EU Clinical Trials Register

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:

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)	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[1]
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
Arm title	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

Arm title	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.

Number of subjects in period 1	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
A 8 one tod(ars			

End points

End points 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	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
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:	
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:	
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:	
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:	
Primary efficacy analysis was conducted in patients in the PPS who had at least 1 joint showing measurable PD at baseline (denoted as PPSPPD)	

Primary: PD Response at Week 48 (FASPPD)

End point title	PD Response at Week 48 (FASPPD)
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	FASPPD	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	59[1]	50[2]	109[3]	
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[4]	27[5]	67[6]	
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

Statistical analysis title	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	

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 PD response	-2.0	-2.0		

Statistical analyses

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

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

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

Statistical analysis title	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

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

Statistical analysis title	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

Statistical analysis title	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

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

Statistical analyses

No statistical analyses for this end point

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

Adverse events

Adverse events information[1]	
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 %

Non-serious adverse events	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	• 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. • Update to SAE reporting requirement within 24 hours of awareness • Clarification on concomitant use adalimumab in year 2 • Clarification on statistical management of missing data and withdrawn participants
30 September 2013	• 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 • Requirement to have TB testing at screening if not done within the previous 24 weeks • 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 • Update to dosage of adalimumab to accommodate global/national guidelines and clarification on maximum dose and escalation of dosage • Inclusion of information on management of Investigational Medicinal Product (IMP)
23 June 2014	• Clarification – non-MTX DMARDS should be stopped if escalated to ADA • Optimisation of MTX dose prior to treatment escalation • Non- escalation to ADA/MTX if DAS28 increase <0.6 • Revisions to treatment algorithm • Aligning EC country specific feedback
01 October 2015	• Clarification regarding Tenosynovitis Ultrasound sub- study in the TURA Protocol • Clarification in the numbering of the Exclusion Criteria in the TURA protocol • Clarification for the capture of alcohol data in e-CRF in the TURA Protocol • Clarification on the exclusion criteria: general safety • Clarification regarding Sample size justification • Guidance on blood and Chemistry tests • Clarification regarding the study schedule
05 May 2017	• Clarification on the exclusion criteria: general safety • New information regarding study duration, number of sites and countries taking part • New information and clarification regarding Sample size justification • Clarification of the blinding status in the Clinical Arm A • New information regarding the SAE Requirements • Clarification regarding the study schedule • Deletion of weeks 72 and 96 and follow-up year 2 • Clarification of visit 48 final visit or early discontinuation and post safety at 10 weeks

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: