



## Clinical trial results: Targeted Ultrasound in Rheumatoid Arthritis (TURA) Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2013-002777-22    |
| Trial protocol           | GB DE HU ES IT DK |
| Global end of trial date | 30 July 2018      |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 01 July 2020 |
| First version publication date | 01 July 2020 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | HG/1096 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02056184 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University of Leeds   |
| Sponsor organisation address | 2nd Floor, Chapel Allerton Hospital, Chapeltown Road, Leeds, United Kingdom, LS7 4SA  |
| Public contact               | Prof. Paul Emery, Leeds Institute of Rheumatic & Musculoskeletal Medicine, University of Leeds, +44 1133924884, p.emery@leeds.ac.uk |
| Scientific contact           | Prof. Paul Emery, Leeds Institute of Rheumatic & Musculoskeletal Medicine, University of Leeds, +44 1133924884, p.emery@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                       | 30 July 2018 |
| Is this the analysis of the primary completion data? | No           |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 30 July 2018 |
| Was the trial ended prematurely? | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

To determine whether therapy modifications (including addition of Ultrasound-guided treatment change) can change Power Doppler (PD) in patients with early Rheumatoid arthritis in a stable clinical disease activity state (clinical remission/LDAS/other physician deemed acceptable state).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, the general principles indicated in the Declaration of Helsinki, and all applicable regulatory requirements. Prior to initiation at each study center, the study protocol was reviewed by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). All subjects were to provide written informed consent prior to entering the study and before initiation of any study-related procedure (including administration of investigational product). The investigator was responsible for explaining the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative and for obtaining written informed consent.

Background therapy:

All participants were required to be on an acceptable (maximal tolerated) dose of methotrexate up to 25 mg weekly prior to the screening visit as a monotherapy or in combination with prednisolone up to a maximum 5 mg daily. Participants were expected to continue on this therapy for the duration of the study. Interruption of dose was permitted in case of intolerance to methotrexate.

Additionally, it was permitted for steroid injection of methylprednisolone to be administered post-randomisation up to a maximum total dose of 160 mg if clinically indicated.

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 09 January 2014 |
| 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 | Spain: 17          |
| Country: Number of subjects enrolled | United Kingdom: 85 |
| Country: Number of subjects enrolled | Denmark: 14        |
| Country: Number of subjects enrolled | France: 13         |
| Country: Number of subjects enrolled | Germany: 9         |
| Country: Number of subjects enrolled | Italy: 5           |
| Country: Number of subjects enrolled | Japan: 42          |
| Worldwide total number of subjects   | 185                |
| EEA total number of subjects         | 143                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 122 |
| From 65 to 84 years                       | 61  |
| 85 years and over                         | 2   |

## Subject disposition

### Recruitment

Recruitment details:

Patients were enrolled at 13 centers in Denmark, France, Germany, Italy, Japan, Spain and the UK. Of the 260 patients screened for this study, 185 met all of the inclusion and none of the exclusion criteria and were randomly assigned to treatment into this study.

### Pre-assignment

Screening details:

Adults diagnosed with rheumatoid arthritis within 5 years of screening, having started methotrexate within 2 years of screening and in a stable clinical disease activity state for at least 8 successive weeks before screening

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall Study (overall period)  |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Single blind <sup>[1]</sup>     |
| Roles blinded                | Subject, Investigator, Assessor |

Blinding implementation details:

This was an open label study with regards to the study medication and hence a pertinent blinding procedure was not applicable. Moreover, according to the study design, patients were aware of which arm they were randomised to, as was the physician. However, the physician (and patient) were blinded to US findings in the Clinical arm. The ultrasonographer in both arms was blinded to the patient's study arm and treatment details.

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Clinical Arm |

Arm description:

Current gold standard clinical Treat to Target (T2T) approach for management of rheumatoid arthritis

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Adalimumab         |
| Investigational medicinal product code |                    |
| Other name                             | Humira             |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Subcutaneous use   |

Dosage and administration details:

Adalimumab 40 mg/0.8 ml solution administered every other week as a single dose via subcutaneous injection

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Imaging Arm |
|------------------|-------------|

Arm description:

Modified treatment approach based on Ultrasound (US) findings as an additional competent to the current gold-standard clinical T2T approach

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Adalimumab         |
| Investigational medicinal product code |                    |
| Other name                             | Humira             |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Subcutaneous use   |

Dosage and administration details:

Adalimumab 40 mg/0.8 ml solution administered every other week as a single dose via subcutaneous injection

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: This was an open label study with regards to the study medication and hence a pertinent blinding procedure was not applicable. The ultra-sonographer in both arms was blinded to the patient's study arm and treatment details. Joint counts were performed by a blinded assessor (blinded to all clinical data except joint counts). Patient and Physician were unblinded to study arm and treatment details. In the Clinical arm only, the physician and patient were blinded to ultrasound (US) findings.

| <b>Number of subjects in period 1</b> | Clinical Arm | Imaging Arm |
|---------------------------------------|--------------|-------------|
| Started                               | 92           | 93          |
| Completed                             | 75           | 75          |
| Not completed                         | 17           | 18          |
| Adverse event, serious fatal          | -            | 1           |
| Consent withdrawn by subject          | 4            | 2           |
| Physician decision                    | 2            | 3           |
| Adverse event, non-fatal              | 4            | 2           |
| Did not complete or discontinue       | 1            | 1           |
| Death                                 | 1            | -           |
| Other                                 | 2            | 3           |
| Sponsor decision                      | 3            | 5           |
| Lost to follow-up                     | -            | 1           |

## Baseline characteristics

### Reporting groups

|   |              |
|---|--------------|
| Reporting group title   | Clinical Arm |
| Reporting group description:  |              |
| Current gold standard clinical Treat to Target (T2T) approach for management of rheumatoid arthritis  |              |
| Reporting group title   | Imaging Arm  |
| Reporting group description:  |              |
| Modified treatment approach based on Ultrasound (US) findings as an additional competent to the current gold-standard clinical T2T approach |              |

| Reporting group values                             | Clinical Arm | Imaging Arm | Total |
|--|--------------|-------------|-------|
| Number of subjects                                 | 92           | 93          | 185   |
| 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                                    | 55.8         | 56.8        |       |
| standard deviation                                 | ± 14.43      | ± 14.14     | -     |
| Gender categorical                                 |              |             |       |
| Units: Subjects                                    |              |             |       |
| Female   | 62           | 67          | 129   |
| Male   | 30           | 26          | 56    |
| Ethnicity  |              |             |       |
| Units: Subjects                                    |              |             |       |
| Asian  | 22           | 21          | 43    |
| White  | 70           | 70          | 140   |
| Other  | 0            | 2           | 2     |
| Employment Status                                  |              |             |       |
| Units: Subjects                                    |              |             |       |
| Full time  | 30           | 28          | 58    |
| Part time  | 7            | 8           | 15    |
| On sick leave                                      | 1            | 0           | 1     |
| Retired  | 21           | 27          | 48    |
| Not in paid employment (but not retired)           | 5            | 5           | 10    |
| Missing  | 28           | 25          | 53    |

## End points

### End points reporting groups

|  |                                 |
|--|---------------------------------|
| Reporting group title  | Clinical Arm                    |
| Reporting group description:<br>Current gold standard clinical Treat to Target (T2T) approach for management of rheumatoid arthritis   |                                 |
| Reporting group title  | Imaging Arm                     |
| Reporting group description:<br>Modified treatment approach based on Ultrasound (US) findings as an additional competent to the current gold-standard clinical T2T approach        |                                 |
| Subject analysis set title   | Full Analysis Set (FAS)         |
| Subject analysis set type  | Full analysis                   |
| Subject analysis set description:<br>All patients from the Randomized Set who have at least one post-randomization primary outcome result recorded                                 |                                 |
| Subject analysis set title   | Per-Protocol Set (PPS)          |
| Subject analysis set type  | Per protocol                    |
| Subject analysis set description:<br>All patients in FAS, who have no major protocol deviations  |                                 |
| Subject analysis set title   | Safety Set                      |
| Subject analysis set type  | Safety analysis                 |
| Subject analysis set description:<br>All patients in the Randomized Set who received at least one dose of study drug   |                                 |
| Subject analysis set title   | FASPPD                          |
| Subject analysis set type  | Sub-group analysis              |
| Subject analysis set description:<br>Primary efficacy analysis was conducted in patients in the FAS who had at least 1 joint showing measurable PD at baseline (denoted as FASPPD) |                                 |
| Subject analysis set title   | PPSPPD                          |
| Subject analysis set type  | Sub-group analysis              |
| Subject analysis set description:<br>Primary efficacy analysis was conducted in patients in the PPS who had at least 1 joint showing measurable PD at baseline (denoted as PPSPPD) |                                 |
| <b>Primary: PD Response at Week 48 (FASPPD)</b>  |                                 |
| End point title  | PD Response at Week 48 (FASPPD) |
| End point description:<br>Response rate is defined as proportion of patient whose total PD (Power Doppler) score decreases at Week 48 relative to baseline                         |                                 |
| End point type   | Primary                         |
| End point timeframe:<br>48 weeks   |                                 |

| End point values            | Clinical Arm      | Imaging Arm       | FASPPD               |  |
|-----------------------------|-------------------|-------------------|----------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Subject analysis set |  |
| Number of subjects analysed | 59 <sup>[1]</sup> | 50 <sup>[2]</sup> | 109 <sup>[3]</sup>   |  |
| Units: Total PD Response    |                   |                   |                      |  |
| number (not applicable)     |                   |                   |                      |  |
| Yes                         | 32                | 36                | 68                   |  |
| No                          | 16                | 5                 | 21                   |  |

Notes:

[1] - 48/59 Clinical arm participants completed Week 48, responses present for 48 participants only

[2] - 41/50 Imaging arm participants completed Week 48, responses present for 41 participants only

[3] - FASPPD set includes participants for whom a response was missing

## Statistical analyses

|   |                                 |
|---|---------------------------------|
| Statistical analysis title              | PD Response at Week 48 (FASPPD) |
| Comparison groups                       | Imaging Arm v Clinical Arm      |
| Number of subjects included in analysis | 109                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| P-value                                 | = 0.029                         |
| Method                                  | Regression, Logistic            |
| Parameter estimate                      | Odds ratio (OR)                 |
| Point estimate                          | 4.49                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 1.17                            |
| upper limit                             | 17.27                           |

## Primary: PD Response at Week 48 (PPSPPD)

|  |                                 |
|--|---------------------------------|
| End point title  | PD Response at Week 48 (PPSPPD) |
| End point description:   |                                 |
| Response rate is defined as proportion of patient whose total PD (Power Doppler) score decreases at Week 48 relative to baseline |                                 |
| End point type   | Primary                         |
| End point timeframe:   |                                 |
| 48 weeks   |                                 |

| End point values            | Clinical Arm      | Imaging Arm       | PPSPPD               |  |
|-----------------------------|-------------------|-------------------|----------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Subject analysis set |  |
| Number of subjects analysed | 40 <sup>[4]</sup> | 27 <sup>[5]</sup> | 67 <sup>[6]</sup>    |  |
| Units: Total PD Response    |                   |                   |                      |  |
| number (not applicable)     |                   |                   |                      |  |
| Yes                         | 18                | 15                | 33                   |  |
| No                          | 14                | 3                 | 17                   |  |

Notes:

[4] - 32/40 Clinical arm participants in PPSPPD completed Week 48, responses present for 32 only

[5] - 18/27 Imaging arm participants in PPSPPD completed Week 48, , responses present for 18 only

[6] - PPSPPD set includes participants for whom a response was missing

## Statistical analyses

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | PD Response at Week 48 (PPSPPD) |
| Comparison groups                       | Imaging Arm v Clinical Arm      |
| Number of subjects included in analysis | 67                              |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| P-value                                 | = 0.0451                        |
| Method                                  | Regression, Logistic            |
| Parameter estimate                      | Odds ratio (OR)                 |
| Point estimate                          | 6.5                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 1.04                            |
| upper limit                             | 40.48                           |

## Secondary: Change from Baseline in Total PD Score at Week 48 (FASPPD Population)

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in Total PD Score at Week 48 (FASPPD Population) |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| 48 weeks               |   |

|                                    |                 |                 |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>            | Clinical Arm    | Imaging Arm     |  |  |
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 59              | 50              |  |  |
| Units: Median change from baseline |                 |                 |  |  |
| number (not applicable)            |                 |                 |  |  |
| Total PD response                  | -2.0            | -2.0            |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change from Baseline in Total PD Score at Week 48 |
| Comparison groups                       | Clinical Arm v Imaging Arm                        |
| Number of subjects included in analysis | 109   |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | other   |
| P-value                                 | = 0.1665  |
| Method                                  | Wilcoxon (Mann-Whitney)                           |

### Secondary: Change from Baseline in Total GS Score at Week 48 (FASPPD Population)

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in Total GS Score at Week 48 (FASPPD Population) |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| 48 weeks               |   |

| End point values                   | Clinical Arm    | Imaging Arm     |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 59              | 50              |  |  |
| Units: Median change from baseline |                 |                 |  |  |
| number (not applicable)            |                 |                 |  |  |
| Total GS response                  | -1.5            | -5.0            |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change from Baseline in Total GS Score at Week 48 |
| Comparison groups                       | Clinical Arm v Imaging Arm                        |
| Number of subjects included in analysis | 109   |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | other   |
| P-value                                 | = 1   |
| Method                                  | Wilcoxon (Mann-Whitney)                           |

### Secondary: Change from Baseline in Modified Sharp Scores at Week 48 (FASPPD Population)

|                        |  |
|------------------------|--|
| End point title        | Change from Baseline in Modified Sharp Scores at Week 48 (FASPPD Population) |
| End point description: |  |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 48 weeks             |           |

| End point values                   | Clinical Arm    | Imaging Arm     |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 59              | 50              |  |  |
| Units: Median change from baseline |                 |                 |  |  |
| number (not applicable)            |                 |                 |  |  |
| Modified Sharp Score               | 1.0             | -1.0            |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Change from Baseline in Modified Sharp Scores |
| Comparison groups                       | Clinical Arm v Imaging Arm                    |
| Number of subjects included in analysis | 109   |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | other   |
| P-value                                 | = 0.4004                                      |
| Method                                  | Wilcoxon (Mann-Whitney)                       |

### Secondary: Change from Baseline in HAQ-DI Score at Week 48 (FASPPD Population)

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in HAQ-DI Score at Week 48 (FASPPD Population) |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| 48 weeks               |   |

| End point values                   | Clinical Arm    | Imaging Arm     |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 59              | 50              |  |  |
| Units: Median change from baseline |                 |                 |  |  |
| number (not applicable)            |                 |                 |  |  |
| HAQ-DI Score                       | 0.0000          | 0.0000          |  |  |

### Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Change from Baseline in HAQ-DI Score |
| Comparison groups                       | Clinical Arm v Imaging Arm           |
| Number of subjects included in analysis | 109                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other                                |
| P-value                                 | = 0.4004                             |
| Method                                  | Wilcoxon (Mann-Whitney)              |

## Secondary: Change from Baseline in Bone Densitometry Scores (Hip)(FASPPD Population)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Bone Densitometry Scores (Hip)(FASPPD Population) |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 weeks

| End point values                 | Clinical Arm    | Imaging Arm     |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 59              | 50              |  |  |
| Units: Mean change from baseline |                 |                 |  |  |
| number (not applicable)          |                 |                 |  |  |
| Hip T-score                      | -0.20           | 0.03            |  |  |

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Change from Baseline Hip T-score |
| Comparison groups                       | Clinical Arm v Imaging Arm       |
| Number of subjects included in analysis | 109                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | other                            |
| P-value                                 | = 0.8016                         |
| Method                                  | ANCOVA                           |
| Parameter estimate                      | Mean difference (final values)   |
| Point estimate                          | -0.19                            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -0.48                            |
| upper limit                             | 0.11                             |
| Variability estimate                    | Standard error of the mean       |
| Dispersion value                        | 0.143                            |

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**Secondary: Change from Baseline in Bone Densitometry Scores (Spine)(FASPPD Population)**

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|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Bone Densitometry Scores (Spine)(FASPPD Population) |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 weeks

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| End point values                 | Clinical Arm    | Imaging Arm     |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 59              | 50              |  |  |
| Units: Mean change from baseline |                 |                 |  |  |
| number (not applicable)          |                 |                 |  |  |
| Spine T-score                    | -0.08           | -0.11           |  |  |

**Statistical analyses**

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | Change from Baseline Spine T-score |
| Comparison groups                       | Clinical Arm v Imaging Arm         |
| Number of subjects included in analysis | 109                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | other                              |
| P-value                                 | = 1                                |
| Method                                  | ANCOVA                             |
| Parameter estimate                      | Mean difference (final values)     |
| Point estimate                          | 0.01                               |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -0.43                              |
| upper limit                             | 0.44                               |
| Variability estimate                    | Standard error of the mean         |
| Dispersion value                        | 0.219                              |

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**Secondary: Change from Baseline in Total RA-WIS Score (FASPPD Population)**

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|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Total RA-WIS Score (FASPPD Population) |
|-----------------|--|

End point description:

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 48 weeks             |           |

| End point values                   | Clinical Arm    | Imaging Arm     |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 59              | 50              |  |  |
| Units: Median change from baseline |                 |                 |  |  |
| number (not applicable)            |                 |                 |  |  |
| Total RA-WIS Score                 | -1.0            | 0.0             |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Change from Baseline in Total RA-WIS Score |
| Comparison groups                       | Clinical Arm v Imaging Arm                 |
| Number of subjects included in analysis | 109  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | other                                      |
| P-value                                 | = 1  |
| Method                                  | Wilcoxon (Mann-Whitney)                    |

### Secondary: Change from Baseline in EQ-5D-3L Score (FASPPD Population)

|                        |  |
|------------------------|--|
| End point title        | Change from Baseline in EQ-5D-3L Score (FASPPD Population) |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| 48 weeks               |  |

| End point values                   | Clinical Arm    | Imaging Arm     |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 59              | 50              |  |  |
| Units: Median change from baseline |                 |                 |  |  |
| number (not applicable)            |                 |                 |  |  |
| EQ-5D-3L Score                     | 0.0000          | 0.0000          |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Change from Baseline in EQ-5D-3L Score |
| Comparison groups                       | Clinical Arm v Imaging Arm             |
| Number of subjects included in analysis | 109                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | other                                  |
| P-value                                 | = 0.603                                |
| Method                                  | Wilcoxon (Mann-Whitney)                |

### Secondary: Proportion of Patients Requiring Biologic Therapy at Week 48 (FASPPD Population)

|                 |  |
|-----------------|--|
| End point title | Proportion of Patients Requiring Biologic Therapy at Week 48 (FASPPD Population) |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 weeks

| End point values                  | Clinical Arm    | Imaging Arm     |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 59              | 50              |  |  |
| Units: Biologic Therapy Required? |                 |                 |  |  |
| number (not applicable)           |                 |                 |  |  |
| Yes                               | 8               | 15              |  |  |
| No                                | 40              | 26              |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Proportion of Patients Requiring Biologic Therapy |
| Comparison groups                       | Clinical Arm v Imaging Arm                        |
| Number of subjects included in analysis | 109   |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | other   |
| P-value                                 | = 0.34  |
| Method                                  | Regression, Logistic                              |
| Parameter estimate                      | Odds ratio (OR)                                   |
| Point estimate                          | 3.17  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.04  |
| upper limit                             | 9.65  |

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**Secondary: Total Steroid Exposure Baseline to Week 48 (FASPPD Population)**

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|                 |  |
|-----------------|--|
| End point title | Total Steroid Exposure Baseline to Week 48 (FASPPD Population) |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
48 weeks

---

| End point values                        | Clinical Arm    | Imaging Arm     |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                      | Reporting group | Reporting group |  |  |
| Number of subjects analysed             | 59              | 50              |  |  |
| Units: Steroid exposure (until week 48) |                 |                 |  |  |
| number (not applicable)                 |                 |                 |  |  |
| Yes                                     | 12              | 24              |  |  |
| No                                      | 47              | 26              |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Total Steroid Exposure Baseline to Week 48 (FASPPD Population)**

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|                 |  |
|-----------------|--|
| End point title | Total Steroid Exposure Baseline to Week 48 (FASPPD Population) |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
48 weeks

---

| End point values                     | Clinical Arm    | Imaging Arm      |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 12              | 24               |  |  |
| Units: Total steroid exposure, days  |                 |                  |  |  |
| arithmetic mean (standard deviation) |                 |                  |  |  |
| Mean                                 | 93.1 (± 141.14) | 101.8 (± 152.63) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Co-morbidity Incidence of Infection (FASPPD Population)

|                 |   |
|-----------------|---|
| End point title | Co-morbidity Incidence of Infection (FASPPD Population) |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 weeks

| End point values              | Clinical Arm    | Imaging Arm     | FASPPD               |  |
|-------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type            | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed   | 59              | 50              | 109                  |  |
| Units: Incidence of infection |                 |                 |                      |  |
| Yes                           | 11              | 17              | 28                   |  |
| No                            | 48              | 33              | 81                   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Co-morbidity Systolic blood pressure > 140 mmHg (FASPPD Population)

|                 |   |
|-----------------|---|
| End point title | Co-morbidity Systolic blood pressure > 140 mmHg (FASPPD Population) |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 weeks

| End point values                          | Clinical Arm    | Imaging Arm     | FASPPD               |  |
|---|-----------------|-----------------|----------------------|--|
| Subject group type                        | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed               | 59              | 50              | 109                  |  |
| Units: Systolic blood pressure > 140 mmHg |                 |                 |                      |  |
| Yes                                       | 24              | 19              | 43                   |  |
| No  | 35              | 31              | 66                   |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Co-morbidity Diastolic blood pressure > 80 mmHg (FASPPD Population)

|                        |   |
|------------------------|---|
| End point title        | Co-morbidity Diastolic blood pressure > 80 mmHg (FASPPD Population) |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| 48 weeks               |   |

| End point values                          | Clinical Arm    | Imaging Arm     | FASPPD               |  |
|---|-----------------|-----------------|----------------------|--|
| Subject group type                        | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed               | 59              | 50              | 109                  |  |
| Units: Diastolic blood pressure > 80 mmHg |                 |                 |                      |  |
| Yes                                       | 37              | 26              | 63                   |  |
| No  | 22              | 24              | 46                   |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in DAS Score (FASPPD Population)

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in DAS Score (FASPPD Population) |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| 48 weeks               |   |

| End point values                     | Clinical Arm      | Imaging Arm       |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 48 <sup>[7]</sup> | 41 <sup>[8]</sup> |  |  |
| Units: Total DAS Score               |                   |                   |  |  |
| arithmetic mean (standard deviation) |                   |                   |  |  |
| Change from Baseline                 | 0.003 (± 0.7136)  | 0.046 (± 0.6949)  |  |  |

Notes:

[7] - 48/59 Clinical arm participants completed Week 48

[8] - 41/50 Imaging arm participants completed Week 48

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in DAS28 Score (FASPPD Population)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in DAS28 Score (FASPPD Population) |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 weeks

| End point values                     | Clinical Arm      | Imaging Arm        |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 48 <sup>[9]</sup> | 41 <sup>[10]</sup> |  |  |
| Units: Total DAS28 Score             |                   |                    |  |  |
| arithmetic mean (standard deviation) |                   |                    |  |  |
| Change from Baseline                 | -0.279 (± 0.8304) | 0.076 (± 0.8642)   |  |  |

Notes:

[9] - 48/59 Clinical arm participants completed Week 48

[10] - 41/50 Imaging arm participants completed Week 48

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Adverse events were reported from the time of participant consent to 70 days after the end of trial participation

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Clinical Arm |
|-----------------------|--------------|

Reporting group description:

Current gold standard clinical Treat to Target (T2T) approach for management of rheumatoid arthritis

|                       |             |
|-----------------------|-------------|
| Reporting group title | Imaging Arm |
|-----------------------|-------------|

Reporting group description:

Modified treatment approach based on Ultrasound (US) findings as an additional competent to the current gold-standard clinical T2T approach

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: Per the Statistical Analysis Plan non-serious AEs were not analysed by frequency due to the early termination of the trial therefore this data is not available. In addition, as this was a standard of care study therefore non-serious AEs that were unrelated to the study medication were not required to be reported.

| Serious adverse events  | Clinical Arm    | Imaging Arm     |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events                   |                 |                 |  |
| subjects affected / exposed   | 2 / 12 (16.67%) | 3 / 30 (10.00%) |  |
| number of deaths (all causes)                                       | 0               | 1               |  |
| number of deaths resulting from adverse events                      | 0               | 1               |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |  |
| Basal cell carcinoma  |                 |                 |  |
| subjects affected / exposed   | 1 / 12 (8.33%)  | 0 / 30 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Plasma cell myeloma   |                 |                 |  |
| subjects affected / exposed   | 0 / 12 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications                      |                 |                 |  |
| Femoral neck fracture   |                 |                 |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Brain injury                                    |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Cerebral infarction                             |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Pancreatitis                                    |                |                |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 30 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Hydronephrosis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Oral infection                                  |                |                |  |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 30 (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 %

| <b>Non-serious adverse events</b>                     | Clinical Arm   | Imaging Arm    |  |
|---|----------------|----------------|--|
| Total subjects affected by non-serious adverse events |                |                |  |
| subjects affected / exposed                           | 0 / 12 (0.00%) | 0 / 30 (0.00%) |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 10 September 2013 | <ul style="list-style-type: none"><li>• Update to Inclusion/exclusion criteria regarding requirement for confirmed participation by Informed Consent, requirement for contraception 5 months after study completion and exclusion of person committed to a psychiatric institution or prison.</li><li>• Update to SAE reporting requirement within 24 hours of awareness</li><li>• Clarification on concomitant use adalimumab in year 2</li><li>• Clarification on statistical management of missing data and withdrawn participants</li></ul>   |
| 30 September 2013 | <ul style="list-style-type: none"><li>• Removal of patient questionnaire Rheumatoid Arthritis Quality of Life questionnaire (RAQoL) and update to clarify use of RA-WIS where available per local site practice</li><li>• Requirement to have TB testing at screening if not done within the previous 24 weeks</li><li>• Requirement to have X-ray of hands and feet performed at baseline if not done in previous 12 weeks and if not done in the format required for study evaluation</li><li>• Update to dosage of adalimumab to accommodate global/national guidelines and clarification on maximum dose and escalation of dosage</li><li>• Inclusion of information on management of Investigational Medicinal Product (IMP)</li></ul> |
| 23 June 2014      | <ul style="list-style-type: none"><li>• Clarification – non-MTX DMARDS should be stopped if escalated to ADA</li><li>• Optimisation of MTX dose prior to treatment escalation</li><li>• Non- escalation to ADA/MTX if DAS28 increase &lt;0.6</li><li>• Revisions to treatment algorithm</li><li>• Aligning EC country specific feedback</li></ul>   |
| 01 October 2015   | <ul style="list-style-type: none"><li>• Clarification regarding Tenosynovitis Ultrasound sub- study in the TURA Protocol</li><li>• Clarification in the numbering of the Exclusion Criteria in the TURA protocol</li><li>• Clarification for the capture of alcohol data in e-CRF in the TURA Protocol</li><li>• Clarification on the exclusion criteria: general safety</li><li>• Clarification regarding Sample size justification</li><li>• Guidance on blood and Chemistry tests</li><li>• Clarification regarding the study schedule</li></ul>   |
| 05 May 2017       | <ul style="list-style-type: none"><li>• Clarification on the exclusion criteria: general safety</li><li>• New information regarding study duration, number of sites and countries taking part</li><li>• New information and clarification regarding Sample size justification</li><li>• Clarification of the blinding status in the Clinical Arm A</li><li>• New information regarding the SAE Requirements</li><li>• Clarification regarding the study schedule</li><li>• Deletion of weeks 72 and 96 and follow-up year 2</li><li>• Clarification of visit 48 final visit or early discontinuation and post safety at 10 weeks</li></ul>  |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption   | Restart date |
|--------------|--|--------------|
| 30 July 2018 | The TURA study was terminated early due to the withdrawal of the original Clinical Research Organisation overseeing the trial (Theorem, which were later acquired by Chiltern) and advice provided by the MHRA GCP Inspectorate. Existing patients were followed up for 10 weeks to allow collection of safety information regarding ongoing SAEs (until resolution or stabilization). Existing patients were also followed up to record any new, initial SAEs that may have occurred after Week 48 (or after early discontinuation). This safety information was not entered into the CRF by the site staff but it was reviewed as per the SAE procedures. The last patient visit occurred on 30 July 2018. | -            |

Notes:

## Limitations and caveats

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

Due to the study terminating early, analyses related to the Week 72 and Week 96 time points, exploratory analyses, lab values, and a number of safety tables were removed. Data from Week 72 and 96 was not fully monitored or 'cleaned'.

Notes: