections to the study schedule.
01 February 2012	Sub Amendment #6 Feb 2012 Protocol (only) changed to v8.0. Study schedule amended. PROMs required at wk 72. Blood tests to be CRP, HS-CRP and ESR.
01 May 2012	Sub Amendment #7 May 2012 Protocol changed to v8.1 & v9.0. Cumulative steroid use added as a secondary objective. Removal of an immunological parameter. Cardiac MRI to be evaluated in a sub-group or patients at baseline, wk 48 and wk 96. Clarification that failure of MRI acquisition at various time points will not constitute a protocol violation or withdrawal from the study. Likewise synovial tissue considered optional as opposed to being mandatory. ETN to be administered up to week 48 only. Correction to the study schedule. Changes to the cardiovascular PIS/ICF.

01 February 2013	Sub Amendment #8 Feb 2013 Protocol (only) changed to v10.0. Change to inclusion / exclusion criteria. Change to the cardiovascular substudy re: cardiac MRI. Change to prohibited medications re: prednisolone and corticosteroids. Correction to the study schedule. Addition of a skull x-ray for any patients thought to have had previous penetrating trauma to the eye or who have had metal injuries to the eye.
02 February 2015	Sub Amendment #9 Feb 2015 Protocol changed to v11.0. Amendment to staff mentioned within the protocol, name of instititute and a PI signature page. Removal of DEXA from the protocol. Synovial biopsy now optional only. Amendment to study duration dates. Cardiovascular substudy formally named as 'CADERA'. Changes to the main and cardiovascular substudy PIS/ICFs.
01 August 2017	Sub Amendment #10 Aug 2017 Protocol (only) changed to v12.0. CI title amended. Definition of end of trial amended. Amendment to the wording of a Research Tissue Bank and what will happen to study samples. Amendment regarding the TSC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: