Clinical trial results:
Prospective, Single-centre, Open-Label, Randomised, Pilot Study Assessing the changes in expression of JAK-STAT and Speed & Depth of Remission Induced by Tocilizumab & Methotrexate Combination and Tocilizumab Monotherapy in Patients with Early Rheumatoid Arthritis (TREMERA).

Summary

EudraCT number	2011-004017-17
Trial protocol	GB
Global end of trial date	29 March 2016

Results information

Result version number	v1 (current)
This version publication date	22 May 2020
First version publication date	22 May 2020
Summary attachment (see zip file)	TREMERA Abstract (TREMERA BMJ Paper (1).pdf)

Trial information

Trial identification

Sponsor protocol code	RR11/9965

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	The University of Leeds
Sponsor organisation address	Woodhouse Lane, Leeds, United Kingdom, LS2 9JT
Public contact	Dr Maya H Buch, University of Leeds, 0113 3923043, M.Buch@Leeds.ac.uk
Scientific contact	Dr Maya H Buch, University of Leeds, 0113 3923043, 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	29 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2016
Global end of trial reached?	Yes
Global end of trial date	29 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Tocilizumab (TCZ) is an anti-IL6 receptor monoclonal antibody. IL6 is a pro-inflammatory cytokine. Dyregulated production of this cytokine is implicated in the pathogenesis of rheumatoid arthritis (RA). It signals via the activation of key proteins - Janus kinases (JAKs) and transcription factors of the STAT family. By disrupting these pathways TCZ may be able to influence key immune cells and their function with minimal to no collateral effect on other systems. Primary Objective: To determine in patients with early, treatment naive RA, how TCZ and Methotrexate (MTX) combination or TCZ monotherapy influences key signalling pathways as well as explore other mechanisms of action including p38δ mitogen activated protein (MAP) kinase, MAP kinase kinase (MKK) 3 and MKK6. There is no information on this. These investigations will elucidate mechanism of action of TCZ/MTX and TCZ monotherapy as well as possibly identify patient subgroups that gain particular benefit from TCZ therapy.

Protection of trial subjects:

Trial Subjects are Protected under standard University indemnity for clinical trials, and also NHS England Indemnity.

Participant data is kept confidential. Only the subject number and subject initials will be recorded in the CRF, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that the Research Ethics Committee (REC), the Medicines and Healthcare products Regulatory Agency (MHRA) and a representatives of the sponsor, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 June 2012
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	17
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period for the trial lasted 18 months. A total of 20 patients were randomised 1:1 to receive either TCZ monotherapy or TCZ + MTX and will be assessed at weeks 4, 12, 24, 36 and 48. There will be a follow up visit and assessment at week 60.

Pre-assignment

Screening details:

- Plain radiography of hands and feet
- Bone densitometry unilateral spine and hip
- HRUS dominant hand metacarpophalangeal joints (MCPJs) and wrist (+/- target biopsy joint if different)
- Research blood samples (total amounting maximum 60mls)
- Research urine sample (total 20mls)
- Research synovial biopsy acquisition if possible (see below)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TCZ monotherapy Arm

Arm description:

Patients receiving TCZ monotherapy

Arm type	Active comparator
Investigational medicinal product name	tocilizumab
Investigational medicinal product code	
Other name	Actemra
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

8mg/kg intravenously at 4 week intervals

Arm title	tocilizumab & methotrexate

Arm description:

methotrexate (MTX) combination therapy compared with TCZ 8mg/kg (4-weekly) monotherapy in patients with early, treatment-naive rheumatoid arthritis (RA).

Arm type	Active comparator
Investigational medicinal product name	Methotrexate and tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

TCZ (8mg/kg, but no more than 800 mg) intravenously at 4-weekly (+/- 1 week) intervals for 48 weeks as monotherapy or in combination with weekly MTX (7.5-25 mg / week as tolerated)

Number of subjects in period 1	TCZ monotherapy Arm	tocilizumab & methotrexate
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial Treatment

Reporting group description: -

Reporting group values	Overall Trial Treatment	Total	
Number of subjects	20	20	
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	55.25		
standard deviation	± 12	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	4	4	

End points

End points reporting groups

Reporting group title	TCZ monotherapy Arm
Reporting group description:	
Patients receiving TCZ monotherapy	
Reporting group title	tocilizumab & methotrexate
Reporting group description:	
methotrexate (MTX) combination therapy compared with TCZ 8mg/kg (4-weekly) monotherapy in patients with early, treatment-naive rheumatoid arthritis (RA).	

Primary: Actual number of patients who achieved a sustained clinical remission rate

End point title	Actual number of patients who achieved a sustained clinical remission rate[1]
End point description:	
End point type	Primary
End point timeframe:	
Final DAS44ESR remission for all patients measured at week 48. For all associated statistical analysis, please see attached results paper.	

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: Please see attached publication for details of all statistical analysis

End point values	TCZ monotherapy Arm	tocilizumab & methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: patients	10	10		

Attachments (see zip file)	TREMERA Remission Tables/TREMERA Remission tables.docx Tremera Adverse events summary/TREMERA adverse events

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All SAE's were reported as per sponsor procedure within 24 hours of date of Awareness. Patients were asked at all trial visits about any ailments which could constitute an adverse event.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Frequency threshold for reporting non-serious adverse events: 0.5 %

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: Please see attached attached supplementary chart 'TREMERA adverse events summary' for details of all Adverse events that occurred in the trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2013	Protocol amended to v2.0, PIS amended to v2.0, Consent form amended to v2.0. Documents amended for consistency and clarification.
19 March 2014	Protocol V3.0 Amended to provide clarification on Steroid Use.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported