



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 p38 δ 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-naïve 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