Clinical trial results:
NOT CONTROLLED STUDY TO ASSESS THE EFFICACY OF TOCILIZUMAB IN PATIENTS WITH MODERATE OR SEVERE RHEUMATOID ARTHRITIS WHO ARE CANDIDATES TO BE TREATED WITH A BIOLOGICAL THERAPY AS MONOTHERAPY

Summary

EudraCT number	2013-004051-20
Trial protocol	ES
Global end of trial date	09 November 2017

Results information

Result version number	v1 (current)
This version publication date	19 January 2019
First version publication date	19 January 2019

Trial information

Trial identification

Sponsor protocol code	FER-TOC-2013-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02087696
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Spanish Foundation of Rhematology
Sponsor organisation address	Calle Marques del Duero n5, Madrid, Spain, 28001
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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	18 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of TCZ given as monotherapy in RA patients with active disease, in terms of rate of patients reaching good or moderate EULAR response, at week 24.

Protection of trial subjects:

No specific measures were applied to protect trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 93
Worldwide total number of subjects	93
EEA total number of subjects	93

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)	76
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Six patients (two without prior treatment with biologic agents, and four with prior biologic treatment) will be recruited consecutively, once it has been verified that the patient meets the selection criteria, until the sample size is reached. At two centers, seven patients meeting the criteria selection will be recruited.

Pre-assignment

Screening details:

Not Applicable

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Naive biological treatment

Arm description:

Rheumatoid arthritis patients with intolerance or poor compliance or contraindication to methotrexate and who have not received previous biological treatment.

Arm type	Experimental
Investigational medicinal product name	Roactemra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg administered every 4 weeks for 24 weeks

Arm title	Previous biological treatment

Arm description:

Rhematoid arthirtis patients with intolerance or poor compliance or contraindication to methotrexate and who have not

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Naive biological treatment	Previous biological treatment
Started	50	43
Completed	34	25
Not completed	16	18
Other reasons not included in the study	2	2
Consent withdrawn by subject	2	3
Adverse event, non-fatal	5	4

Lost to follow-up	1	2
Protocol deviation	1	1
Lack of efficacy	5	6

Baseline characteristics

Reporting groups	
Reporting group title	Naive biological treatment
Reporting group description:	
Rheumatoid arthritis patients with intolerance or poor compliance or contraindication to methotrexate and who have not received previous biological treatment.	
Reporting group title	Previous biological treatment
Reporting group description:	
Rhematoid arthirtis patients with intolerance or poor compliance or contraindication to methotrexate and who have not	

Reporting group values	Naive biological treatment	Previous biological treatment	Total
Number of subjects	50	43	93
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	51.5	57.9	
standard deviation	± 12.4	± 12.5	-
Gender categorical Units: Subjects			
Female	8	6	14
Male	42	37	79
Number of previous DMARDs			
Number of previous DMARDs			
Units: Subjects			
0 DMARDs	2	0	2
1 DMARDs	8	7	15
>1 DMARDs	36	31	67
No data	4	5	9
Contraindication to methotrexate Units: Subjects			
YES	1	3	4
NO	49	40	89
Lack of adhesion of methotrexate Units: Subjects			
YES	1	0	1
NO	49	43	92

Intolerance of methotrexate Units: Subjects			
YES	44	33	77
NO	6	10	16
Hypertension Units: Subjects			
YES	12	17	29
NO	38	26	64
Mellitus diabetes Units: Subjects			
YES	3	3	6
NO	47	40	87
Dyslipidemia Units: Subjects			
YES	6	13	19
NO	44	30	74
Solid Tumor Units: Subjects			
YES	1	0	1
NO	49	43	92
Cerebrovascular accident Units: Subjects			
YES	1	2	3
NO	49	41	90
Lung disease Units: Subjects			
YES	0	3	3
NO	50	40	90
Chronic renal failure Units: Subjects			
YES	1	4	5
NO	49	39	88
Extra-articular manifestations Units: Subjects			
YES	4	5	9
NO	46	38	84
NSAID			
Nonsteroidal anti-inflammatory drug			
Units: Subjects			
YES	23	22	45
NO	27	21	48
Corticosteroids Units: Subjects			
YES	34	32	66
NO	16	11	27
Disease duration			
Disease duration			
Units: years			
arithmetic mean	6.4	13.3	
standard deviation	± 6.6	± 11.5	-
DAS28-erythrocyte sedimentation rate			

Units: Disease activation score			
arithmetic mean	5.6	5.5	
standard deviation	± 1.2	± 1.1	-
Clinical Disease Activity Index			
CDAI			
Units: units on a scale			
arithmetic mean	29.1	31	
standard deviation	± 10	± 12	-
Simple Disease Activity Index			
SDAI			
Units: units on a scale			
arithmetic mean	34.3	38.5	
standard deviation	± 17	± 17.1	-
Short Form-36			
SF-36			
Units: units on a scale			
arithmetic mean	90.3	91.2	
standard deviation	± 6.8	± 6.9	-
FACIT-F			
Units: units on a scale			
arithmetic mean	23.6	25.6	
standard deviation	± 10.3	± 9	-
C-reactive protein CRP			
Units: mg/L			
arithmetic mean	13.6	12.8	
standard deviation	± 20.7	± 11.5	-
ESR			
Erythrocite sedimentation rate			
Units: mm/h			
arithmetic mean	27.9	40.3	
standard deviation	± 27	± 30.6	-
Number of tender joints			
Units: joints			
arithmetic mean	9.7	9.9	
standard deviation	± 6.0	± 5.7	-
Number of swollen joints			
Units: joints			
arithmetic mean	5.8	6.3	
standard deviation	± 3.1	± 4.4	-
Health Assessment Questionnaire			
HAQ			
Units: units on a scale			
arithmetic mean	1.7	1.8	
standard deviation	± 0.7	± 0.6	-
Visual Analogue scale of the patient			
VAS of the patient			
Units: units on a scale			
arithmetic mean	7.4	6.9	
standard deviation	± 1.6	± 1.9	-
Visual analogue scale of the physician			
VAS of the Physician			
Units: units on a scale			

arithmetic mean	6.7	6.6	
standard deviation	± 1.2	± 1.4	-
VAS Pain			
Units: units on a scale			
arithmetic mean	7.4	6.8	
standard deviation	± 1.7	± 1.9	-
Body Mass Index			
Units: Kg/m2			
arithmetic mean	26	28.1	
standard deviation	± 5	± 5.5	-

End points

End points reporting groups

Reporting group title	Naive biological treatment
Reporting group description:	
Rheumatoid arthritis patients with intolerance or poor compliance or contraindication to methotrexate and who have not received previous biological treatment.	
Reporting group title	Previous biological treatment
Reporting group description:	
Rhematoid arthirtis patients with intolerance or poor compliance or contraindication to methotrexate and who have not	

Primary: Percentage patients achieving good or moderate European League Against Rheumatism Response

End point title	Percentage patients achieving good or moderate European League Against Rheumatism Response
End point description:	
End point type	Primary
End point timeframe:	
Week 0 to week 24	

End point values	Naive biological treatment	Previous biological treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	36		
Units: Patients				
Good response EULAR	1	0		
Moderate response EULAR	41	33		

Statistical analyses

Statistical analysis title	Patients Achieving good or moderate EULAR response
Comparison groups	Previous biological treatment v Naive biological treatment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.528
Method	Chi-squared

Secondary: Percentage of patients complying American College of Rheumatology

(ACR) criteria	
End point title	Percentage of patients complying American College of Rheumatology (ACR) criteria

End point description:

End point type	Secondary

End point timeframe:

At 24 weeks of treatment

End point values	Naive biological treatment	Previous biological treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	36		
Units: Patients				
ACR 20 response	26	23		
ACR 50 response	22	14		
ACR 70 response	7	3		

Statistical analyses

Statistical analysis title	Percentage of patients complying ACR criteria
Comparison groups	Previous biological treatment v Naive biological treatment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.661
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All the patients were offered open-label treatment with 8 mg/kg every 4 weeks for 6 months between may 2014 and april 2017

Adverse event reporting additional description:

Adverse effects for all patients who have received at least one dose of tociluzumab

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Patients have received al least one dose

Reporting group description:

Patients have received al least one dose of tocilizumab

Serious adverse events	Patients have received al least one dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 93 (6.45%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Myelopathy			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
spine stenosis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			

Aborted pregnancy			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Paresis of vocal cords			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Rash			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Type IV hypersensitivity reaction			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colonic abscess			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Syncope			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint swelling			

subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral swelling			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal osteoarthritis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Patients have received al least one dose		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 93 (49.46%)		
Vascular disorders			
Hemorrhoids			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Systolic hypertension			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Surgical and medical procedures			
Skin biopsy			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
General disorders and administration site conditions			

Feeling tightness in the throat			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Odinophagy			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Sickness			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Worsening of the disease			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Immune system disorders			
Erythema			
subjects affected / exposed	5 / 93 (5.38%)		
occurrences (all)	5		
erythema in application area			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Acute bronchitis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Faringoamigdalitis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Pharyngitis			

subjects affected / exposed occurrences (all) Sinus Catarrh subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1 3 / 93 (3.23%) 3		
Product issues Anaphylactic reaction subjects affected / exposed occurrences (all) Fixed Rash subjects affected / exposed occurrences (all)	 1 / 93 (1.08%) 1 1 / 93 (1.08%) 1		
Injury, poisoning and procedural complications Accident subjects affected / exposed occurrences (all) Traumatic limb injury subjects affected / exposed occurrences (all)	 1 / 93 (1.08%) 1 1 / 93 (1.08%) 1		
Cardiac disorders Atrial tachycardia subjects affected / exposed occurrences (all)	 1 / 93 (1.08%) 1		
Nervous system disorders Facial paralysis subjects affected / exposed occurrences (all)	 1 / 93 (1.08%) 1		
Blood and lymphatic system disorders Epistaxis subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia	 1 / 93 (1.08%) 1 3 / 93 (3.23%) 3		

subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Detachment of the vitrious body			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
Gastric reflux			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Viral gastroenteritis			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Boil			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Cutaneous reaction			

subjects affected / exposed occurrences (all) Dermatophytosis subjects affected / exposed occurrences (all) Dry mucus subjects affected / exposed occurrences (all) Local reaction subjects affected / exposed occurrences (all) Papular eruption subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2 1 / 93 (1.08%) 1 1 / 93 (1.08%) 1 1 / 93 (1.08%) 1 1 / 93 (1.08%) 1		
Renal and urinary disorders Cystitis subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2		
Musculoskeletal and connective tissue disorders Lumbar hernia subjects affected / exposed occurrences (all) Lumbar radiculopathy subjects affected / exposed occurrences (all) Muscular contracture subjects affected / exposed occurrences (all) Tendinitis subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1 2 / 93 (2.15%) 2 1 / 93 (1.08%) 1 2 / 93 (2.15%) 2		
Infections and infestations cutaneous infection subjects affected / exposed occurrences (all) Herpes simplex	1 / 93 (1.08%) 1		

subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Infection of the lower respiratory tract			
subjects affected / exposed	2 / 93 (2.15%)		
occurrences (all)	2		
Infection with human papillomavirus			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Dyslipidemia			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Elevated transaminases			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
High Blood cholesterol			
subjects affected / exposed	4 / 93 (4.30%)		
occurrences (all)	4		
High triglycerides in blood			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 93 (1.08%)		
occurrences (all)	1		
Hyperlipidaemia			

subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

We ara unable to reach the programmed recruitment of 122 patients, although the time of recruitment was prolonged for 18 additional months.

Notes: