Clinical trial results:
Efficacy and Safety Study of a Sequential Therapy of Tocilizumab (TCZ) and, if Initially Inadequately Responded to Tocilizumab (TCZ), Followed by Rituximab (RTX) in DMARD-IR Patients With Rheumatoid Arthritis (MIRAI)

Summary

EudraCT number	2010-022049-88
Trial protocol	DE
Global end of trial date	19 February 2014

Results information

Result version number	v2 (current)
This version publication date	21 July 2016
First version publication date	16 March 2016
Version creation reason	• Correction of full data set Errors have been identified that need to be corrected.

Trial information

Trial identification

Sponsor protocol code	ML22985

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01332994
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 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, 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	19 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This open-label, national, multicenter, two-arm, non-controlled, nonrandomized study evaluated the efficacy and safety of TCZ with or without sequential RTX in participants with moderate to severe active rheumatoid arthritis (RA) with inadequate response to disease-modifying antirheumatic drugs (DMARD-IR) at the time of enrollment. Participants were treated with TCZ and, if applicable, with subsequent RTX in combination with traditional disease-modifying antirheumatic drugs (DMARDs) taken before study entry.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki (version 1996) as amended, international Good Clinical Practice (ICH-GCP) standards, and local laws and regulations concerning clinical studies.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 519
Worldwide total number of subjects	519
EEA total number of subjects	519

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)	388
From 65 to 84 years	131
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After a screening period of up to 4 weeks, eligible participants were treated according to a predefined treatment algorithm based on disease response. In certain cases a re-screening was allowed. Participants were enrolled into the study with the administration of their first dose.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	TCZ/TCZ or TCZ/RTX

Arm description:

All participants were assigned to receive TCZ 8 milligrams per kilogram (mg/kg) via intravenous (IV) infusion every 4 weeks for a total of 4 infusions from Baseline to Week 12. Clinical response was assessed at Week 16 using Disease Activity Score Based on 28-Joint Count (DAS28) to determine subsequent treatment assignment. Participants who achieved early remission, defined as a DAS28 score of less than (<) 2.6, were transferred to clinical routine care and no longer received study medication. Participants who were considered partial responders, defined as a decrease from Baseline in DAS28 score greater than (>) 1.2 or a score between 2.6 and 3.2, inclusive, received TCZ 8 mg/kg via IV infusion every 4 weeks for a total of 4 additional infusions from Week 16 to 28. Those with assessed as having no response, defined as a decrease from Baseline in DAS28 score less than or equal to (≤) 1.2 or a score >3.2, received RTX 1000 milligrams (mg) via IV infusion at Weeks 16 and 18.

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:

Participants received TCZ 8 mg/kg via IV infusion every 4 weeks for a total of 4 infusions from Baseline to Week 12. Participants with a partial response received an additional 4 infusions of TCZ 8 mg/kg every 4 weeks from Week 16 to 28.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants assessed as having no response received RTX 1000 mg via IV infusion at Weeks 16 and 18.

Number of subjects in period 1	TCZ/TCZ or TCZ/RTX
Started	519
Completed Week 16	463
Completed Week 32 (TCZ/TCZ)	200 [1]
Completed Week 32 (TCZ/RTX)	26 [2]
Completed Week 66 (TCZ/RTX)	25 [3]
Completed	448
Not completed	71
Consent withdrawn by subject	15
Protocol violation	6
Death	1
Not specified	8
Adverse event	34
Administrative problem	2
Lost to follow-up	4
Lack of efficacy	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only select participants continued assessment visits through the end of safety follow-up (Week 66). Participants achieving early remission or partial response could complete the study earlier.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only select participants continued assessment visits through the end of safety follow-up (Week 66). Participants achieving early remission or partial response could complete the study earlier.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only select participants continued assessment visits through the end of safety follow-up (Week 66). Participants achieving early remission or partial response could complete the study earlier.

Baseline characteristics

Reporting groups	
Reporting group title	TCZ/TCZ or TCZ/RTX

Reporting group description:

All participants were assigned to receive TCZ 8 milligrams per kilogram (mg/kg) via intravenous (IV) infusion every 4 weeks for a total of 4 infusions from Baseline to Week 12. Clinical response was assessed at Week 16 using Disease Activity Score Based on 28-Joint Count (DAS28) to determine subsequent treatment assignment. Participants who achieved early remission, defined as a DAS28 score of less than (<) 2.6, were transferred to clinical routine care and no longer received study medication. Participants who were considered partial responders, defined as a decrease from Baseline in DAS28 score greater than (>) 1.2 or a score between 2.6 and 3.2, inclusive, received TCZ 8 mg/kg via IV infusion every 4 weeks for a total of 4 additional infusions from Week 16 to 28. Those with assessed as having no response, defined as a decrease from Baseline in DAS28 score less than or equal to (≤) 1.2 or a score >3.2, received RTX 1000 milligrams (mg) via IV infusion at Weeks 16 and 18.

Reporting group values	TCZ/TCZ or TCZ/RTX	Total	
Number of subjects	519	519	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	55.7		
standard deviation	± 11.9	-	
Gender categorical			
Units: Subjects			
Female	352	352	
Male	167	167	

End points

End points reporting groups

Reporting group title	TCZ/TCZ or TCZ/RTX

Reporting group description:

All participants were assigned to receive TCZ 8 milligrams per kilogram (mg/kg) via intravenous (IV) infusion every 4 weeks for a total of 4 infusions from Baseline to Week 12. Clinical response was assessed at Week 16 using Disease Activity Score Based on 28-Joint Count (DAS28) to determine subsequent treatment assignment. Participants who achieved early remission, defined as a DAS28 score of less than (<) 2.6, were transferred to clinical routine care and no longer received study medication. Participants who were considered partial responders, defined as a decrease from Baseline in DAS28 score greater than (>) 1.2 or a score between 2.6 and 3.2, inclusive, received TCZ 8 mg/kg via IV infusion every 4 weeks for a total of 4 additional infusions from Week 16 to 28. Those with assessed as having no response, defined as a decrease from Baseline in DAS28 score less than or equal to (≤) 1.2 or a score >3.2, received RTX 1000 milligrams (mg) via IV infusion at Weeks 16 and 18.

Primary: Percentage of Participants Achieving Remission at Week 16 According to DAS28

End point title	Percentage of Participants Achieving Remission at Week 16 According to DAS28[1]

End point description:

The DAS28 was calculated as [0.28 times (x) the square root of number of swollen joints] plus (+) [0.56 x the square root of number of tender joints] + [0.7 x the natural log of erythrocyte sedimentation rate (ESR)] + [0.014 x Visual Analog Scale (VAS) patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Remission was defined as a DAS28 score <2.6 at the assessment visit. Main Intent-to-Treat (ITT) Population: All participants who received at least one dose of TCZ.

End point type	Primary

End point timeframe:

Week 16

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis could not be entered due to system limitations for a single-arm study. An exact one-sided binomial test on single proportions was performed, with a significance level of alpha equals (=) 0.025. Null hypothesis: Proportion of participants reaching DAS28 remission (<2.6) at Week 16 is ≤45 percent (%). The result was p-value = 0.1648.

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	519			
Units: percentage of participants				
number (confidence interval 95%)	42.8 (38.5 to 47.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Remission According to DAS28 at Weeks 4, 8, and 12

End point title	Percentage of Participants Achieving Remission According to DAS28 at Weeks 4, 8, and 12

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Remission was defined as a DAS28 score <2.6 at the assessment visit. Main ITT Population.

End point type	Secondary

End point timeframe:

Weeks 4, 8, and 12

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	519			
Units: percentage of participants				
number (confidence interval 95%)				
Week 4	21.6 (18.1 to 25.4)			
Week 8	40.1 (35.8 to 44.4)			
Week 12	43.2 (38.9 to 47.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Remission According to DAS28 at Weeks 16, 20, 24, and 28 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Percentage of Participants Achieving Remission According to DAS28 at Weeks 16, 20, 24, and 28 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Remission was defined as a DAS28 score <2.6 at the assessment visit. ITT2 Population: All participants who received at least one dose of TCZ in the first treatment period with at least one efficacy measurement under TCZ, receiving TCZ in the second treatment period.

End point type	Secondary

End point timeframe:

Weeks 16, 20, 24, and 28

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: percentage of participants				
number (confidence interval 95%)				
Week 16	1.4 (0.3 to 4.1)			
Week 20	41.3 (34.6 to 48.2)			
Week 24	51.2 (44.3 to 58.1)			
Week 28	55.9 (48.9 to 62.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Remission According to DAS28 at Week 32 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Percentage of Participants Achieving Remission According to DAS28 at Week 32 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Remission was defined as a DAS28 score <2.6 at the assessment visit. ITT2 Population.

End point type	Secondary

End point timeframe:

Week 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: percentage of participants				
number (confidence interval 95%)	54.9 (48 to 61.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Low Disease Activity Score (LDAS) According to DAS28

End point title	Percentage of Participants Achieving Low Disease Activity Score (LDAS) According to DAS28

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x the patient global assessment of disease activity using a VAS]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. LDAS was defined as a DAS28 score <3.2 at the assessment visit. Main ITT Population.

End point type	Secondary

End point timeframe:

Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	519			
Units: percentage of participants				
number (confidence interval 95%)	68.8 (64.6 to 72.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Clinically Relevant Reduction From Baseline in DAS28 at Week 16

End point title	Percentage of Participants Achieving a Clinically Relevant Reduction From Baseline in DAS28 at Week 16

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Reductions >1.2 points from Baseline to the assessment visit were considered clinically relevant. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	519			
Units: percentage of participants				
number (confidence interval 95%)	86.1 (82.9 to 89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Clinically Relevant Reduction From Baseline in DAS28 at Weeks 4, 8, and 12

End point title	Percentage of Participants Achieving a Clinically Relevant Reduction From Baseline in DAS28 at Weeks 4, 8, and 12

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Reductions >1.2 points from Baseline to the assessment visit were considered clinically relevant. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, and 12

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	519			
Units: percentage of participants				
number (confidence interval 95%)				
Week 4	74.6 (70.6 to 78.3)			
Week 8	81.5 (77.9 to 84.8)			
Week 12	83.4 (79.9 to 86.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Clinically Relevant Reduction in DAS28 From Week 16 to Week 32 Among Nonresponding Participants Treated With Rituximab

End point title	Percentage of Participants Achieving a Clinically Relevant Reduction in DAS28 From Week 16 to Week 32 Among Nonresponding Participants Treated With Rituximab

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square

root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Reductions >1.2 points from the reference visit (Week 16) to the assessment visit were considered clinically relevant. ITT3 Population: All participants who received at least one dose of TCZ in the first treatment period and at least one dose of RTX in the second treatment period with at least one efficacy measurement under RTX.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of participants				
number (confidence interval 95%)	37 (19.4 to 57.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 Scores During and After Treatment

End point title	DAS28 Scores During and After Treatment

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	516[2]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=516)	5.7 (± 1)			
Week 4 (n=508)	3.6 (± 1.3)			
Week 8 (n=491)	3 (± 1.4)			
Week 12 (n=483)	2.8 (± 1.4)			
Week 16 (n=485)	2.6 (± 1.3)			

Notes:

[2] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 Scores During Safety Follow-Up Among Nonresponding Participants Treated With Rituximab

End point title	DAS28 Scores During Safety Follow-Up Among Nonresponding Participants Treated With Rituximab

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 40, 48, 56, and 66

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	26[3]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 40 (n=26)	3.9 (± 1.5)			
Week 48 (n=25)	3.9 (± 1.2)			
Week 56 (n=22)	4.1 (± 1.8)			
Week 66 (n=25)	3.9 (± 1.5)			

Notes:

[3] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Response According to European League Against Rheumatism (EULAR) Criteria at Weeks 4, 8, 12 and 16

End point title	Percentage of Participants Achieving a Response According to European League Against Rheumatism (EULAR) Criteria at Weeks 4, 8, 12 and 16

End point description:

Response was determined using EULAR criteria based upon DAS28 absolute scores at the assessment visit and the DAS28 reduction from Baseline. Participants with a score ≤3.2 and reduction of >1.2 points were assessed as having a 'good' response. Participants with a score >3.2 with reduction of >1.2 points, or a score ≤5.1 with reduction of >0.6 to ≤1.2 points, were assessed as having a 'moderate' response. Participants with a score >5.1 with reduction of >0.6 to ≤1.2 points, or any score with reduction ≤0.6

points, were assessed as nonresponders with response recorded as 'none.' Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, and 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	519			
Units: percentage of participants				
number (confidence interval 95%)				
Week 4, Good	36 (31.9 to 40.3)			
Week 4, Moderate	47.8 (43.4 to 52.2)			
Week 4, None	16.2 (13.1 to 19.6)			
Week 8, Good	56.1 (51.7 to 60.4)			
Week 8, Moderate	30.6 (26.7 to 34.8)			
Week 8, None	13.3 (10.5 to 16.5)			
Week 12, Good	61.1 (56.7 to 65.3)			
Week 12, Moderate	25.6 (21.9 to 29.6)			
Week 12, None	13.3 (10.5 to 16.5)			
Week 16, Good	68.2 (64 to 72.2)			
Week 16, Moderate	20.2 (16.9 to 23.9)			
Week 16, None	11.6 (8.9 to 14.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Response According to EULAR Criteria at Week 32 Compared to Week 16 Among Nonresponding Participants Treated With Rituximab

End point title	Percentage of Participants Achieving a Response According to EULAR Criteria at Week 32 Compared to Week 16 Among Nonresponding Participants Treated With Rituximab

End point description:

Response was determined using EULAR criteria based upon DAS28 absolute scores at the assessment visit and the DAS28 reduction from the reference visit (Week 16). Participants with a score ≤3.2 and reduction of >1.2 points were assessed as having a 'good' response. Participants with a score >3.2 with reduction of >1.2 points, or a score ≤5.1 with reduction of >0.6 to ≤1.2 points, were assessed as having a 'moderate' response. Participants with a score >5.1 with reduction of >0.6 to ≤1.2 points, or any score with reduction ≤0.6 points, were assessed as nonresponders with response recorded as

'none.' ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of participants				
number (confidence interval 95%)				
Good	25.9 (11.1 to 46.3)			
Moderate	29.6 (13.8 to 50.2)			
None	44.4 (25.5 to 64.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Response According to EULAR Criteria at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Percentage of Participants Achieving a Response According to EULAR Criteria at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

Response was determined using EULAR criteria based upon DAS28 absolute scores at the assessment visit and the DAS28 reduction from Baseline. Participants with a score ≤3.2 and reduction of >1.2 points were assessed as having a 'good' response. Participants with a score >3.2 with reduction of >1.2 points, or a score ≤5.1 with reduction of >0.6 to ≤1.2 points, were assessed as having a 'moderate' response. Participants with a score >5.1 with reduction of >0.6 to ≤1.2 points, or any score with reduction ≤0.6 points, were assessed as nonresponders with response recorded as 'none.' ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 20, 24, 28, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: percentage of participants				
number (confidence interval 95%)				
Week 20, Good	65.3 (58.5 to 71.6)			
Week 20, Moderate	30 (24 to 36.7)			

Week 20, None	4.7 (2.3 to 8.5)			
Week 24, Good	68.1 (61.4 to 74.3)			
Week 24, Moderate	23.9 (18.4 to 30.3)			
Week 24, None	8 (4.7 to 12.5)			
Week 28, Good	72.8 (66.3 to 78.6)			
Week 28, Moderate	19.2 (14.2 to 25.2)			
Week 28, None	8 (4.7 to 12.5)			
Week 32, Good	66.7 (59.9 to 73)			
Week 32, Moderate	20.7 (15.4 to 26.7)			
Week 32, None	12.7 (8.5 to 17.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Response According to American College of Rheumatology (ACR) Criteria at Weeks 4, 8, 12, and 16

End point title	Percentage of Participants Achieving a Response According to American College of Rheumatology (ACR) Criteria at Weeks 4, 8, 12, and 16

End point description:

Response was determined using ACR criteria based upon assessment of 66 joints for swelling and 68 joints for tenderness; joints were classified dichotomously as swollen or not swollen and tender or not tender. Respectively, these assessments were used to generate a swollen joint count (SJC) ranging from 0 to 66 swollen joints and a tender joint count (TJC) ranging from 0 to 68 tender joints. Response was defined as a reduction from Baseline of at least 20% for one of the following: VAS scores for patient-reported pain, patient global assessment of disease activity, or physician global assessment of disease activity, Health Assessment Questionnaire Disability Index (HAQ-DI), or C-reactive protein (CRP); plus a reduction in individual SJC and TJC of 20% (ACR20), 50% (ACR50), or 70% (ACR70). VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, and 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	519			
Units: percentage of participants				
number (confidence interval 95%)				
Week 4, ACR20	39.1 (34.9 to 43.5)			
Week 4, ACR50	15 (12.1 to 18.4)			
Week 4, ACR70	5.8 (3.9 to 8.1)			

Week 8, ACR20	61.1 (56.7 to 65.3)			
Week 8, ACR50	33.5 (29.5 to 37.8)			
Week 8, ACR70	15.2 (12.2 to 18.6)			
Week 12, ACR20	64 (59.7 to 68.1)			
Week 12, ACR50	42.8 (38.5 to 47.2)			
Week 12, ACR70	20.2 (16.9 to 23.9)			
Week 16, ACR20	67.1 (62.8 to 71.1)			
Week 16, ACR50	45.7 (41.3 to 50.1)			
Week 16, ACR70	24.5 (20.8 to 28.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Response According to ACR Criteria at Week 32 Compared to Week 16 Among Nonresponding Participants Treated With Rituximab

End point title	Percentage of Participants Achieving a Response According to ACR Criteria at Week 32 Compared to Week 16 Among Nonresponding Participants Treated With Rituximab

End point description:

Response was determined using ACR criteria based upon assessment of 66 joints for swelling and 68 joints for tenderness; joints were classified dichotomously as swollen or not swollen and tender or not tender. Respectively, these assessments were used to generate an SJC ranging from 0 to 66 swollen joints and a TJC ranging from 0 to 68 tender joints. Response was defined as a reduction from the reference visit (Week 16) of at least 20% for one of the following: VAS scores for patient-reported pain, patient global assessment of disease activity, or physician global assessment of disease activity, HAQDI, or CRP; plus a reduction in individual SJC and TJC of 20% (ACR20), 50% (ACR50), or 70% (ACR70). VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of participants				
number (confidence interval 95%)				
ACR20	40.7 (22.4 to 61.2)			
ACR50	33.3 (16.5 to 54)			

ACR70	22.2 (8.6 to 42.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Response According to ACR Criteria at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Percentage of Participants Achieving a Response According to ACR Criteria at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

Response was determined using ACR criteria based upon assessment of 66 joints for swelling and 68 joints for tenderness; joints were classified dichotomously as swollen or not swollen and tender or not tender. Respectively, these assessments were used to generate an SJC ranging from 0 to 66 swollen joints and a TJC ranging from 0 to 68 tender joints. Response was defined as a reduction from Baseline of at least 20% for one of the following: VAS scores for patient-reported pain, patient global assessment of disease activity, or physician global assessment of disease activity, HAQ-DI, or CRP; plus a reduction in individual SJC and TJC of 20% (ACR20), 50% (ACR50), or 70% (ACR70). VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 20, 24, 28, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: percentage of participants				
number (confidence interval 95%)				
Week 20, ACR20	74.2 (67.8 to 79.9)			
Week 20, ACR50	45.1 (38.3 to 52)			
Week 20, ACR70	21.1 (15.8 to 27.2)			
Week 24, ACR20	72.8 (66.3 to 78.6)			
Week 24, ACR50	49.8 (42.9 to 56.7)			
Week 24, ACR70	21.6 (16.3 to 27.7)			
Week 28, ACR20	73.2 (66.8 to 79.1)			
Week 28, ACR50	53.1 (46.1 to 59.9)			
Week 28, ACR70	30.5 (24.4 to 37.2)			
Week 32, ACR20	75.6 (69.2 to 81.2)			

Week 32, ACR50	54.9 (48 to 61.7)			
Week 32, ACR70	34.3 (27.9 to 41.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) Scores at Weeks 4, 8, 12, and 16

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) Scores at Weeks 4, 8, 12, and 16

End point description:

The CDAI was calculated as [SJC + TJC + VAS patient global assessment of disease activity + VAS physician global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. The SDAI was determined by adding CRP level to the CDAI score. Scores ranged from 0 to 86, with higher scores also indicating increased disease activity. A reduction in either score at the assessment visit reflects improvement in disease. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, and 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	509[4]			
Units: units of a scale				
arithmetic mean (standard deviation)				
CDAI, Week 4 (n=509)	-10.9 (± 10.2)			
CDAI, Week 8 (n=497)	-16.5 (± 11.1)			
CDAI, Week 12 (n=486)	-18.3 (± 11.5)			
CDAI, Week 16 (n=485)	-19.4 (± 11.5)			
SDAI, Week 4 (n=496)	-12.3 (± 10.6)			
SDAI, Week 8 (n=489)	-17.9 (± 11.5)			
SDAI, Week 12 (n=474)	-19.7 (± 11.9)			
SDAI, Week 16 (n=471)	-20.7 (± 12.2)			

Notes:

[4] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 16 to 32 in CDAI and SDAI Scores Among Nonresponding Participants Treated With Rituximab

End point title	Change From Week 16 to 32 in CDAI and SDAI Scores Among

	Nonresponding Participants Treated With Rituximab

End point description:

The CDAI was calculated as [SJC + TJC + VAS patient global assessment of disease activity + VAS physician global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. The SDAI was determined by adding CRP level to the CDAI score. Scores ranged from 0 to 86, with higher scores also indicating increased disease activity. A reduction in either score at the assessment visit reflects improvement in disease. ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	25[5]			
Units: units on a scale				
arithmetic mean (standard deviation)				
CDAI (n=25)	-14.2 (± 12)			
SDAI (n=24)	-14 (± 12.5)			

Notes:

[5] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CDAI and SDAI Scores at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Change From Baseline in CDAI and SDAI Scores at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

The CDAI was calculated as [SJC + TJC + VAS patient global assessment of disease activity + VAS physician global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity. The SDAI was determined by adding CRP level to the CDAI score. Scores ranged from 0 to 86, with higher scores also indicating increased disease activity. A reduction in either score at the assessment visit reflects improvement in disease. ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 20, 24, 28, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	208[6]			
Units: units on a scale				
arithmetic mean (standard deviation)				
CDAI, Week 20 (n=208)	-21.7 (± 11.7)			

CDAI, Week 24 (n=199)	-22.8 (± 11.4)			
CDAI, Week 28 (n=200)	-24.6 (± 12.5)			
CDAI, Week 32 (n=194)	-24 (± 13.4)			
SDAI, Week 20 (n=200)	-22.9 (± 12.5)			
SDAI, Week 24 (n=190)	-24.3 (± 12.1)			
SDAI, Week 28 (n=195)	-25.9 (± 13.2)			
SDAI, Week 32 (n=189)	-25.2 (± 14)			

Notes:

[6] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemoglobin at Weeks 4, 8, 12, and 16

End point title	Change From Baseline in Hemoglobin at Weeks 4, 8, 12, and 16

End point description:

Blood samples for laboratory assessments, including hemoglobin level, were collected prior to each dose of study medication. The mean hemoglobin level was determined at Baseline and for assessment visits by averaging the observed hemoglobin level among all participants providing evaluable blood samples. Change from Baseline was calculated as [mean hemoglobin at the assessment visit minus mean hemoglobin at Baseline] and expressed in grams per liter (g/L). Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, and 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	509[7]			
Units: g/L				
arithmetic mean (standard deviation)				
Week 4 (n=509)	4.9 (± 7.2)			
Week 8 (n=496)	6.4 (± 8.8)			
Week 12 (n=483)	6.9 (± 9.1)			
Week 16 (n=477)	7.5 (± 9.1)			

Notes:

[7] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CRP at Weeks 4, 8, 12, and 16

End point title	Change From Baseline in CRP at Weeks 4, 8, 12, and 16

End point description:

Blood samples for laboratory assessments, including CRP level, were collected prior to each dose of study medication. The mean CRP level was determined at Baseline and for assessment visits by averaging the observed CRP level among all participants providing evaluable blood samples. Change

from Baseline was calculated as [mean CRP at the assessment visit minus mean CRP at Baseline] and expressed in milligrams per deciliter (mg/dL). Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, and 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	497[8]			
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 4 (n=497)	-1.4 (± 1.9)			
Week 8 (n=492)	-1.4 (± 1.9)			
Week 12 (n=476)	-1.4 (± 1.9)			
Week 16 (n=471)	-1.3 (± 1.9)			

Notes:

[8] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESR at Weeks 4, 8, 12, and 16

End point title	Change From Baseline in ESR at Weeks 4, 8, 12, and 16

End point description:

Blood samples for laboratory assessments, including ESR, were collected prior to each dose of study medication. The mean ESR was determined at Baseline and for assessment visits by averaging the observed ESR among all participants providing evaluable blood samples. Change from Baseline was calculated as [mean ESR at the assessment visit minus mean ESR at Baseline] and expressed in millimeters per hour (mm/h). Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, and 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	507[9]			
Units: mm/h				
arithmetic mean (standard deviation)				
Week 4 (n=507)	-25.2 (± 18.1)			
Week 8 (n=494)	-26.6 (± 18.9)			
Week 12 (n=484)	-26.3 (± 19.1)			
Week 16 (n=484)	-27.5 (± 18.7)			

Notes:

[9] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hemoglobin From Week 16 to 32 Among Nonresponding Participants Treated With Rituximab

End point title	Change in Hemoglobin From Week 16 to 32 Among Nonresponding Participants Treated With Rituximab

End point description:

Blood samples for laboratory assessments, including hemoglobin level, were collected prior to each dose of study medication. The mean hemoglobin level was determined at Baseline and for assessment visits by averaging the observed hemoglobin level among all participants providing evaluable blood samples. Change was calculated as [mean hemoglobin at Week 32 minus mean hemoglobin at Week 16] and expressed in g/L. ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	26[10]			
Units: g/L				
arithmetic mean (standard deviation)	-2 (± 8.3)			

Notes:

[10] - Participants with evaluable data at the designated visit were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CRP From Week 16 to 32 Among Nonresponding Participants Treated With Rituximab

End point title	Change in CRP From Week 16 to 32 Among Nonresponding Participants Treated With Rituximab

End point description:

Blood samples for laboratory assessments, including CRP level, were collected prior to each dose of study medication. The mean CRP level was determined at Baseline and for assessment visits by averaging the observed CRP level among all participants providing evaluable blood samples. Change was calculated as [mean CRP at Week 32 minus mean CRP at Week 16] and expressed in mg/dL. ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	25[11]			
Units: mg/dL				
arithmetic mean (standard deviation)	0.7 (± 1.7)			

Notes:

[11] - Participants with evaluable data at the designated visit were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ESR From Week 16 to 32 Among Nonresponding Participants Treated With Rituximab

End point title	Change in ESR From Week 16 to 32 Among Nonresponding Participants Treated With Rituximab

End point description:

Blood samples for laboratory assessments, including ESR, were collected prior to each dose of study medication. The mean ESR was determined at Baseline and for assessment visits by averaging the observed ESR among all participants providing evaluable blood samples. Change was calculated as [mean ESR at Week 32 minus mean ESR at Week 16] and expressed in mm/h. ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	26[12]			
Units: mm/h				
arithmetic mean (standard deviation)	11.5 (± 17.9)			

Notes:

[12] - Participants with evaluable data at the designated visit were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemoglobin at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Change From Baseline in Hemoglobin at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

Blood samples for laboratory assessments, including hemoglobin level, were collected prior to each dose of study medication. The mean hemoglobin level was determined at Baseline and for assessment visits by averaging the observed hemoglobin level among all participants providing evaluable blood samples.

Change from Baseline was calculated as [mean hemoglobin at the assessment visit minus mean hemoglobin at Baseline] and expressed in g/L. ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 20, 24, 28, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	207[13]			
Units: g/L				
arithmetic mean (standard deviation)				
Week 20 (n=207)	5.5 (± 9)			
Week 24 (n=198)	6.6 (± 9.4)			
Week 28 (n=197)	6.9 (± 9.5)			
Week 32 (n=197)	8.3 (± 10.4)			

Notes:

[13] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CRP at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Change From Baseline in CRP at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

Blood samples for laboratory assessments, including CRP level, were collected prior to each dose of study medication. The mean CRP level was determined at Baseline and for assessment visits by averaging the observed CRP level among all participants providing evaluable blood samples. Change from Baseline was calculated as [mean CRP at the assessment visit minus mean CRP at Baseline] and expressed in mg/dL. ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 20, 24, 28, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	200[14]			
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 20 (n=200)	-1.3 (± 1.9)			
Week 24 (n=191)	-1.4 (± 1.9)			
Week 28 (n=195)	-1.3 (± 1.9)			
Week 32 (n=192)	-1.3 (± 1.9)			

Notes:

[14] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESR at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Change From Baseline in ESR at Weeks 20, 24, 28, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

Blood samples for laboratory assessments, including ESR, were collected prior to each dose of study medication. The mean ESR was determined at Baseline and for assessment visits by averaging the observed ESR among all participants providing evaluable blood samples. Change from Baseline was calculated as [mean ESR at the assessment visit minus mean ESR at Baseline] and expressed in mm/h. ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 20, 24, 28, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	206[15]			
Units: mm/h				
arithmetic mean (standard deviation)				
Week 20 (n=206)	-28.6 (± 17.6)			
Week 24 (n=197)	-29.4 (± 18)			
Week 28 (n=200)	-29.4 (± 18.1)			
Week 32 (n=196)	-28.6 (± 20.2)			

Notes:

[15] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Withdrawing From the Study for Insufficient Therapeutic Response

End point title	Percentage of Participants Withdrawing From the Study for Insufficient Therapeutic Response

End point description:

Study discontinuation was documented by reason for each participant prematurely withdrawing from the study. The percentage of participants was calculated as the number withdrawing for insufficient therapeutic response divided by the total number of participants who began treatment. Main ITT Population.

End point type	Secondary

End point timeframe: Baseline to Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	485[16]			
Units: percentage of participants				
number (confidence interval 95%)	0.2 (0 to 1.1)			

Notes:

[16] - Participants who withdrew from the study for other reasons were excluded from the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of B-Cells at Baseline by B-Cell Subpopulation Among Participants With Early Remission

End point title	Percentage of B-Cells at Baseline by B-Cell Subpopulation Among Participants With Early Remission

End point description:

Blood samples were collected to analyze total B-cell panel via immunophenotyping. Subpopulations were as follows: transitional (cluster of differentiation [CD] 19-positive, immunoglobulin (Ig) D-positive, CD38 medium, CD10-positive); naive (CD19-positive, IgD-positive, CD38 medium, CD27-negative); preswitch memory (CD19-positive, CD27-positive, IgD-positive); post-switch memory (CD19-positive, CD27-positive, IgD-negative); IgG-positive class-switched (CD19-positive, IgG-positive); IgA-positive class-switched (CD19-positive, IgA-positive); double-negative memory (CD19-positive, IgD-negative, CD27-negative); and plasmablasts (CD19-positive, IgD-negative, CD38 high, CD27 high). Naive B-cell compartment was defined as the sum of transitional and naive B-cells. The sum of memory B-cell subsets with or without double-negative B-cells was also determined. ITT1 Population: Those who received at least one dose of TCZ in the first treatment period and completed at Week 16 reaching remission.

End point type	Secondary

End point timeframe:

Baseline

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	196[17]			
Units: percentage of B-cells				
median (full range (min-max))				
Naive B-cell compartment (n=196)	61.1 (5.3 to 102.9)			
Transitional B-cells (n=196)	1.4 (0.1 to 18.8)			
Naive B-cells (n=196)	58.1 (3.4 to 94.2)			
Memory including double-negative (n=46)	56.4 (20.2 to 103.5)			

Memory excluding double-negative (n=194)	46.5 (5.6 to 125.8)			
Pre-switch memory B-cells (n=196)	11.1 (1.3 to 73.6)			
Post-switch memory B-cells (n=196)	16.4 (0.8 to 58.1)			
IgG-positive class-switched B-cells (n=195)	9.9 (0.3 to 42)			
IgA-positive class-switched B-cells (n=194)	7.4 (0.7 to 35.6)			
Double-negative B-cells (n=46)	6.1 (2.5 to 16.3)			
Plasmablasts (n=196)	0.3 (0 to 19.9)			

Notes:

[17] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Spearman's Rank Correlation Coefficient Between Percentage of B-Cells at Baseline and Difference in DAS28 Scores Between Baseline and Week 16 Among Participants With Early Remission

End point title	Spearman's Rank Correlation Coefficient Between Percentage of B-Cells at Baseline and Difference in DAS28 Scores Between Baseline and Week 16 Among Participants With Early Remission

End point description:

Blood samples were collected to analyze total B-cell panel via immunophenotyping. Subpopulations were as follows: transitional, naïve, pre-switch memory, post-switch memory, IgG-positive class-switched, IgA-positive class-switched, double-negative memory, and plasmablasts. Naive B-cell compartment was defined as the sum of transitional and naive B-cells. The sum of memory B-cell subsets with or without double-negative B-cells was also determined. Extent of disease response, using change from Baseline to Week 16 in DAS28 score, was correlated to the percentage of B-cells within each subpopulation at Baseline. Correlation is indicated by a correlation coefficient (r) >0.2, with greater values indicating a stronger correlation. ITT1 Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	217[18]			
Units: coefficient				
number (not applicable)				
Naive B-cell compartment (n=192)	-0.02258			
Transitional B-cells (n=192)	-0.00949			
Naive B-cells (n=192)	-0.0192			
Memory B-cells (n=62)	-0.03148			
Pre-switch memory B-cells (n=192)	0.03221			
Post-switch memory B-cells (n=192)	0.05419			
IgG-positive class-switched B-cells (n=192)	0.08864			

IgA-positive class-switched B-cells (n=192)	0.01041			
Double-negative B-cells (n=62)	-0.02134			
Plasmablasts (n=192)	0.00397			

Notes:

[18] - n = number of data pairs included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Spearman's Rank Correlation Coefficient Between Percentage of B-Cells at Baseline and Difference in DAS28 Scores Between Baseline and Weeks 16, 24, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point title	Spearman's Rank Correlation Coefficient Between Percentage of B-Cells at Baseline and Difference in DAS28 Scores Between Baseline and Weeks 16, 24, and 32 Among Participants Treated With 8 Courses of Tocilizumab

End point description:

Blood samples were collected to analyze total B-cell panel via immunophenotyping. Subpopulations were as follows: transitional, naïve, pre-switch memory, post-switch memory, IgG-positive class-switched, IgA-positive class-switched, double-negative memory, and plasmablasts. Naive B-cell compartment was defined as the sum of transitional and naive B-cells. The sum of memory B-cell subsets with or without double-negative B-cells was also determined. Extent of disease response, using change from Baseline in DAS28 score, was correlated to the percentage of B-cells within each subpopulation at Baseline. Correlation is indicated by a correlation coefficient (r) >0.2, with greater values indicating a stronger correlation. ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 16, 24, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	213[19]			
Units: coefficient				
number (not applicable)				
Week 16, Naive B-cell compartment (n=199)	0.00007			
Week 16, Transitional B-cells (n=199)	-0.06529			
Week 16, Naive B-cells (n=199)	0.02334			
Week 16, Memory B-cells (n=75)	-0.03478			
Week 16, Pre-switch memory B-cells (n=199)	-0.01889			
Week 16, Post-switch memory B-cells (n=199)	-0.04161			
Week 16, IgG-positive class-switched (n=199)	-0.06235			
Week 16, IgA-positive class-switched (n=199)	-0.06492			
Week 16, Double-negative B-cells (n=75)	-0.04352			
Week 16, Plasmablasts (n=199)	-0.13161			

Week 24, Naive B-cell compartment (n=162)	-0.18469			
Week 24, Transitional B-cells (n=162)	-0.21966			
Week 24, Naive B-cells (n=162)	-0.15683			
Week 24, Memory B-cells (n=76)	0.15135			
Week 24, Pre-switch memory B-cells (n=162)	0.08074			
Week 24, Post-switch memory B-cells (n=162)	0.10798			
Week 24, IgG-positive class-switched (n=161)	0.10752			
Week 24, IgA-positive class-switched (n=162)	0.11023			
Week 24, Double-negative B-cells (n=76)	0.05609			
Week 24, Plasmablasts (n=162)	0.07468			
Week 32, Naive B-cell compartment (n=179)	-0.12635			
Week 32, Transitional B-cells (n=179)	-0.09234			
Week 32, Naive B-cells (n=179)	-0.11114			
Week 32, Memory B-cells (n=88)	0.05361			
Week 32, Pre-switch memory B-cells (n=179)	0.12265			
Week 32, Post-switch memory B-cells (n=179)	0.05867			
Week 32, IgG-positive class-switched (n=181)	0.06381			
Week 32, IgA-positive class-switched (n=181)	0.06036			
Week 32, Double-negative B-cells (n=90)	-0.0631			
Week 32, Plasmablasts (n=179)	0.02205			

Notes:

[19] - n = number of data pairs included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Spearman's Rank Correlation Coefficient Between Percentage of B-Cells at Baseline and Difference in DAS28 Scores Between Baseline and Weeks 16, 32, 40, 48, and 66 Among Nonresponding Participants Treated With Rituximab

End point title	Spearman's Rank Correlation Coefficient Between Percentage of B-Cells at Baseline and Difference in DAS28 Scores Between Baseline and Weeks 16, 32, 40, 48, and 66 Among Nonresponding Participants Treated With Rituximab

End point description:

Blood samples were collected to analyze total B-cell panel via immunophenotyping. Subpopulations were as follows: transitional, naïve, pre-switch memory, post-switch memory, IgG-positive class-switched, IgA-positive class-switched, double-negative memory, and plasmablasts. Naive B-cell compartment was defined as the sum of transitional and naive B-cells. The sum of memory B-cell subsets with or without double-negative B-cells was also determined. Extent of disease response, using change from Baseline in DAS28 score, was correlated to the percentage of B-cells within each subpopulation at Baseline. Correlation is indicated by a correlation coefficient (r) >0.2, with greater values indicating a stronger correlation. ITT3 Population. (99999 = not estimable because participants in this population were followed for changes in DAS28 up to Week 16 compared to Baseline, and for changes up to Week 66 compared to Week 16; 9999 = not estimable for 0 pairs; 999 = not estimable for 1 pair.)

End point type	Secondary

End point timeframe:
Baseline and Weeks 16, 32, 40, 48, and 66

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	27[20]			
Units: coefficient				
number (not applicable)				
Week 16, Naive B-cell compartment (n=24)	0.09611			
Week 16, Transitional B-cells (n=24)	0.08571			
Week 16, Naive B-cells (n=24)	0.0087			
Week 16, Memory B-cells (n=6)	-0.6			
Week 16, Pre-switch memory B-cells (n=24)	-0.15217			
Week 16, Post-switch memory B-cells (n=24)	-0.04004			
Week 16, IgG-positive class-switched (n=24)	-0.07528			
Week 16, IgA-positive class-switched (n=24)	0.27049			
Week 16, Double-negative B-cells (n=6)	-0.14286			
Week 16, Plasmablasts (n=24)	0.13232			
Week 32, Naive B-cell compartment (n=0)	99999			
Week 32, Transitional B-cells (n=0)	99999			
Week 32, Naive B-cells (n=0)	99999			
Week 32, Memory B-cells (n=0)	99999			
Week 32, Pre-switch memory B-cells (n=0)	99999			
Week 32, Post-switch memory B-cells (n=0)	99999			
Week 32, IgG-positive class-switched (n=0)	99999			
Week 32, IgA-positive class-switched (n=0)	99999			
Week 32, Double-negative B-cells (n=0)	99999			
Week 32, Plasmablasts (n=0)	99999			
Week 40, Naive B-cell compartment (n=2)	1			
Week 40, Transitional B-cells (n=2)	-1			
Week 40, Naive B-cells (n=2)	1			
Week 40, Memory B-cells (n=0)	9999			
Week 40, Pre-switch memory B-cells (n=2)	1			
Week 40, Post-switch memory B-cells (n=2)	1			
Week 40, IgG-positive class-switched (n=2)	1			
Week 40, IgA-positive class-switched (n=2)	1			
Week 40, Double-negative B-cells (n=0)	9999			
Week 40, Plasmablasts (n=2)	1			

Week 48, Naive B-cell compartment (n=5)	0.3			
Week 48, Transitional B-cells (n=5)	-0.6			
Week 48, Naive B-cells (n=5)	0.3			
Week 48, Memory B-cells (n=1)	999			
Week 48, Pre-switch memory B-cells (n=5)	0.6			
Week 48, Post-switch memory B-cells (n=5)	0.2			
Week 48, IgG-positive class-switched (n=5)	0.2			
Week 48, IgA-positive class-switched (n=5)	0.5			
Week 48, Double-negative B-cells (n=1)	999			
Week 48, Plasmablasts (n=5)	0.1			
Week 66, Naive B-cell compartment (n=10)	0.12727			
Week 66, Transitional B-cells (n=10)	-0.0303			
Week 66, Naive B-cells (n=10)	0.04242			
Week 66, Memory B-cells (n=3)	1			
Week 66, Pre-switch memory B-cells (n=10)	-0.0303			
Week 66, Post-switch memory B-cells (n=10)	0.16364			
Week 66, IgG-positive class-switched (n=10)	0.07295			
Week 66, IgA-positive class-switched (n=10)	0.12805			
Week 66, Double-negative B-cells (n=3)	1			
Week 66, Plasmablasts (n=10)	0.30909			

Notes:

[20] - n = number of data pairs included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Work Days Missed Per Week

End point title	Mean Number of Work Days Missed Per Week

End point description:

Work days missed were documented by reason (either RA or other reasons) for each participant over the preceding 7-day period. The mean number of work days missed was calculated by averaging the number of days missed per week among all participants. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	241[21]			
Units: days				
arithmetic mean (standard deviation)				
Due to RA, Baseline (n=241)	1.03 (± 2.3)			
Due to RA, Week 16 (n=221)	0.39 (± 1.51)			
Due to other reasons, Baseline (n=233)	0.14 (± 0.87)			
Due to other reasons, Week 16 (n=222)	0.32 (± 1.26)			

Notes:

[21] - Employed participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life as Assessed Using Short Form 36 (SF-36)

End point title	Quality of Life as Assessed Using Short Form 36 (SF-36)

End point description:

The SF-36 evaluates participant-rated quality of life using 8 domains: physical and social functioning, physical and emotional role limitations, bodily pain, general health, vitality, and mental health. The score for each section is the average of the individual question scores, which are scaled from 0 to 100, with higher scores indicating better functioning. The mean score at each timepoint was determined by averaging the scores among all participants. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	513[22]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical functioning, Baseline (n=511)	49.6 (± 23.7)			
Physical functioning, Week 16 (n=473)	64.1 (± 25.5)			
Role (physical), Baseline (n=508)	12.9 (± 18.1)			
Role (physical), Week 16 (n=472)	29.9 (± 21.4)			
Bodily pain, Baseline (n=512)	31.3 (± 18.2)			
Bodily pain, Week 16 (n=474)	55.3 (± 17.8)			
General health, Baseline (n=504)	43.6 (± 16.7)			
General health, Week 16 (n=468)	54.3 (± 18.3)			
Vitality, Baseline (n=512)	44 (± 19.7)			
Vitality, Week 16 (n=474)	58.1 (± 20.4)			
Social functioning, Baseline (n=507)	68.1 (± 24.8)			
Social functioning, Week 16 (n=464)	80.1 (± 21.6)			
Role (emotional), Baseline (n=505)	55.9 (± 45)			
Role (emotional), Week 16 (n=472)	70.9 (± 42.1)			
Mental health, Baseline (n=513)	63.5 (± 18.7)			

Mental health, Week 16 (n=474)	72.3 (± 17.9)			

Notes:

[22] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life as Assessed Using SF-36 at Week 16

End point title	Change From Baseline in Quality of Life as Assessed Using SF-36 at Week 16

End point description:

The SF-36 evaluates participant-rated quality of life using 8 domains: physical and social functioning, physical and emotional role limitations, bodily pain, general health, vitality, and mental health. The score for each section is the average of the individual question scores, which are scaled from 0 to 100, with higher scores indicating better functioning. The mean score at each timepoint was determined by averaging the scores among all participants, and the change in each domain score was calculated as [mean score at Week 16 minus mean score at Baseline]. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	470[23]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical functioning (n=466)	14.3 (± 21.8)			
Role (physical) (n=461)	17 (± 22)			
Bodily pain (n=470)	23.9 (± 21.1)			
General health (n=454)	10.4 (± 18.5)			
Vitality (n=468)	13.9 (± 19.3)			
Social functioning (n=456)	12 (± 23.8)			
Role (emotional) (n=459)	14.7 (± 46.1)			
Mental health (n=468)	8.7 (± 16.8)			

Notes:

[23] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 16 to 32 in Quality of Life as Assessed Using SF-36 Scores Among Participants Treated With 8 Courses of Tocilizumab

End point title	Change From Week 16 to 32 in Quality of Life as Assessed Using SF-36 Scores Among Participants Treated With 8 Courses of Tocilizumab

End point description:

The SF-36 evaluates participant-rated quality of life using 8 domains: physical and social functioning, physical and emotional role limitations, bodily pain, general health, vitality, and mental health. The score for each section is the average of the individual question scores, which are scaled from 0 to 100, with higher scores indicating better functioning. The mean score at each timepoint was determined by averaging the scores among all participants, and the change in each domain score was calculated as [mean score at Week 32 minus mean score at Week 16]. ITT2 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	188[24]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical functioning (n=188)	3.6 (± 16.6)			
Role (physical) (n=187)	2 (± 20.6)			
Bodily pain (n=188)	3.2 (± 16.5)			
General health (n=184)	2.6 (± 14.3)			
Vitality (n=186)	2.7 (± 14.2)			
Social functioning (n=184)	-0.3 (± 19.6)			
Role (emotional) (n=184)	5.5 (± 42.3)			
Mental health (n=186)	0.7 (± 15.3)			

Notes:

[24] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life as Assessed Using HAQ-DI

End point title	Quality of Life as Assessed Using HAQ-DI

End point description:

The HAQ-DI evaluates participant-reported quality of life using 8 categories: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other common activities such as running errands and performing household chores. Each category contains multiple questions, which are answered using a 4-point scale from 0 to 3. The overall index score is taken as an average of the individual item responses and may range from 0 to 3, where higher scores indicate more difficulty in daily living activities. The mean index score at each timepoint was determined by averaging the scores among all participants. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	513[25]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=513)	1.24 (± 0.67)			
Week 16 (n=472)	0.75 (± 0.67)			

Notes:

[25] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life as Assessed Using HAQ-DI at Week 16

End point title	Change From Baseline in Quality of Life as Assessed Using HAQ-DI at Week 16

End point description:

The HAQ-DI evaluates participant-reported quality of life using 8 categories: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other common activities such as running errands and performing household chores. Each category contains multiple questions, which are answered using a 4-point scale from 0 to 3. The overall index score is taken as an average of the individual item responses and may range from 0 to 3, where higher scores indicate more difficulty in daily living activities. The mean index score at each timepoint was determined by averaging the scores among all participants, and the change in score was calculated as [mean score at Week 16 minus mean score at Baseline]. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	466[26]			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.48 (± 0.58)			

Notes:

[26] - Participants with evaluable data at the designated visit were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 16 to 32 in Quality of Life as Assessed Using HAQ-DI Among Participants Treated With 8 Courses of Tocilizumab

End point title	Change From Week 16 to 32 in Quality of Life as Assessed Using HAQ-DI Among Participants Treated With 8 Courses of Tocilizumab

End point description:

The HAQ-DI evaluates participant-reported quality of life using 8 categories: dressing/grooming, arising,

eating, walking, hygiene, reach, grip, and other common activities such as running errands and performing household chores. Each category contains multiple questions, which are answered using a 4-point scale from 0 to 3. The overall index score is taken as an average of the individual item responses and may range from 0 to 3, where higher scores indicate more difficulty in daily living activities. The mean index score at each timepoint was determined by averaging the scores among all participants, and the change in score was calculated as [mean score at Week 32 minus the mean score at Week 16]. ITT2 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	187[27]			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.06 (± 0.34)			

Notes:

[27] - Participants with evaluable data at the designated visit were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a Response According to HAQ-DI Criteria

End point title	Percentage of Participants Achieving a Response According to HAQ-DI Criteria

End point description:

The HAQ-DI evaluates participant-reported quality of life using 8 categories: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other common activities such as running errands and performing household chores. Each category contains multiple questions, which are answered using a 4-point scale from 0 to 3. The overall index score is taken as an average of the individual item responses and may range from 0 to 3, where higher scores indicate more difficulty in daily living activities. Response was defined as a change in index score >0.22 from Baseline to Week 16. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	519			
Units: percentage of participants				
number (not applicable)	61.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life as Assessed Using Functional Assessment of Chronic Illness Therapy (FACIT)

End point title	Quality of Life as Assessed Using Functional Assessment of Chronic Illness Therapy (FACIT)

End point description:

The FACIT-F evaluates quality of life using 5 categories: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and fatigue (FS). Participants answer each item on a 5-point scale from 0 to 4. The total score is the sum of individual responses across all 5 categories and may range from 0 to 160. The FACIT-General (FACIT-G; range 0 to 108) is the sum of scores for PWB, SWB, EWB, and FWB; the FACIT-Fatigue (FACIT-F) trial outcome index (TOI; range 0 to 108) is the sum of scores for PWB, FWB, and FS; and the FACIT-F fatigue (range 0 to 52) is the sum of scores for the FS only. For derivations of the FACIT-F reported here, higher scores indicate better quality of life. The mean score at each timepoint was determined by averaging scores among all participants. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	510[28]			
Units: units on a scale				
arithmetic mean (standard deviation)				
FACIT-F TOI, Baseline (n=498)	66.2 (± 20.6)			
FACIT-F TOI, Week 16 (n=460)	80.8 (± 19.3)			
FACIT-G total, Baseline (n=498)	71.1 (± 15.7)			
FACIT-G total, Week 16 (n=462)	82.6 (± 15.9)			
FACIT-F total, Baseline (n=494)	103.8 (± 25.5)			
FACIT-F total, Week 16 (n=458)	121.9 (± 25.3)			
FACIT-F fatigue, Baseline (n=510)	32.7 (± 11.6)			
FACIT-F fatigue, Week 16 (n=475)	39.2 (± 10.6)			

Notes:

[28] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life as Assessed Using FACIT at Week 16

End point title	Change From Baseline in Quality of Life as Assessed Using FACIT at Week 16

End point description:

The FACIT-F evaluates quality of life using 5 categories: PWB, SWB, EWB, FWB, and FS. Participants answer each item on a 5-point scale from 0 to 4. The total score is the sum of individual responses across all 5 categories and may range from 0 to 160. The FACIT-G (range 0 to 108) is the sum of scores for PWB, SWB, EWB, and FWB; the FACIT-F TOI (range 0 to 108) is the sum of scores for PWB, FWB, and FS; and the FACIT-F fatigue (range 0 to 52) is the sum of scores for the FS only. For derivations of the FACIT-F reported here, higher scores indicate better quality of life. The mean score at each timepoint was determined by averaging scores among all participants, and the change in score was

calculated as [mean score at Week 16 minus mean score at Baseline]. Main ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	467[29]			
Units: units on a scale				
arithmetic mean (standard deviation)				
FACIT-F TOI (n=445)	14.2 (± 17.9)			
FACIT-G total (n=445)	10.8 (± 13.6)			
FACIT-F total (n=439)	17.5 (± 21.8)			
FACIT-F fatigue (n=467)	6.6 (± 9.9)			

Notes:

[29] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 16 to 32 in Quality of Life as Assessed Using FACIT Among Participants Treated With 8 Courses of Tocilizumab

End point title	Change From Week 16 to 32 in Quality of Life as Assessed Using FACIT Among Participants Treated With 8 Courses of Tocilizumab

End point description:

The FACIT-F evaluates quality of life using 5 categories: PWB, SWB, EWB, FWB, and FS. Participants answer each item on a 5-point scale from 0 to 4. The total score is the sum of individual responses across all 5 categories and may range from 0 to 160. The FACIT-G (range 0 to 108) is the sum of scores for PWB, SWB, EWB, and FWB; the FACIT-F TOI (range 0 to 108) is the sum of scores for PWB, FWB, and FS; and the FACIT-F fatigue (range 0 to 52) is the sum of scores for the FS only. For derivations of the FACIT-F reported here, higher scores indicate better quality of life. The mean score at each timepoint was determined by averaging scores among all participants, and the change in score was calculated as [mean score at Week 32 minus mean score at Week 16]. ITT2 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	186[30]			
Units: units on a scale				
arithmetic mean (standard deviation)				
FACIT-F TOI (n=172)	1.7 (± 12.9)			
FACIT-G total (n=174)	1.1 (± 9.2)			
FACIT-F total (n=170)	2 (± 15.1)			

FACIT-F fatigue (n=186)	0.8 (± 7.4)			

Notes:

[30] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Remission According to DAS28 at Week 32 Among Nonresponding Participants Treated With Rituximab

End point title	Percentage of Participants Achieving Remission According to DAS28 at Week 32 Among Nonresponding Participants Treated With Rituximab

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. Remission was defined as a DAS28 score <2.6 at the assessment visit. ITT3 Population.

End point type	Secondary

End point timeframe:

Week 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of participants				
number (confidence interval 95%)	14.8 (4.2 to 33.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving LDAS According to DAS28 Among Nonresponding Participants Treated With Rituximab

End point title	Percentage of Participants Achieving LDAS According to DAS28 Among Nonresponding Participants Treated With Rituximab

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x the patient global assessment of disease activity using a VAS]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. LDAS was defined as a DAS28 score <3.2 at the assessment visit. ITT3 Population.

End point type	Secondary

End point timeframe:

Week 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of participants				
number (confidence interval 95%)	33.3 (16.5 to 54)			

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 Scores During and After Treatment Among Participants Treated With 8 Courses of Tocilizumab

End point title	DAS28 Scores During and After Treatment Among Participants Treated With 8 Courses of Tocilizumab

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	213[31]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=213)	6 (± 0.9)			
Week 4 (n=213)	4 (± 1.2)			
Week 8 (n=205)	3.4 (± 1.2)			
Week 12 (n=207)	3.3 (± 1.1)			
Week 16 (n=213)	3.3 (± 0.6)			
Week 20 (n=206)	2.8 (± 1)			
Week 24 (n=197)	2.6 (± 1.1)			
Week 28 (n=200)	2.4 (± 1.1)			
Week 32 (n=193)	2.5 (± 1.2)			

Notes:

[31] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 Scores During and After Treatment Among Nonresponding Participants Treated With Rituximab

End point title	DAS28 Scores During and After Treatment Among Nonresponding Participants Treated With Rituximab

End point description:

The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x VAS patient global assessment of disease activity]. VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity.' DAS28 scores ranged from 0 to 10, with higher scores indicating increased disease activity. ITT3 Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, 16, 24, and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	27[32]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=27)	5.7 (± 1)			
Week 4 (n=27)	4.5 (± 1.2)			
Week 8 (n=26)	4.2 (± 1.5)			
Week 12 (n=27)	4.8 (± 1.6)			
Week 16 (n=27)	5.1 (± 1.2)			
Week 24 (n=26)	4.6 (± 1.4)			
Week 32 (n=26)	4 (± 1.5)			

Notes:

[32] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of B-Cells at Baseline by B-Cell Subpopulation Among Participants Treated With 8 Courses of Tocilizumab

End point title	Percentage of B-Cells at Baseline by B-Cell Subpopulation Among Participants Treated With 8 Courses of Tocilizumab

End point description:

Blood samples were collected to analyze total B-cell panel via immunophenotyping. Subpopulations were

as follows: transitional (cluster of differentiation [CD] 19-positive, immunoglobulin (Ig) D-positive, CD38 medium, CD10-positive); naive (CD19-positive, IgD-positive, CD38 medium, CD27-negative); pre-switch memory (CD19-positive, CD27-positive, IgD-positive); post-switch memory (CD19-positive, CD27-positive, IgD-negative); IgG-positive class-switched (CD19-positive, IgG-positive); IgA-positive class-switched (CD19-positive, IgA-positive); double-negative memory (CD19-positive, IgD-negative, CD27-negative); and plasmablasts (CD19-positive, IgD-negative, CD38 high, CD27 high). Naive B-cell compartment was defined as the sum of transitional and naive B-cells. The sum of memory B-cell subsets with or without double-negative B-cells was also determined. ITT2 Population.

End point type	Secondary

End point timeframe:

Baseline

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	197[33]			
Units: percentage of B-cells				
median (full range (min-max))				
Naive B-cell compartment (n=197)	57.1 (5.6 to 91.2)			
Transitional B-cells (n=197)	1.3 (0 to 13.4)			
Naive B-cells (n=197)	55.5 (4.7 to 87.1)			
Memory including double-negative (n=57)	63.2 (18.8 to 113.7)			
Memory excluding double-negative (n=196)	49.7 (10.9 to 120.1)			
Pre-switch memory B-cells (n=197)	11.6 (0.9 to 74.1)			
Post-switch memory B-cells (n=197)	17.2 (2.8 to 52.7)			
IgG-positive class-switched B-cells (n=196)	10 (0.2 to 38.4)			
IgA-positive class-switched B-cells (n=196)	8 (1.4 to 34.4)			
Double-negative B-cells (n=57)	6.6 (1.2 to 19.1)			
Plasmablasts (n=197)	0.3 (0 to 7.6)			

Notes:

[33] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of B-Cells at Baseline by B-Cell Subpopulation Among Nonresponding Participants Treated With Rituximab

End point title	Percentage of B-Cells at Baseline by B-Cell Subpopulation Among Nonresponding Participants Treated With Rituximab

End point description:

Blood samples were collected to analyze total B-cell panel via immunophenotyping. Subpopulations were as follows: transitional (cluster of differentiation [CD] 19-positive, immunoglobulin (Ig) D-positive, CD38 medium, CD10-positive); naive (CD19-positive, IgD-positive, CD38 medium, CD27-negative); pre-switch memory (CD19-positive, CD27-positive, IgD-positive); post-switch memory (CD19-positive, CD27-positive, IgD-negative); IgG-positive class-switched (CD19-positive, IgG-positive); IgA-positive

class-switched (CD19-positive, IgA-positive); double-negative memory (CD19-positive, IgD-negative, CD27-negative); and plasmablasts (CD19-positive, IgD-negative, CD38 high, CD27 high). Naive B-cell compartment was defined as the sum of transitional and naive B-cells. The sum of memory B-cell subsets with or without double-negative B-cells was also determined. ITT3 Population.

End point type	Secondary

End point timeframe:

Baseline

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	25[34]			
Units: percentage of B-cells				
median (full range (min-max))				
Naive B-cell compartment (n=25)	65.9 (9.8 to 85)			
Transitional B-cells (n=25)	1.6 (0.2 to 7)			
Naive B-cells (n=25)	61.9 (5.8 to 83.4)			
Memory including double-negative (n=4)	45.1 (37.1 to 86.7)			
Memory excluding double-negative (n=25)	41.5 (21.6 to 139.6)			
Pre-switch memory B-cells (n=25)	9.1 (2.4 to 36.2)			
Post-switch memory B-cells (n=25)	16.1 (6.9 to 64.1)			
IgG-positive class-switched B-cells (n=25)	8.7 (5 to 32.7)			
IgA-positive class-switched B-cells (n=25)	7.7 (3.4 to 29.3)			
Double-negative B-cells (n=4)	7.5 (5.9 to 9.1)			
Plasmablasts (n=25)	0.3 (0 to 3.2)			

Notes:

[34] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 16 to 32 in Quality of Life as Assessed Using SF-36 Scores Among Nonresponding Participants Treated With Rituximab

End point title	Change From Week 16 to 32 in Quality of Life as Assessed Using SF-36 Scores Among Nonresponding Participants Treated With Rituximab

End point description:

The SF-36 evaluates participant-rated quality of life using 8 domains: physical and social functioning, physical and emotional role limitations, bodily pain, general health, vitality, and mental health. The score for each section is the average of the individual question scores, which are scaled from 0 to 100, with higher scores indicating better functioning. The mean score at each timepoint was determined by averaging the scores among all participants, and the change in each domain score was calculated as [mean score at Week 32 minus mean score at Week 16]. ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	26[35]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical functioning (n=26)	2.5 (± 20)			
Role (physical) (n=24)	-1 (± 21.5)			
Bodily pain (n=26)	10.6 (± 20.8)			
General health (n=24)	5.2 (± 18.1)			
Vitality (n=26)	1 (± 9.3)			
Social functioning (n=24)	-3.1 (± 17.4)			
Role (emotional) (n=24)	2.8 (± 35.3)			
Mental health (n=26)	3.4 (± 10.7)			

Notes:

[35] - Participants with evaluable data at the designated visit (number shown = n) were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 16 to 32 in Quality of Life as Assessed Using HAQ-DI Among Nonresponding Participants Treated With Rituximab

End point title	Change From Week 16 to 32 in Quality of Life as Assessed Using HAQ-DI Among Nonresponding Participants Treated With Rituximab

End point description:

The HAQ-DI evaluates participant-reported quality of life using 8 categories: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other common activities such as running errands and performing household chores. Each category contains multiple questions, which are answered using a 4-point scale from 0 to 3. The overall index score is taken as an average of the individual item responses and may range from 0 to 3, where higher scores indicate more difficulty in daily living activities. The mean index score at each timepoint was determined by averaging the scores among all participants, and the change in score was calculated as [mean score at Week 32 minus the mean score at Week 16]. ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	26[36]			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.1 (± 0.39)			

Notes:

[36] - Participants with evaluable data at the designated visit were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 16 to 32 in Quality of Life as Assessed Using FACIT Among Nonresponding Participants Treated With Rituximab

End point title	Change From Week 16 to 32 in Quality of Life as Assessed Using FACIT Among Nonresponding Participants Treated With Rituximab

End point description:

The FACIT-F evaluates quality of life using 5 categories: PWB, SWB, EWB, FWB, and FS. Participants answer each item on a 5-point scale from 0 to 4. The total score is the sum of individual responses across all 5 categories and may range from 0 to 160. The FACIT-G (range 0 to 108) is the sum of scores for PWB, SWB, EWB, and FWB; the FACIT-F TOI (range 0 to 108) is the sum of scores for PWB, FWB, and FS; and the FACIT-F fatigue (range 0 to 52) is the sum of scores for the FS only. For derivations of the FACIT-F reported here, higher scores indicate better quality of life. The mean score at each timepoint was determined by averaging scores among all participants, and the change in score was calculated as [mean score at Week 32 minus mean score at Week 16]. ITT3 Population.

End point type	Secondary

End point timeframe:

Weeks 16 and 32

End point values	TCZ/TCZ or TCZ/RTX			
Subject group type	Reporting group			
Number of subjects analysed	26[37]			
Units: units on a scale				
arithmetic mean (standard deviation)				
FACIT-F TOI	2.9 (± 9.8)			
FACIT-G total	3 (± 8.3)			
FACIT-F total	4.4 (± 12.5)			
FACIT-F fatigue	1.4 (± 5.8)			

Notes:

[37] - Participants with evaluable data at the designated visit were included.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 66 weeks

Adverse event reporting additional description:

Adverse events (AEs) were assessed at each treatment visit from Baseline to Week 16, at which point participants having achieved early remission completed the study. Those who did not achieve early remission continued to receive treatment, and AEs were assessed until 4 weeks after last dose (TCZ/TCZ) or until Week 66 (TCZ/RTX).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	TCZ/TCZ or TCZ/RTX

Reporting group description:

All participants were assigned to receive TCZ 8 mg/kg via IV infusion every 4 weeks for a total of 4 infusions from Baseline to Week 12. Clinical response was assessed at Week 16 using DAS28 to determine subsequent treatment assignment. Participants who achieved early remission, defined as a DAS28 score of <2.6, were transferred to clinical routine care and no longer received study medication. Participants who were considered partial responders, defined as a decrease from Baseline in DAS28 score >1.2 or a score between 2.6 and 3.2, inclusive, received TCZ 8 mg/kg via IV infusion every 4 weeks for a total of 4 additional infusions from Week 16 to 28. Those with assessed as having no response, defined as a decrease from Baseline in DAS28 score ≤1.2 or a score >3.2, received RTX 1000 mg via IV infusion at Weeks 16 and 18.

Serious adverse events	TCZ/TCZ or TCZ/RTX		
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 519 (10.40%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			

subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 519 (0.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Allergic cough			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			

subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperventilation				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibrin D dimer increased				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver function test abnormal				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Craniocerebral injury				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Fall				
subjects affected / exposed	2 / 519 (0.39%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Contusion				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infusion related reaction				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				

subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial haematoma			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			

subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 519 (0.39%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal perforation			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	3 / 519 (0.58%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Rheumatoid arthritis			
subjects affected / exposed	2 / 519 (0.39%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Joint destruction			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Osteoarthritis				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sacroiliitis				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	3 / 519 (0.58%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	2 / 519 (0.39%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 519 (0.39%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Abscess limb				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	1 / 519 (0.19%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gangrene				

subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 519 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TCZ/TCZ or TCZ/RTX		
Total subjects affected by non-serious adverse events subjects affected / exposed	104 / 519 (20.04%)		
Vascular disorders Hypertension subjects affected / exposed	30 / 519 (5.78%)		
occurrences (all)	32		
Infections and infestations Nasopharyngitis subjects affected / exposed	77 / 519 (14.84%)		
occurrences (all)	91		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2012	The protocol was amended to clarify inclusion and exclusion criteria, and to allow the enrollment of participants receiving methotrexate and leflunomide up to 4 weeks prior to Baseline. Safety follow-up was also planned for participants who withdrew from the study early. Definitions and procedures for TCZ-related hypersensitivity were implemented, and the reporting requirements for AEs were also modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported