Clinical trial results:
Multicenter, randomized, double-blind study to evaluate the safety and efficacy of tocilizumab (TCZ) in combination with methotrexate (MTX) versus switching to TCZ (placebo-controlled) in patients with active rheumatoid arthritis (RA) who have inadequately responded to prior MTX treatment and have achieved a low disease activity (DAS28 < 3.2) with TCZ in combination with MTX.

Summary

EudraCT number	2011-001626-15
Trial protocol	ES
Global end of trial date	14 March 2014

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	ML27828

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01399697
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline , F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline , F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com

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	14 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2014
Global end of trial reached?	Yes
Global end of trial date	14 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the maintenance of response in patients after switching to managed TCZ monotherapy compared with combination therapy continued TCZ and MTX.

Protection of trial subjects:

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it afforded greater protection to the participant. For studies conducted in the EU/EEA countries, the investigator ensured compliance with the EU Clinical Trial Directive (2001/20/EC). For studies conducted in the USA or under US IND, the investigator additionally ensured adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CRF, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards."

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2011
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: 261
Worldwide total number of subjects	261
EEA total number of subjects	261

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	221
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 44 centers in Spain between 31 August 2011 and 14 March 2014.

Pre-assignment

Screening details:

A total of 264 subjects were screened of whom 1 was screen failure and 263 subjects were included. Two subjects were included but did not receive any treatment, hence they were excluded from all analysis.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	TCZ plus (+) MTX (Non Randomized)

Arm description:

Participants received tocilizumab (TCZ) 8 milligrams per kilogram (mg/kg; maximum 800 mg) via intravenous (IV) infusion every 4 weeks (q4w) through Week 24 (total of 7 infusions). Participants also received MTX capsules orally, at a stable dose (10, 15, 17.5, or 20 mg, no maximum dose was defined) weekly from Week 1 through 16.

Arm type	Non-Randomized Arm
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

TCZ 8 mg/kg (maximum 800 mg) IV infusion q4w from Weeks 1 thorough 16 (total of 4 infusions).

Investigational medicinal product name	Methorexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Methotrexate 10, 15, 17.5, or 20 mg capsules, administered orally once per week from Weeks 1 through 16.

Arm title	TCZ + MTX (Randomized)

Arm description:

Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w through Week 24 (total of 7 infusions). Participants also received MTX capsules, orally, at a stable dose (10, 15, 17.5, or 20 mg/week, but no maximum dose was defined), weekly, from Weeks 1 through 24.

Arm type	Active comparator
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

TCZ 8 mg/Kg (maximum 800 mg) IV infusion q4w from Weeks 1 thorough 16 (total of 4 infusions).

Investigational medicinal product name	Methorexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Methotrexate 10, 15, 17.5, or 20 mg capsules, administered orally once per week from Weeks 1 through 16

Arm title	Tocilizumab + Placebo (Randomized)

Arm description:

Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w through Week 24 (total of 7 infusions). Participants also received MTX capsules, orally, at stable dose (10, 15, 17.5, or 20 mg per week, but no maximum dose was defined) weekly, from Weeks 1 through 16 followed by matching placebo capsules, orally, weekly through Week 24.

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

Dosage and administration details:

TCZ 8 mg/Kg (maximum 800 mg) IV infusion q4w from Weeks 1 thorough 16 (total of 4 infusions).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to Methotrexate 10, 15, 17.5, or 20 mg capsules, administered orally once per week from Weeks 1 through 16.

Number of subjects in period 1	TCZ plus (+) MTX (Non Randomized)	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)
Started	96	83	82
Completed	55	80	78
Not completed	41	3	4
Consent withdrawn by subject	8	-	-
Inclusion error	2	-	-
Clinical RA remission	1	-	-
Physician decision	-	-	2
Sponsor decisión	1	-	-
Non-compliant	1	-	-
Positive result for hepatitis B	1	-	-
Adverse event	13	3	1

Sponsor decision	1	-	-
Lost to follow-up	2	-	-
Protocol deviation	2	-	-
Lack of efficacy	9	-	1

Baseline characteristics

Reporting groups	
Reporting group title	TCZ plus (+) MTX (Non Randomized)
Reporting group description:	
Participants received tocilizumab (TCZ) 8 milligrams per kilogram (mg/kg; maximum 800 mg) via intravenous (IV) infusion every 4 weeks (q4w) through Week 24 (total of 7 infusions). Participants also received MTX capsules orally, at a stable dose (10, 15, 17.5, or 20 mg, no maximum dose was defined) weekly from Week 1 through 16.	
Reporting group title	TCZ + MTX (Randomized)
Reporting group description:	
Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w through Week 24 (total of 7 infusions). Participants also received MTX capsules, orally, at a stable dose (10, 15, 17.5, or 20 mg/week, but no maximum dose was defined), weekly, from Weeks 1 through 24.	
Reporting group title	Tocilizumab + Placebo (Randomized)
Reporting group description:	
Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w through Week 24 (total of 7 infusions). Participants also received MTX capsules, orally, at stable dose (10, 15, 17.5, or 20 mg per week, but no maximum dose was defined) weekly, from Weeks 1 through 16 followed by matching placebo capsules, orally, weekly through Week 24.	

Reporting group values	TCZ plus (+) MTX (Non Randomized)	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)
Number of subjects	96	83	82
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	81	71	69
From 65-84 years	15	12	13
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.3	50.2	51
standard deviation	± 13.2	± 12.5	± 12.2
Gender categorical Units: Subjects			
Female	76	62	65
Male	20	21	17

Reporting group values	Total		
Number of subjects	261		
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)	221		
From 65-84 years	40		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	203		
Male	58		

End points

End points reporting groups

Reporting group title	TCZ plus (+) MTX (Non Randomized)
Reporting group description:	
Participants received tocilizumab (TCZ) 8 milligrams per kilogram (mg/kg; maximum 800 mg) via intravenous (IV) infusion every 4 weeks (q4w) through Week 24 (total of 7 infusions). Participants also received MTX capsules orally, at a stable dose (10, 15, 17.5, or 20 mg, no maximum dose was defined) weekly from Week 1 through 16.	
Reporting group title	TCZ + MTX (Randomized)
Reporting group description:	
Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w through Week 24 (total of 7 infusions). Participants also received MTX capsules, orally, at a stable dose (10, 15, 17.5, or 20 mg/week, but no maximum dose was defined), weekly, from Weeks 1 through 24.	
Reporting group title	Tocilizumab + Placebo (Randomized)
Reporting group description:	
Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w through Week 24 (total of 7 infusions). Participants also received MTX capsules, orally, at stable dose (10, 15, 17.5, or 20 mg per week, but no maximum dose was defined) weekly, from Weeks 1 through 16 followed by matching placebo capsules, orally, weekly through Week 24.	

Primary: Change in Disease Activity Score Based on 28-Joint Count (DAS28) From Week 16 to Week 28

End point title	Change in Disease Activity Score Based on 28-Joint Count (DAS28) From Week 16 to Week 28[1]
End point description:	
The DAS28 is a combined index for measuring disease activity in rheumatoid arthritis (RA). The index includes swollen (range 0-28) and tender (range 0-28) joint counts, acute phase response (erythrocyte sedimentation rate [ESR] in millimeters per hour [mm/hr]), and general health status (participant global assessment of disease activity using visual analog scale [VAS], range 1-100 mm). DAS28, which uses a 28-joint count, is derived from the original DAS, which includes a 44-swollen joint count. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. Intent-to-treat (ITT) population: all randomized participants who received at least one dose of study medication and who had at least one efficacy measurement performed.	
End point type	Primary
End point timeframe:	
Baseline, Week 16, and Week 28	
Notes:	
[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were planned to be analyzed only for those participants who were randomized as per protocol.	

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82[2]	82[3]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 82, 81)	5.42 (± 1.01)	5.29 (± 1.01)		
Week 16 (n = 81, 82)	1.77 (± 0.77)	1.96 (± 0.76)		
Week 28 (n = 79, 79)	1.82 (± 1.18)	1.98 (± 1.13)		

Notes:

[2] - n (number) = number of participants assessed for the given parameter at the specified visit.

[3] - n (number) = number of participants assessed for the given parameter at the specified visit.

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	Tocilizumab + Placebo (Randomized) v TCZ + MTX (Randomized)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	ANCOVA

Secondary: Percentage of Participants With DAS28 Score Less Than (<) 2.6 at Week 28

End point title	Percentage of Participants With DAS28 Score Less Than (<) 2.6 at Week 28[4]

End point description:

The DAS28 is a combined index for measuring disease activity in RA. The index includes swollen (range 0-28) and tender (range 0-28) joint counts, acute phase response (ESR in mm/hr), and general health status (participant global assessment of disease activity using VAS, range 1-100 mm). DAS28, which uses a 28-joint count, is derived from the original DAS, which includes a 44-swollen joint count. The DAS28 scale ranges from 0 to 10, where higher scores indicate worsening. DAS28 <2.6 equals (=) remission. ITT Population; only participants with Week 28 DAS28 values were included in the analysis.

End point type	Secondary

End point timeframe:

Week 28

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were planned to be analyzed only for those participants who were randomized as per protocol.

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: percentage of participants				
number (not applicable)	82.3	75.9		

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	Tocilizumab + Placebo (Randomized) v TCZ + MTX (Randomized)

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.328
Method	Chi-squared

Secondary: Percentage of Participants with Clinical Disease Activity Index (CDAI) <2.8 at Week 28

End point title	Percentage of Participants with Clinical Disease Activity Index (CDAI) <2.8 at Week 28[5]

End point description:

CDAI is the sum of tender and swollen joint count based on 28 joints and the participant and physician global disease assessment (VAS 0-10 centimeters [cm]). CDAI total score 0-76; higher scores = greater affect due to disease activity. CDAI <2.8 = clinical remission. ITT Population; only participants with CDAI scores at Weeks 28 were included in the analysis.

End point type	Secondary

End point timeframe:

Week 28

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be analyzed only for those participants who were randomized as per protocol.

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: percentage of participants				
number (not applicable)	40.7	35.8		

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	TCZ + MTX (Randomized) v Tocilizumab + Placebo (Randomized)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.518
Method	Chi-squared

Secondary: Percentage of Participants With Simplified Disease Activity Index (SDAI) <3.3 at Week 28

End point title	Percentage of Participants With Simplified Disease Activity Index (SDAI) <3.3 at Week 28[6]

End point description:

SDAI is calculated by a simple numerical sum of tender and swollen joint count (based on a 28-joint assessment), participant and physician global assessment of disease activity (VAS 0-10 cm), and level of C-reactive protein in milligram per deciliter (mg/dL). SDAI total score 0-86; higher scores = greater affect due to disease activity. SDAI <3.3 = clinical remission. ITT Population; only participants with SDAI scores at Week 28 were included in the analysis.

End point type	Secondary

End point timeframe:

28 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be analyzed only for those participants who were randomized as per protocol.

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: percentage of participant				
number (not applicable)	35.1	28.2		

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	TCZ + MTX (Randomized) v Tocilizumab + Placebo (Randomized)
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	Chi-squared

Secondary: Change in the Health Assessment Questionnaire Disability Index (HAQ-DI) From Week 16 to Week 28

End point title	Change in the Health Assessment Questionnaire Disability Index (HAQ-DI) From Week 16 to Week 28[7]

End point description:

HAQ-DI: participant-reported assessment of ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week. Each item scored on 4-point scale from 0 to 3: 0 = no difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty. ITT Population; only participants with nonmissing values were included in the analysis.

End point type	Secondary

End point timeframe:

Week 16 and Week 28

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be analyzed only for those participants who were randomized as per

protocol.

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	82		
Units: units on a scale				
arithmetic mean (standard deviation)	0.08 (± 0.47)	0 (± 0.52)		

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	TCZ + MTX (Randomized) v Tocilizumab + Placebo (Randomized)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.674
Method	ANCOVA
Parameter estimate	Difference in Least Square (LS) Mean
Point estimate	0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.119
upper limit	0.184

Secondary: Change in the Quality of Life Questionnaire (Short Form-12 [SF-12]) From Week 16 to Week 28 in Mental Health

End point title	Change in the Quality of Life Questionnaire (Short Form-12 [SF-12]) From Week 16 to Week 28 in Mental Health[8]

End point description:

Quality of life questionnaire (SF-12) scores were computed using the scores of 12 questions and ranged from 0 to 100, where a 0 score indicated the lowest level of health measured by the scales and 100 indicated the highest level of health. A negative change from baseline indicated decline in health and higher scores indicated improvement in health. ITT Population; only participants with nonmissing values were included in the analysis.

End point type	Secondary

End point timeframe:

Week 16 and Week 28

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were planned to be analyzed only for those participants who were randomized as per protocol.

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.36 (± 10.22)	-0.38 (± 9.25)		

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	TCZ + MTX (Randomized) v Tocilizumab + Placebo (Randomized)
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.204
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-1.873
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.775
upper limit	1.03

Secondary: Change in the Quality of Life Questionnaire (SF-12) From Week 16 to Week 28 in Physical Health

End point title	Change in the Quality of Life Questionnaire (SF-12) From Week 16 to Week 28 in Physical Health[9]

End point description:

Quality of life questionnaire (SF-12) scores were computed using the scores of 12 questions and ranged from 0 to 100, where a 0 score indicated the lowest level of health measured by the scales and 100 indicated the highest level of health. A negative change from baseline indicated a worsening of quality of life. ITT Population; only participants with nonmissing data were included in the analysis.

End point type	Secondary

End point timeframe:

Week 16 and Week 28

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data were planned to be analyzed only for those participants who were randomized as per protocol.

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: units on a scale				
arithmetic mean (standard deviation)	0.48 (± 9.49)	-2.26 (± 8.82)		

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	TCZ + MTX (Randomized) v Tocilizumab + Placebo (Randomized)
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	ANCOVA
Parameter estimate	difference in LS Mean
Point estimate	3.376
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.676
upper limit	6.076

Secondary: Change From Week 16 to Week 28 in Global Assessment of Disease Activity as Assessed With the Visual Analogue Scale (VAS) Performed by Participant

End point title	Change From Week 16 to Week 28 in Global Assessment of Disease Activity as Assessed With the Visual Analogue Scale (VAS) Performed by Participant[10]

End point description:

Participants were asked to rate their global assessment of disease activity on a scale ranging from 0=very good to 100=very bad. The scale was represented by a line with 0 at the left edge and 100 at the right edge. The participant was asked to mark the line corresponding to the assessment of their disease activity . The distance from the left edge was measured in mm. ITT Population; only participants with nonmissing values were included in the analysis.

End point type	Secondary

End point timeframe:

Week 16 and Week 28

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be analyzed only for those participants who were randomized as per protocol.

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: units on a scale				
arithmetic mean (standard deviation)	1.68 (± 23.8)	0.56 (± 20.42)		

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	TCZ + MTX (Randomized) v Tocilizumab + Placebo (Randomized)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	0.969
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.526
upper limit	7.464

Secondary: Change From Week 16 to Week 28 in Global Assessment of Disease Activity Assessed Using the VAS Performed by the Investigator

End point title	Change From Week 16 to Week 28 in Global Assessment of Disease Activity Assessed Using the VAS Performed by the Investigator[11]

End point description:

Participants were asked to rate their global assessment of disease activity on a scale ranging from 0=very good to 100=very bad. The scale was represented by a line with 0 at the left edge and 100 at the right edge. The participant was asked to mark the line corresponding to the assessment of their disease activity . The distance from the left edge was measured in mm. ITT Population; only participants with nonmissing values were included in the analysis.

End point type	Secondary

End point timeframe:

Week 16 and Week 28

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were planned to be analyzed only for those participants who were randomized as per protocol.

End point values	TCZ + MTX (Randomized)	Tocilizumab + Placebo (Randomized)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: units on a scale				
arithmetic mean (standard deviation)	2.71 (± 16.96)	2.85 (± 18.48)		

Statistical analyses

Statistical analysis title	TCZ+MTX vs. TCZ+Placebo
Comparison groups	TCZ + MTX (Randomized) v Tocilizumab + Placebo (Randomized)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.655
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-1.216
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.573
upper limit	4.141

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to Week 36

Adverse event reporting additional description:

The data were planned per the protocol to be reported separately for pre-randomization period and post-randomization period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	TCZ + MTX (Non Randomized)

Reporting group description:

Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w through Week 24 (total of 7 infusions). Participants also received MTX capsules orally, at a stable dose (10, 15, 17.5, or 20 mg, no maximum dose was defined) weekly from Week 1 through 16.

Reporting group title	TCZ + MTX (Pre-randomization)

Reporting group description:

Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w up to Week 16 (total of 4 infusions). Participants also received MTX capsules, orally at a stable dose (10, 15, 17.5, or 20 mg/week but no maximum dose was set) weekly, up to Week 16. Participants with a response were randomized to receive TCZ and MTX in the second part of the study. Response was defined as participants having DAS28 score less than or equal to (<=)3.2.

Reporting group title	TCZ + Placebo (Pre-randomization)

Reporting group description:

Participants received TCZ 8 mg/kg (maximum 800 mg) via IV infusion q4w up to Week 16 (total of 4 infusions). Participants also received MTX capsules, orally at a stable dose (10, 15, 17.5, or 20 mg/week but no maximum dose was set) weekly, up to Week 16. Participants with a response were randomized to receive TCZ and matching MTX placebo in the second part of the study. Response was defined as participants having DAS28 score <=3.2.

Reporting group title	TCZ + MTX (Post-randomization)

Reporting group description:

TCZ 8 mg/kg (maximum 800 mg) q4w via IV infusion up to Week 16 (total of 4 infusions). Participants also received MTX capsules, orally, at a stable dose (10, 15, 17.5, or 20 mg/week but no maximum dose was set) weekly, up to Week 16. Participants with a response were randomized to receive 3 additional IV infusions of TCZ 8 mg/kg between Week 16 and Week 24 and MTX capsules, orally, at a stable dose (10, 15, 17.5, or 20 mg per week, but no maximum dose was set), weekly through Week 24. Response was defined as participants having DAS28 score <=3.2.

Reporting group title	TCZ + Placebo (Post-randomization)

Reporting group description:

TCZ 8 mg/kg (maximum 800 mg) q4w via IV infusion up to Week 16 (total of 4 infusions). Participants also received MTX capsules, orally, at a stable dose (10, 15, 17.5, or 20 mg/week but no maximum dose was set) weekly, up to Week 16. Participants with a response were randomized to receive 3 additional IV infusions of TCZ 8 mg/kg between Week 16 and Week 24 and matching placebo MTX capsules, orally, at a stable dose (10, 15, 17.5, or 20 mg per week, but no maximum dose was set), weekly through Week 24. Response was defined as participants having DAS28 score <=3.2.

Serious adverse events	TCZ + MTX (Non Randomized)	TCZ + MTX (Pre-randomization)	TCZ + Placebo (Pre-randomization)
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 96 (11.46%)	0 / 83 (0.00%)	1 / 82 (1.22%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Deep vein thrombosis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 96 (2.08%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 96 (0.00%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hypertransaminasaemia			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 96 (3.13%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Lupus-like syndrome			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bursitis infective			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 96 (0.00%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis bacterial			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 96 (0.00%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal skin infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 96 (0.00%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 96 (0.00%)	0 / 83 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 96 (1.04%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TCZ + MTX (Post-randomization)	TCZ + Placebo (Post-randomization)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 83 (1.20%)	4 / 82 (4.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lupus-like syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Bursitis infective			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 83 (1.20%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	TCZ + MTX (Non Randomized)	TCZ + MTX (Pre-randomization)	TCZ + Placebo (Pre-randomization)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 96 (29.17%)	20 / 83 (24.10%)	24 / 82 (29.27%)
Blood and lymphatic system disorders			
Leukopenia			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 96 (7.29%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences (all)	7	0	0
Neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 96 (7.29%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences (all)	8	0	0

Gastrointestinal disorders			
Aphthous stomatitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 96 (0.00%)	3 / 83 (3.61%)	6 / 82 (7.32%)
occurrences (all)	0	3	8
Hepatobiliary disorders			
Hypertransaminasaemia			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 96 (15.63%)	12 / 83 (14.46%)	10 / 82 (12.20%)
occurrences (all)	20	13	11
Infections and infestations			
Respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 96 (5.21%)	0 / 83 (0.00%)	0 / 82 (0.00%)
occurrences (all)	5	0	0
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 96 (0.00%)	3 / 83 (3.61%)	5 / 82 (6.10%)
occurrences (all)	0	3	6
Metabolism and nutrition disorders			
Hypercholesterolaemia			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 96 (9.38%)	2 / 83 (2.41%)	6 / 82 (7.32%)
occurrences (all)	10	2	6

Non-serious adverse events	TCZ + MTX (Post-randomization)	TCZ + Placebo (Post-randomization)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 83 (9.64%)	4 / 82 (4.88%)	
Blood and lymphatic system disorders			
Leukopenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Aphthous stomatitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Hypertransaminasaemia			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 83 (9.64%)	4 / 82 (4.88%)	
occurrences (all)	9	6	
Infections and infestations			
Respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 83 (0.00%)	0 / 82 (0.00%)	
occurrences (all)	0	0	

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

None reported