



## 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 Rheumatology
Sponsor organisation address	Calle Marques del Duero n5, Madrid, Spain, 28001
Public contact	MARIA AUXILIADORA MARTIN MARTINEZ, FUNDACIÓN ESPAÑOLA DE REUMATOLOGÍA, +34 915767799273, mauxiliadora.martin@ser.es
Scientific contact	MARIA AUXILIADORA MARTIN MARTINEZ, FUNDACIÓN ESPAÑOLA DE REUMATOLOGÍA, +34 915767799273, mauxiliadora.martin@ser.es

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
<b>Arm title</b>	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

<b>Arm title</b>	Previous biological treatment
------------------	-------------------------------

Arm description:

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

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

<b>Statistical analysis title</b>	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 tocilizumab

Assessment type	Non-systematic
-----------------	----------------

### Dictionary used

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

Dictionary version	19
--------------------	----

### Reporting groups

Reporting group title	Patients have received at least one dose
-----------------------	--

Reporting group description:

Patients have received at least one dose of tocilizumab

Serious adverse events	Patients have received at 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 %

<b>Non-serious adverse events</b>	Patients have received at 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 occurrences (all)	1 / 93 (1.08%) 1		
Headache subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Odinophagy subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Sickness subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Worsening of the disease subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Immune system disorders Erythema subjects affected / exposed occurrences (all)	5 / 93 (5.38%) 5		
erythema in application area subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Respiratory, thoracic and mediastinal disorders Acute bronchitis subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Bronchitis subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Faringoamigdalitis subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Laryngitis subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Pharyngitis			

subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Sinus Catarrh subjects affected / exposed occurrences (all)	3 / 93 (3.23%) 3		
Product issues Anaphylactic reaction subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Fixed Rash subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Injury, poisoning and procedural complications Accident subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1		
Traumatic limb injury subjects affected / exposed occurrences (all)	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)	1 / 93 (1.08%) 1		
Leukopenia subjects affected / exposed occurrences (all)	3 / 93 (3.23%) 3		
Neutropenia			

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



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

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	1 / 93 (1.08%)		
occurrences (all)	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 are unable to reach the programmed recruitment of 122 patients, although the time of recruitment was prolonged for 18 additional months.
---

Notes: