Clinical trial results:
Open-Label, Phase IIIb Study to Evaluate the Efficacy and Safety of Subcutaneous (SC) Tocilizumab Monotherapy or Combination Therapy with Methotrexate (MTX) or Other Non-Biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) in Patients With Active Rheumatoid Arthritis (RA) Who Have an Inadequate Response to Current Non-Biologic DMARD Therapy or the First Anti-Tumour Necrosis Factor (Anti-TNF) Biologic Agent

Summary

EudraCT number	2013-000054-22
Trial protocol	GB
Global end of trial date	04 August 2016

Results information

Result version number	v2 (current)
This version publication date	10 June 2018
First version publication date	21 July 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	ML28641

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02046603
WHO universal trial number (UTN)	-
Other trial identifiers	Hoffmann-La Roche: ACT-MOVE

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy of switching to subcutaneous (SC) tocilizumab (as monotherapy or in combination with methotrexate or other non-biologic disease modifying antirheumatic drugs [DMARDs]) in participants who had an inadequate response to current non-biologic methotrexate therapy or the first anti-tumor necrosis factor (anti-TNF) biologic agent (as monotherapy or in combination with methotrexate or other non-biologic DMARDs).

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice according to the regulations and procedures described in the study protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 161
Worldwide total number of subjects	161
EEA total number of subjects	161

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)	126
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 162 participants were enrolled. One participant who did not receive a dose of tocilizumab was excluded from the full analysis set (FAS) and the results are reported for 161 participants.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tocilizumab Monotherapy

Arm description:

Participants received a weekly SC injection of tocilizumab 162 milligrams (mg) as monotherapy for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra, Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Tocilizumab 162 mg was administered once a week by SC injection and as a single fixed dose, irrespective of body weight, for the treatment duration of 52 weeks.

Arm title	Tocilizumab in Combination With Methotrexate or Other DMARDs

Arm description:

Participants received a weekly SC injection of tocilizumab 162 mg in combination with methotrexate or other non-biologic DMARDs for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra, Actemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Tocilizumab 162 mg was administered once a week by SC injection and as a single fixed dose, irrespective of body weight, for the treatment duration of 52 weeks.

Number of subjects in period 1	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs
Started	21	140
Completed	7	65
Not completed	14	75
Participant/legal guardian decision	1	3
Physician decision	1	1
Adverse Event	-	1
Death	-	1
Unspecified	11	66
Lost to follow-up	1	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab Monotherapy
Reporting group description:	
Participants received a weekly SC injection of tocilizumab 162 milligrams (mg) as monotherapy for 52 weeks.	
Reporting group title	Tocilizumab in Combination With Methotrexate or Other DMARDs
Reporting group description:	
Participants received a weekly SC injection of tocilizumab 162 mg in combination with methotrexate or other non-biologic DMARDs for 52 weeks.	

Reporting group values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs	Total
Number of subjects	21	140	161
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	53.9	55.3	
standard deviation	± 13.63	± 10.76	-
Gender Categorical			
Units: Subjects			
Female	16	104	120
Male	5	36	41

End points

End points reporting groups

Reporting group title	Tocilizumab Monotherapy
Reporting group description:	
Participants received a weekly SC injection of tocilizumab 162 milligrams (mg) as monotherapy for 52 weeks.	
Reporting group title	Tocilizumab in Combination With Methotrexate or Other DMARDs
Reporting group description:	
Participants received a weekly SC injection of tocilizumab 162 mg in combination with methotrexate or other non-biologic DMARDs for 52 weeks.	

Primary: Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 2

End point title	Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 2[1]
End point description:	
DAS28 was calculated from swollen joint count (SJC) and tender joint count (TJC) using 28 joints count, erythrocyte sedimentation rate (ESR; millimeters per hour [mm/hour]), and patient's global assessment of disease activity (measured on 0 to 100 mm Visual Analog Scale [VAS] where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56×square root of TJC] + [0.28×square root of SJC] + [0.70×natural log (ESR)] + [0.014×VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR greater than or equal to (≥) 2.6 to less than or equal to (≤) 3.2 implied low disease activity, greater than (>) 3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and less than (<)2.6 implied clinical remission. FAS population included all participants who received at least 1 dose of SC tocilizumab. "Number of subjects analysed"=participants evaluable for this outcome. "n"=participants evaluable at specified timepoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 2	
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: No statistical analysis was planned for this end point.	

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	139		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=21, 139)	5.52 (± 1.014)	5.53 (± 1.257)		
Change at Week 2 (n=21, 137)	-1.41 (± 0.994)	-1.22 (± 1.131)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 4

End point title	Change From Baseline in DAS28-ESR at Week 4[2]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome

End point type	Primary

End point timeframe:

Baseline, Week 4

Notes:

[2] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	137		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.86 (± 1.016)	-2.11 (± 1.215)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 8

End point title	Change From Baseline in DAS28-ESR at Week 8[3]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 8

Notes:

[3] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	131		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.42 (± 1.352)	-2.62 (± 1.482)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 12

End point title	Change From Baseline in DAS28-ESR at Week 12[4]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 12

Notes:

[4] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	128		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.33 (± 1.522)	-2.99 (± 1.510)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 16

End point title	Change From Baseline in DAS28-ESR at Week 16[5]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 16

Notes:

[5] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	125		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.93 (± 1.218)	-3.07 (± 1.532)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 20

End point title	Change From Baseline in DAS28-ESR at Week 20[6]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 20

Notes:

[6] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	121		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.17 (± 1.346)	-3.13 (± 1.525)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 24

End point title	Change From Baseline in DAS28-ESR at Week 24[7]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[7] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	117		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.28 (± 1.379)	-3.33 (± 1.470)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 28

End point title	Change From Baseline in DAS28-ESR at Week 28[8]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 28

Notes:

[8] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	115		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.54 (± 1.260)	-3.32 (± 1.552)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 32

End point title	Change From Baseline in DAS28-ESR at Week 32[9]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 32

Notes:

[9] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	115		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.19 (± 1.418)	-3.54 (± 1.448)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 36

End point title	Change From Baseline in DAS28-ESR at Week 36[10]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 36

Notes:

[10] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	114		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.57 (± 1.358)	-3.55 (± 1.589)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 40

End point title	Change From Baseline in DAS28-ESR at Week 40[11]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 40

Notes:

[11] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	111		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.82 (± 1.143)	-3.64 (± 1.524)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 44

End point title	Change From Baseline in DAS28-ESR at Week 44[12]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 44

Notes:

[12] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	107		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.61 (± 1.325)	-3.65 (± 1.574)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 48

End point title	Change From Baseline in DAS28-ESR at Week 48[13]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 48

Notes:

[13] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	107		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.54 (± 1.146)	-3.65 (± 1.552)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 52

End point title	Change From Baseline in DAS28-ESR at Week 52[14]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 52

Notes:

[14] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	107		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.75 (± 1.361)	-3.67 (± 1.592)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Early Withdrawal

End point title	Change From Baseline in DAS28-ESR at Early Withdrawal[15]

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity, >3.2 to ≤5.1 implied moderate disease activity, >5.1 implied high/severe disease, and <2.6 implied clinical remission. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, early withdrawal (up to Week 52)

Notes:

[15] - 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: No statistical analysis was planned for this end point.

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	28		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.88 (± 1.236)	-1.63 (± 1.480)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an American College of Rheumatology Criteria 20 (ACR20) Response

End point title	Number of Participants Achieving an American College of Rheumatology Criteria 20 (ACR20) Response

End point description:

A participant had an ACR20 response if there was at least a 20 percent (%) improvement, ie, reduction from Baseline, in TJC (68 joints) and SJC (66 joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 2) Patient's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 3) Patient's Assessment of Pain [VAS: 0 mm=no pain to 100 mm=unbearable pain]; 4) Health Assessment Questionnaire [20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, averaged to 0=without difficulty to 3=unable to do] and 5) an acute-phase reactant (either C-reactive protein [CRP] or ESR). FAS population. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Week 2 (n=21, 137)	6	23		
Week 4 (n=21, 137)	6	68		
Week 8 (n=18, 132)	11	69		
Week 12 (n=19, 128)	10	83		
Week 16 (n=19, 125)	13	83		
Week 20 (n=19, 122)	15	86		
Week 24 (n=19, 117)	15	90		

Week 28 (n=19, 115)	14	87		
Week 32 (n=19, 115)	13	89		
Week 36 (n=18, 114)	12	92		
Week 40 (n=17, 111)	13	91		
Week 44 (n=17, 108)	12	88		
Week 48 (n=16, 107)	12	87		
Week 52 (n=16, 107)	12	88		
Early withdrawal (n=5, 29)	3	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an ACR50 Response

End point title	Number of Participants Achieving an ACR50 Response

End point description:

A participant had an ACR50 response if there was at least a 50% improvement, ie, reduction from Baseline, in TJC (68 joints) and SJC (66 joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 2) Patient's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 3) Patient's Assessment of Pain [VAS: 0 mm=no pain to 100 mm=unbearable pain]; 4) Health Assessment Questionnaire [20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, averaged to 0=without difficulty to 3=unable to do] and 5) an acute-phase reactant (either CRP or ESR). FAS population. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Week 2 (n=21, 137)	0	5		
Week 4 (n=21, 137)	3	20		
Week 8 (n=18, 132)	6	43		
Week 12 (n=19, 128)	8	54		
Week 16 (n=19, 125)	7	62		
Week 20 (n=19, 122)	9	61		
Week 24 (n=19, 117)	9	64		
Week 28 (n=19, 115)	13	68		
Week 32 (n=19, 115)	8	69		
Week 36 (n=18, 114)	9	74		

Week 40 (n=17, 111)	9	71		
Week 44 (n=17, 108)	10	72		
Week 48 (n=16, 107)	11	73		
Week 52 (n=16, 107)	8	73		
Early withdrawal (n=5, 29)	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an ACR70 Response

End point title	Number of Participants Achieving an ACR70 Response

End point description:

A participant had an ACR70 response if there was at least a 70% improvement, ie, reduction from Baseline, in TJC (68 joints) and SJC (66 joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 2) Patient's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 3) Patient's Assessment of Pain [VAS: 0 mm=no pain to 100 mm=unbearable pain]; 4) Health Assessment Questionnaire [20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, averaged to 0=without difficulty to 3=unable to do] and 5) an acute-phase reactant (either CRP or ESR). FAS population. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Week 2 (n=21, 137)	0	0		
Week 4 (n=21, 137)	1	9		
Week 8 (n=18, 132)	4	19		
Week 12 (n=19, 128)	3	30		
Week 16 (n=19, 125)	3	32		
Week 20 (n=19, 122)	7	37		
Week 24 (n=19, 117)	5	38		
Week 28 (n=19, 115)	6	44		
Week 32 (n=19, 115)	6	47		
Week 36 (n=18, 114)	7	48		
Week 40 (n=17, 111)	8	49		
Week 44 (n=17, 108)	6	53		
Week 48 (n=16, 107)	8	56		

Week 52 (n=16, 107)	7	54		
Early withdrawal (n=5, 29)	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With European League Against Rheumatism (EULAR) Response (Good, Moderate or No Response) Based on DAS28-ESR

End point title	Number of Participants With European League Against Rheumatism (EULAR) Response (Good, Moderate or No Response) Based on DAS28-ESR

End point description:

DAS28-ESR was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (VAS: 0 mm=no disease activity to 100 mm=maximum disease activity). DAS28-ESR scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. DAS28-ESR based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on extent of change from baseline and level of disease activity reached. Good responders had a change from baseline >1.2 with a DAS28 score ≤3.2; moderate responders had a change from baseline >1.2 with a DAS28 score >3.2 or a change from baseline >0.6 to ≤1.2 with a DAS28 score ≤5.1. Participants with change from baseline >0.6 to ≤1.2 with a DAS28 score >5.1, or any score with change from baseline ≤0.6, were assessed as non-responders. FAS population. "n"=participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Week 2 (n=21, 137): No response	4	56		
Week 2 (n=21, 137): Moderate response	10	56		
Week 2 (n=21, 137): Good response	7	25		
Week 4 (n=21, 137): No response	3	22		
Week 4 (n=21, 137): Moderate response	7	58		
Week 4 (n=21, 137): Good response	11	57		
Week 8 (n=18, 131): No response	1	11		
Week 8 (n=18, 131): Moderate response	9	48		
Week 8 (n=18, 131): Good response	8	72		

Week 12 (n=19, 128): No response	4	11		
Week 12 (n=19, 128): Moderate response	3	34		
Week 12 (n=19, 128): Good response	12	83		
Week 16 (n=18, 125): No response	1	9		
Week 16 (n=18, 125): Moderate response	4	30		
Week 16 (n=18, 125): Good response	13	86		
Week 20 (n=19, 121): No response	0	9		
Week 20 (n=19, 121): Moderate response	5	27		
Week 20 (n=19, 121): Good response	14	85		
Week 24 (n=19, 117): No response	1	7		
Week 24 (n=19, 117): Moderate response	2	21		
Week 24 (n=19, 117): Good response	16	89		
Week 28 (n=19, 115): No response	1	5		
Week 28 (n=19, 115): Moderate response	0	24		
Week 28 (n=19, 115): Good response	18	86		
Week 32 (n=19, 115): No response	1	3		
Week 32 (n=19, 115): Moderate response	2	21		
Week 32 (n=19, 115): Good response	16	91		
Week 36 (n=18, 114): No response	0	4		
Week 36 (n=18, 114): Moderate response	3	19		
Week 36 (n=18, 114): Good response	15	91		
Week 40 (n=17, 111): No response	0	2		
Week 40 (n=17, 111): Moderate response	1	15		
Week 40 (n=17, 111): Good response	16	94		
Week 44 (n=17, 107): No response	0	5		
Week 44 (n=17, 107): Moderate response	2	15		
Week 44 (n=17, 107): Good response	15	87		
Week 48 (n=16, 107): No response	0	4		
Week 48 (n=16, 107): Moderate response	2	13		
Week 48 (n=16, 107): Good response	14	90		
Week 52 (n=15, 107): No response	0	5		
Week 52 (n=15, 107): Moderate response	3	12		
Week 52 (n=15, 107): Good response	12	90		
Early Withdrawal (n=5, 28): No response	0	11		
Early Withdrawal (n=5, 28): Moderate response	1	8		
Early Withdrawal (n=5, 28): Good response	4	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simplified Disease Activity Index (SDAI) at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Early Withdrawal

End point title	Change From Baseline in Simplified Disease Activity Index (SDAI) at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Early Withdrawal

End point description:

The SDAI is the numerical sum of five outcome parameters: TJC and SJC based on a 28-joint assessment, patient and physician global assessment of disease activity assessed on 0-10 centimeter (cm) VAS (0 cm= no disease activity and 10 cm= worst disease activity), and CRP in milligrams per liter (mg/L). SDAI total score = 0-86. SDAI ≤3.3 indicates clinical remission, >3.3 to 11 = low disease activity, >11 to 26 = moderate disease activity, and >26 = high (or severe) disease activity. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	136		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=21, 136)	31.23 (± 11.892)	32.33 (± 11.620)		
Change at Week 2 (n=21, 132)	-9.80 (± 10.406)	-6.94 (± 9.710)		
Change at Week 4 (n=19, 131)	-12.64 (± 10.502)	-13.92 (± 10.666)		
Change at Week 8 (n=17, 127)	-19.75 (± 12.978)	-17.21 (± 12.900)		
Change at Week 12 (n=16, 120)	-14.65 (± 15.003)	-20.26 (± 12.739)		
Change at Week 16 (n=16, 118)	-19.48 (± 9.649)	-21.16 (± 11.945)		
Change at Week 20 (n=18, 115)	-23.67 (± 14.015)	-20.50 (± 11.630)		
Change at Week 24 (n=19, 112)	-24.31 (± 13.469)	-23.48 (± 12.417)		
Change at Week 28 (n=19, 109)	-24.87 (± 12.554)	-23.26 (± 12.418)		
Change at Week 32 (n=19, 109)	-22.98 (± 12.850)	-24.94 (± 11.399)		
Change at Week 36 (n=18, 107)	-26.32 (± 12.795)	-24.65 (± 11.268)		
Change at Week 40 (n=17, 106)	-27.29 (± 13.280)	-25.46 (± 12.210)		
Change at Week 44 (n=16, 101)	-27.71 (± 12.851)	-26.08 (± 11.835)		

Change at Week 48 (n=16, 102)	-26.83 (± 13.615)	-26.13 (± 11.189)		
Change at Week 52 (n=15, 104)	-27.45 (± 14.351)	-26.15 (± 12.791)		
Change at early withdrawal (n=5, 28)	-18.94 (± 14.681)	-9.45 (± 12.533)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Early Withdrawal

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Early Withdrawal

End point description:

The CDAI is the numerical sum of four outcome parameters: TJC and SJC based on a 28-joint assessment, patient and physician's global assessment of disease activity assessed on 0-10 cm VAS (0 cm= no disease activity and 10 cm= worst disease activity). CDAI total score = 0-76. CDAI ≤2.8 indicates clinical remission, >2.8 to 10 = low disease activity, >10 to 22 = moderate disease activity, and >22 = high (or severe) disease activity. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	139		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=21, 139)	29.69 (± 11.209)	30.88 (± 10.953)		
Change at Week 2 (n=21, 137)	-8.35 (± 10.433)	-5.16 (± 9.323)		
Change at Week 4 (n=21, 137)	-11.87 (± 10.062)	-12.26 (± 10.137)		
Change at Week 8 (n=18, 130)	-17.74 (± 12.289)	-15.63 (± 11.873)		
Change at Week 12 (n=19, 128)	-15.39 (± 14.216)	-18.66 (± 11.895)		
Change at Week 16 (n=19, 125)	-20.70 (± 11.694)	-19.51 (± 11.124)		
Change at Week 20 (n=18, 121)	-22.19 (± 13.545)	-19.23 (± 11.433)		

Change at Week 24 (n=19, 117)	-22.88 (± 12.720)	-21.96 (± 11.825)		
Change at Week 28 (n=19, 115)	-23.43 (± 11.573)	-21.48 (± 11.585)		
Change at Week 32 (n=19, 115)	-21.55 (± 12.019)	-23.20 (± 10.842)		
Change at Week 36 (n=18, 114)	-24.86 (± 11.854)	-23.10 (± 11.263)		
Change at Week 40 (n=17, 111)	-25.74 (± 12.488)	-24.01 (± 11.282)		
Change at Week 44 (n=17, 106)	-25.42 (± 11.971)	-24.42 (± 11.186)		
Change at Week 48 (n=16, 106)	-25.36 (± 12.718)	-24.59 (± 10.645)		
Change at Week 52 (n=16, 107)	-25.48 (± 13.049)	-24.42 (± 12.599)		
Change at early withdrawal (n=5, 29)	-17.78 (± 14.667)	-8.68 (± 11.909)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total TJC on 68 Joints at Week 52

End point title	Percent Change From Baseline in Total TJC on 68 Joints at Week 52

End point description:

Number of tender joints was determined by examining 68 joints and identified the joints that were painful under pressure or to passive motion. The number of tender joints was recorded on the joint assessment form at each visit, no tenderness = 0, tenderness = 1; total was calculated by adding all the joints for a maximum score of 68. A reduction in number of tender joints compared to baseline indicates improvement. The outcome is reported as the percent change from baseline to end of treatment (52 weeks). FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	106		
Units: percent change				
arithmetic mean (standard deviation)	-83.12 (± 26.607)	-80.44 (± 41.226)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total TJC on 28 Joints at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Early Withdrawal

End point title	Change From Baseline in Total TJC on 28 Joints at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Early Withdrawal

End point description:

Number of tender joints was determined by examining 28 joints and identified the joints that were painful under pressure or to passive motion. The number of tender joints was recorded on the joint assessment form at each visit, no tenderness = 0, tenderness = 1; total was calculated by adding all the joints for a maximum score of 28. A reduction in number of tender joints compared to baseline indicates improvement. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	139		
Units: tender joints				
arithmetic mean (standard deviation)				
Baseline (n=21, 139)	10.4 (± 6.46)	12.9 (± 7.06)		
Change at Week 2 (n=21, 137)	-3.4 (± 5.62)	-2.4 (± 5.63)		
Change at Week 4 (n=21, 137)	-3.9 (± 5.80)	-5.4 (± 6.14)		
Change at Week 8 (n=18, 132)	-6.6 (± 6.41)	-6.4 (± 6.94)		
Change at Week 12 (n=19, 128)	-6.0 (± 6.71)	-8.0 (± 7.35)		
Change at Week 16 (n=19, 125)	-7.9 (± 6.35)	-8.2 (± 7.05)		
Change at Week 20 (n=19, 122)	-8.5 (± 6.59)	-8.3 (± 7.09)		
Change at Week 24 (n=19, 117)	-8.3 (± 7.41)	-9.3 (± 7.53)		
Change at Week 28 (n=19, 115)	-8.7 (± 6.26)	-9.2 (± 7.04)		
Change at Week 32 (n=19, 115)	-7.6 (± 6.64)	-10.1 (± 6.76)		
Change at Week 36 (n=18, 114)	-9.4 (± 6.25)	-9.7 (± 7.23)		
Change at Week 40 (n=17, 111)	-10.1 (± 6.64)	-10.3 (± 6.74)		
Change at Week 44 (n=17, 108)	-9.7 (± 6.46)	-10.4 (± 6.63)		
Change at Week 48 (n=16, 107)	-9.6 (± 6.36)	-10.5 (± 6.70)		
Change at Week 52 (n=16, 107)	-9.4 (± 7.15)	-10.4 (± 8.01)		
Change at early withdrawal (n=5, 29)	-7.0 (± 6.24)	-3.3 (± 7.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total SJC on 66 Joints at Week 52

End point title	Percent Change From Baseline in Total SJC on 66 Joints at Week 52

End point description:

Number of swollen joints was determined by examination of 66 joints and identifying when swelling was present. The number of swollen joints was recorded on the joint assessment form at each visit, no swelling = 0, swelling =1; total was calculated by adding all the joints for a maximum score of 66. A reduction in number of swollen joints compared to baseline indicates improvement. The outcome is reported as the percent change from baseline to end of treatment (52 weeks). FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	102		
Units: percent change				
arithmetic mean (standard deviation)	-89.31 (± 20.059)	-74.77 (± 66.277)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total SJC on 28 Joints at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Early Withdrawal

End point title	Change From Baseline in Total SJC on 28 Joints at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at Early Withdrawal

End point description:

Number of swollen joints was determined by examination of 28 joints and identifying when swelling was present. The number of swollen joints was recorded on the joint assessment form at each visit, no swelling = 0, swelling =1; total was calculated by adding all the joints for a maximum score of 28. A reduction in number of swollen joints compared to baseline indicates improvement. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	139		
Units: swollen joints				
arithmetic mean (standard deviation)				
Baseline (n=21, 139)	7.0 (± 4.64)	5.6 (± 4.43)		
Change at Week 2 (n=21, 137)	-2.5 (± 4.31)	-0.8 (± 3.95)		
Change at Week 4 (n=21, 137)	-4.2 (± 3.79)	-2.5 (± 3.81)		
Change at Week 8 (n=18, 132)	-4.8 (± 4.21)	-3.2 (± 4.40)		
Change at Week 12 (n=19, 128)	-4.2 (± 4.37)	-3.8 (± 4.36)		
Change at Week 16 (n=19, 125)	-5.3 (± 4.67)	-3.9 (± 4.41)		
Change at Week 20 (n=19, 122)	-5.6 (± 5.08)	-4.2 (± 4.60)		
Change at Week 24 (n=19, 117)	-5.9 (± 5.12)	-4.7 (± 4.21)		
Change at Week 28 (n=19, 115)	-6.4 (± 4.90)	-4.4 (± 4.63)		
Change at Week 32 (n=19, 115)	-5.4 (± 5.10)	-4.8 (± 4.37)		
Change at Week 36 (n=18, 114)	-6.5 (± 4.57)	-4.9 (± 4.41)		
Change at Week 40 (n=17, 111)	-6.6 (± 5.12)	-5.0 (± 4.82)		
Change at Week 44 (n=17, 108)	-6.6 (± 5.28)	-5.2 (± 4.71)		
Change at Week 48 (n=16, 107)	-6.4 (± 4.83)	-5.0 (± 4.48)		
Change at Week 52 (n=16, 107)	-6.3 (± 4.81)	-5.1 (± 4.51)		
Change at early withdrawal (n=5, 29)	-5.8 (± 5.59)	-1.7 (± 4.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Achieved Low Disease Activity as Defined by DAS28-ESR ≤3.2

End point title	Number of Participants Who Achieved Low Disease Activity as Defined by DAS28-ESR ≤3.2

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR ≥2.6 to ≤3.2 implied low disease activity. FAS population. Here, "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Baseline (n=21, 139)	0	5		
Week 2 (n=21, 137)	7	18		
Week 4 (n=21, 137)	9	30		
Week 8 (n=18, 131)	3	25		
Week 12 (n=19, 128)	6	23		
Week 16 (n=18, 125)	3	20		
Week 20 (n=19, 121)	3	15		
Week 24 (n=19, 117)	2	15		
Week 28 (n=19, 115)	4	15		
Week 32 (n=19, 115)	5	14		
Week 36 (n=18, 114)	1	14		
Week 40 (n=17, 111)	3	14		
Week 44 (n=17, 107)	5	10		
Week 48 (n=16, 107)	3	12		
Week 52 (n=15, 107)	0	11		
Early withdrawal (n=5, 29)	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Achieved Remission as Defined by DAS28-ESR <2.6

End point title	Number of Participants Who Achieved Remission as Defined by DAS28-ESR <2.6

End point description:

DAS28 was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (measured on a 0 to 100 mm VAS where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as [0.56 × square root of TJC] + [0.28 × square root of SJC] + [0.70 × natural log (ESR)] + [0.014 × VAS]. Total score range: 0-10, higher score=higher disease activity. DAS28-ESR <2.6 implied clinical remission. FAS population. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Baseline (n=21, 139)	0	3		
Week 2 (n=21, 137)	1	15		
Week 4 (n=21, 137)	2	34		
Week 8 (n=18, 131)	5	53		
Week 12 (n=19, 128)	6	66		
Week 16 (n=18, 125)	10	72		
Week 20 (n=19, 121)	11	75		
Week 24 (n=19, 117)	14	76		
Week 28 (n=19, 115)	14	73		
Week 32 (n=19, 115)	12	80		
Week 36 (n=18, 114)	14	80		
Week 40 (n=17, 111)	13	81		
Week 44 (n=17, 107)	10	80		
Week 48 (n=16, 107)	11	78		
Week 52 (n=15, 107)	12	80		
Early withdrawal (n=5, 29)	3	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Non-Biologic DMARD/Corticosteroid Dose Reductions and/or Discontinuation

End point title	Number of Participants With Non-Biologic DMARD/Corticosteroid Dose Reductions and/or Discontinuation

End point description:

Results are reported for number of participants who had non-biologic DMARD/corticosteroid dose reductions and/or discontinuation by reasons for dose reductions or discontinuation (safety reasons, discomfort, lack of efficacy, other reasons, and unknown reasons). Participants may be included under more than one reason. FAS population. Here, "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, at early withdrawal (up to Week 52), follow-up Week 4 (up to Week 56), and follow-up Week 8 (up to Week 60)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Baseline: Safety (n=21, 140)	0	1		
Baseline: Discomfort (n=21, 140)	0	0		
Baseline: Lack of efficacy (n=21, 140)	0	1		
Baseline: Other (n=21, 140)	0	2		
Baseline: Unknown (n=21, 140)	0	0		
Week 2: Safety (n=21, 137)	0	4		
Week 2: Discomfort (n=21, 137)	0	0		
Week 2: Lack of efficacy (n=21, 137)	0	0		
Week 2: Other (n=21, 137)	0	7		
Week 2: Unknown (n=21, 137)	0	0		
Week 4: Safety (n=21, 137)	0	6		
Week 4: Discomfort (n=21, 137)	0	0		
Week 4: Lack of efficacy (n=21, 137)	0	1		
Week 4: Other (n=21, 137)	1	9		
Week 4: Unknown (n=21, 137)	0	1		
Week 8: Safety (n=18, 132)	0	8		
Week 8: Discomfort (n=18, 132)	0	0		
Week 8: Lack of efficacy (n=18, 132)	0	0		
Week 8: Other (n=18, 132)	1	13		
Week 8: Unknown (n=18, 132)	0	1		
Week 12: Safety (n=19, 128)	0	6		
Week 12: Discomfort (n=19, 128)	0	2		
Week 12: Lack of efficacy (n=19, 128)	0	0		
Week 12: Other (n=19, 128)	2	14		
Week 12: Unknown (n=19, 128)	0	0		
Week 16: Safety (n=19, 126)	0	7		
Week 16: Discomfort (n=19, 126)	0	0		
Week 16: Lack of efficacy (n=19, 126)	0	1		
Week 16: Other (n=19, 126)	2	13		
Week 16: Unknown (n=19, 126)	0	0		
Week 20: Safety (n=19, 122)	0	6		
Week 20: Discomfort (n=19, 122)	0	0		
Week 20: Lack of efficacy (n=19, 122)	0	0		
Week 20: Other (n=19, 122)	2	9		
Week 20: Unknown (n=19, 122)	0	1		
Week 24: Safety (n=19, 117)	0	5		
Week 24:Discomfort (n=19, 117)	0	0		
Week 24: Lack of efficacy (n=19, 117)	0	0		
Week 24: Other (n=19, 117)	1	13		
Week 24: Unknown (n=19, 117)	0	1		
Week 28: Safety (n=19, 116)	0	3		
Week 28: Discomfort (n=19, 116)	0	0		
Week 28: Lack of efficacy (n=19, 116)	0	1		

Week 28: Other (n=19, 116)	1	7		
Week 28: Unknown (n=19, 116)	0	0		
Week 32: Safety (n=19, 115)	0	4		
Week 32: Discomfort (n=19, 115)	0	0		
Week 32: Lack of efficacy (n=19, 115)	0	2		
Week 32: Other (n=19, 115)	1	11		
Week 32: Unknown (n=19, 115)	0	0		
Week 36: Safety (n=18, 114)	0	3		
Week 36: Discomfort (n=18, 114)	0	1		
Week 36: Lack of efficacy (n=18, 114)	0	0		
Week 36: Other (n=18, 114)	2	3		
Week 36: Unknown (n=18, 114)	0	0		
Week 40: Safety (n=17, 111)	0	4		
Week 40: Discomfort (n=17, 111)	0	1		
Week 40: Lack of efficacy (n=17, 111)	0	1		
Week 40: Other (n=17, 111)	1	1		
Week 40: Unknown (n=17, 111)	0	0		
Week 44: Safety (n=17, 108)	0	3		
Week 44: Discomfort (n=17, 108)	0	0		
Week 44: Lack of efficacy (n=17, 108)	0	0		
Week 44: Other (n=17, 108)	0	7		
Week 44: Unknown (n=17, 108)	0	0		
Week 48: Safety (n=16, 107)	0	3		
Week 48: Discomfort (n=16, 107)	0	0		
Week 48: Lack of efficacy (n=16, 107)	0	1		
Week 48: Other (n=16, 107)	1	3		
Week 48: Unknown (n=16, 107)	0	0		
Week 52: Safety (n=16, 107)	0	0		
Week 52: Discomfort (n=16, 107)	0	0		
Week 52: Lack of efficacy (n=16, 107)	0	0		
Week 52: Other (n=16, 107)	0	1		
Week 52: Unknown (n=16, 107)	0	0		
Early withdrawal: Safety (n=5, 30)	0	0		
Early withdrawal: Discomfort (n=5, 30)	0	0		
Early withdrawal: Lack of efficacy (n=5, 30)	0	0		
Early withdrawal: Other (n=5, 30)	1	8		
Early withdrawal: Unknown (n=5, 30)	0	0		
Follow-up Week 4: Safety (n=8, 70)	0	0		
Follow-up Week 4: Discomfort (n=8, 70)	0	0		
Follow-up Week 4: Lack of efficacy (n=8, 70)	0	0		
Follow-up Week 4: Other (n=8, 70)	0	2		
Follow-up Week 4: Unknown (n=8, 70)	0	1		
Follow-up Week 8: Safety (n=9, 65)	0	0		
Follow-up Week 8: Discomfort (n=9, 65)	0	0		
Follow-up Week 8: Lack of efficacy (n=9, 65)	0	0		
Follow-up Week 8: Other (n=9, 65)	0	0		
Follow-up Week 8: Unknown (n=9, 65)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Methotrexate Adherence as Assessed by Methotrexate Adherence Questionnaire

End point title	Percentage of Methotrexate Adherence as Assessed by Methotrexate Adherence Questionnaire[16]

End point description:

Methotrexate adherence was determined from responses to the question 'Over the last 3 months you were prescribed 12 doses of methotrexate, how many (approximately) have you taken?' Adherence (%) was calculated as: (Approximate number of doses taken/12)*100. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 52, and at early withdrawal (up to Week 52)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statisticaResults are provided for single arm as participants in "Tocilizumab Monotherapy" arm did not receive methotrexate.l analysis was planned for this end point.

End point values	Tocilizumab in Combination With Methotrexate or Other DMARDs			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: percentage of methotrexate adherence				
arithmetic mean (standard deviation)				
Baseline (n=97)	96.82 (± 7.747)			
Week 12 (n=80)	92.92 (± 14.412)			
Week 24 (n=65)	91.54 (± 20.915)			
Week 36 (n=60)	90.14 (± 21.456)			
Week 52 (n=60)	95.28 (± 11.417)			
Early withdrawal (n=17)	90.69 (± 18.367)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment of Disease Activity VAS Score

End point title	Patient Global Assessment of Disease Activity VAS Score

End point description:

Patient global assessment of disease activity was measured on a 0 to 100 mm horizontal VAS where 0 mm=no disease activity and 100 mm=maximum disease activity. FAS population. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=21, 139)	59.6 (± 26.94)	62.3 (± 20.72)		
Week 2 (n=21, 137)	50.3 (± 24.01)	54.5 (± 22.12)		
Week 4 (n=21, 137)	46.4 (± 26.43)	42.3 (± 23.22)		
Week 8 (n=18, 131)	35.8 (± 24.73)	36.2 (± 24.43)		
Week 12 (n=19, 128)	41.3 (± 27.67)	32.1 (± 23.91)		
Week 16 (n=19, 126)	29.6 (± 21.59)	29.2 (± 22.55)		
Week 20 (n=19, 122)	25.7 (± 23.77)	29.9 (± 22.99)		
Week 24 (n=19, 117)	23.8 (± 19.55)	26.6 (± 21.92)		
Week 28 (n=19, 116)	23.2 (± 16.47)	26.7 (± 23.12)		
Week 32 (n=19, 115)	24.0 (± 17.81)	24.3 (± 21.66)		
Week 36 (n=18, 114)	24.1 (± 19.13)	22.3 (± 21.86)		
Week 40 (n=17, 111)	22.5 (± 19.31)	21.4 (± 20.81)		
Week 44 (n=17, 107)	22.7 (± 20.62)	22.0 (± 22.83)		
Week 48 (n=16, 107)	22.9 (± 23.31)	18.9 (± 20.57)		
Week 52 (n=16, 107)	20.6 (± 18.96)	21.4 (± 23.07)		
Early withdrawal (n=5, 30)	30.8 (± 28.78)	52.4 (± 24.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Pain VAS Score

End point title	Patient Pain VAS Score

End point description:

This assessment represents the participant’s assessment of his/her current level of pain on a 100 mm horizontal VAS where 0 mm= no pain to 100 mm= unbearable pain. FAS population. “n” = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=21, 139)	50.5 (± 23.78)	57.5 (± 21.06)		
Week 2 (n=21, 137)	46.1 (± 22.43)	51.1 (± 22.58)		
Week 4 (n=21, 137)	47.0 (± 26.69)	42.4 (± 23.80)		
Week 8 (n=18, 131)	37.8 (± 25.75)	35.3 (± 24.30)		
Week 12 (n=19, 128)	40.9 (± 29.56)	30.8 (± 23.29)		
Week 16 (n=19, 126)	29.7 (± 20.83)	26.8 (± 22.61)		
Week 20 (n=19, 122)	27.6 (± 25.48)	28.6 (± 23.74)		
Week 24 (n=19, 117)	29.9 (± 22.76)	25.2 (± 22.16)		
Week 28 (n=19, 116)	24.8 (± 19.15)	25.6 (± 23.18)		
Week 32 (n=19, 115)	25.1 (± 17.92)	22.6 (± 21.30)		
Week 36 (n=18, 114)	29.6 (± 20.03)	22.1 (± 21.68)		
Week 40 (n=17, 111)	27.6 (± 22.70)	20.9 (± 21.24)		
Week 44 (n=17, 107)	26.7 (± 24.25)	20.0 (± 21.26)		
Week 48 (n=16, 107)	28.6 (± 28.98)	17.6 (± 19.66)		
Week 52 (n=16, 107)	22.4 (± 19.70)	19.0 (± 19.83)		
Early withdrawal (n=5, 30)	30.4 (± 29.57)	51.6 (± 26.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Assessment Questionnaire-Disability Index (HAQ-DI) Score

End point title	Health Assessment Questionnaire-Disability Index (HAQ-DI) Score

End point description:

The HAQ-DI questionnaire measures functional status (disability) and health-related quality of life. It measures the participant's ability to perform everyday tasks. The index consists of 20 questions regarding the function of the upper and lower extremities. These questions are summarized in 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common activities over past week. Each question is evaluated according to the degree of severity on a 4-point scale. Total score for HAQ-DI was the average of all questions and ranges from 0 = without any difficulty to 3 = unable to do. FAS population. “n” = participants who were evaluable at specified timepoint for

respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=21, 139)	1.806 (± 0.5551)	1.738 (± 0.6406)		
Week 2 (n=20, 137)	1.558 (± 0.7319)	1.659 (± 0.6210)		
Week 4 (n=21, 137)	1.616 (± 0.7720)	1.546 (± 0.7351)		
Week 8 (n=18, 132)	1.508 (± 0.7597)	1.404 (± 0.8115)		
Week 12 (n=19, 128)	1.488 (± 0.9304)	1.333 (± 0.8272)		
Week 16 (n=19, 126)	1.351 (± 0.9586)	1.312 (± 0.8621)		
Week 20 (n=19, 119)	1.409 (± 0.9071)	1.318 (± 0.8608)		
Week 24 (n=19, 117)	1.330 (± 0.8379)	1.261 (± 0.8915)		
Week 28 (n=19, 116)	1.330 (± 0.9412)	1.221 (± 0.8730)		
Week 32 (n=19, 114)	1.351 (± 0.8816)	1.232 (± 0.8870)		
Week 36 (n=18, 113)	1.432 (± 0.9048)	1.170 (± 0.8757)		
Week 40 (n=17, 111)	1.479 (± 0.8975)	1.199 (± 0.8908)		
Week 44 (n=17, 108)	1.442 (± 0.9392)	1.130 (± 0.9206)		
Week 48 (n=16, 107)	1.361 (± 0.9685)	1.114 (± 0.8815)		
Week 52 (n=16, 107)	1.338 (± 0.9796)	1.154 (± 0.9187)		
Early withdrawal (n=5, 30)	1.252 (± 1.1232)	1.756 (± 0.7820)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Score

End point title	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Score

End point description:

The FACIT-F score was calculated according to a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. FACIT-F is a 13-item questionnaire. Participants scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the participant's response to the questions (with the exception of 2 negatively stated), the greater the participant's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the participant's response). The sum of all responses resulted in the FACIT-F score for a total possible score of 0 (worse score) to 52 (better score). FAS population. "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=21, 139)	18.4 (± 11.14)	24.3 (± 11.55)		
Week 2 (n=21, 137)	23.1 (± 12.37)	27.9 (± 11.03)		
Week 4 (n=21, 136)	25.1 (± 12.28)	30.7 (± 12.10)		
Week 8 (n=18, 132)	30.2 (± 11.58)	32.8 (± 11.91)		
Week 12 (n=19, 128)	28.4 (± 11.71)	33.7 (± 11.85)		
Week 16 (n=19, 126)	31.3 (± 13.80)	34.0 (± 12.53)		
Week 20 (n=19, 121)	33.2 (± 13.57)	34.1 (± 12.05)		
Week 24 (n=19, 117)	33.8 (± 15.28)	35.3 (± 10.98)		
Week 28 (n=19, 115)	32.9 (± 12.06)	35.5 (± 11.59)		
Week 32 (n=19, 115)	34.1 (± 12.68)	36.2 (± 11.32)		
Week 36 (n=18, 114)	30.3 (± 13.62)	36.8 (± 11.48)		
Week 40 (n=17, 111)	31.7 (± 12.87)	37.1 (± 11.69)		
Week 44 (n=17, 106)	31.0 (± 14.02)	37.2 (± 11.75)		
Week 48 (n=16, 107)	31.6 (± 14.63)	37.9 (± 11.73)		
Week 52 (n=16, 106)	33.4 (± 14.17)	38.1 (± 11.16)		
Early withdrawal (n=4, 30)	31.3 (± 2.63)	24.5 (± 12.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Compliant to Tocilizumab Treatment as

Measured by Diary Cards and Return Records

End point title	Number of Participants Compliant to Tocilizumab Treatment as Measured by Diary Cards and Return Records

End point description:

A diary card was provided to participants to record home injections. Participants were asked to return all empty drug supply boxes, unused pre-filled syringe, and diary cards to the clinic at each visit as a measure of drug accountability and participant compliance. A participant was considered compliant if the participant correctly administered all scheduled doses of SC tocilizumab during the assessment period. FAS population. Here, "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and at early withdrawal (up to Week 52)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Baseline (n=21, 139)	21	137		
Week 2 (n=21, 137)	20	126		
Week 4 (n=21, 137)	20	132		
Week 8 (n=18, 132)	18	124		
Week 12 (n=19, 128)	18	121		
Week 16 (n=19, 126)	19	120		
Week 20 (n=19, 122)	18	114		
Week 24 (n=19, 117)	16	107		
Week 28 (n=19, 116)	19	112		
Week 32 (n=19, 115)	17	111		
Week 36 (n=18, 114)	17	105		
Week 40 (n=17, 111)	16	104		
Week 44 (n=17, 108)	16	102		
Week 48 (n=16, 107)	13	107		
Week 52 (n=16, 107)	16	98		
Early withdrawal (n=5, 30)	4	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Tocilizumab Antibodies

End point title	Number of Participants With Anti-Tocilizumab Antibodies

End point description:

FAS population. Here, "n" = participants who were evaluable at specified timepoint for respective groups. "99999" indicates results are not reported as no participants were evaluable at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24, at early withdrawal (up to Week 52), and follow-up visit (8 weeks after last dose of tocilizumab, up to 60 weeks)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: participants				
number (not applicable)				
Baseline (n=20, 138)	3	6		
Week 12 (n=1, 0)	0	99999		
Week 24 (n=19, 116)	0	2		
Early withdrawal (n=5, 27)	0	0		
Follow-up visit (n=3, 21)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Levels of Tocilizumab

End point title	Serum Levels of Tocilizumab

End point description:

FAS population. Here, "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24, at early withdrawal (up to Week 52), and follow-up visit (8 weeks after last dose of tocilizumab, up to 60 weeks)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: micrograms per milliliter				

(mcg/mL)				
arithmetic mean (standard deviation)				
Baseline (n=20, 138)	0.0000 (± 0.0000)	0.0082 (± 0.09619)		
Week 12 (n=18, 125)	35.3953 (± 22.69069)	40.2529 (± 21.05801)		
Week 24 (n=19, 115)	53.0416 (± 39.06367)	43.9047 (± 30.41603)		
Early withdrawal (n=5, 25)	44.7160 (± 38.81521)	17.6160 (± 22.92477)		
Follow-up visit (n=3, 22)	0.0597 (± 0.10335)	2.3123 (± 7.40931)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Levels of Soluble Interleukin-6 Receptors (sIL-6Rs)

End point title	Serum Levels of Soluble Interleukin-6 Receptors (sIL-6Rs)

End point description:

FAS population. Here, "n" = participants who were evaluable at specified timepoint for respective groups.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24, at early withdrawal (up to Week 52), and follow-up visit (8 weeks after last dose of tocilizumab, up to 60 weeks)

End point values	Tocilizumab Monotherapy	Tocilizumab in Combination With Methotrexate or Other DMARDs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	140		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=8, 48)	43.63 (± 10.947)	42.40 (± 12.087)		
Week 12 (n=12, 57)	577.42 (± 175.649)	548.70 (± 131.079)		
Week 24 (n=12, 80)	602.25 (± 158.541)	521.07 (± 160.464)		
Early withdrawal (n=4, 18)	639.75 (± 99.644)	327.95 (± 229.481)		
Follow-up visit (n=3, 20)	132.23 (± 93.048)	125.07 (± 211.038)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 60	
Adverse event reporting additional description:	
FAS population	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Tocilizumab in Combination With Methotrexate or Other DMARDs
Reporting group description:	
Participants received a weekly SC injection of tocilizumab 162 mg in combination with methotrexate or other non-biologic DMARDs for 52 weeks.	
Reporting group title	Tocilizumab Monotherapy
Reporting group description:	
Participants received a weekly SC injection of tocilizumab 162 mg as monotherapy for 52 weeks.	

Serious adverse events	Tocilizumab in Combination With Methotrexate or Other DMARDs	Tocilizumab Monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 140 (5.00%)	3 / 21 (14.29%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 140 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 140 (0.71%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			

subjects affected / exposed	0 / 140 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 140 (0.71%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 140 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 140 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 140 (0.71%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Arthritis bacterial			
subjects affected / exposed	1 / 140 (0.71%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 140 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 140 (0.71%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tocilizumab in Combination With Methotrexate or Other DMARDs	Tocilizumab Monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 140 (96.43%)	19 / 21 (90.48%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	31 / 140 (22.14%)	2 / 21 (9.52%)	
occurrences (all)	50	4	
Neutrophil count decreased			
subjects affected / exposed	13 / 140 (9.29%)	0 / 21 (0.00%)	
occurrences (all)	15	0	
Blood cholesterol increased			

subjects affected / exposed	5 / 140 (3.57%)	3 / 21 (14.29%)	
occurrences (all)	5	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	13 / 140 (9.29%)	2 / 21 (9.52%)	
occurrences (all)	17	2	
Fall			
subjects affected / exposed	14 / 140 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	14	1	
Laceration			
subjects affected / exposed	7 / 140 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	10	0	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 140 (9.29%)	4 / 21 (19.05%)	
occurrences (all)	20	4	
Dizziness			
subjects affected / exposed	8 / 140 (5.71%)	2 / 21 (9.52%)	
occurrences (all)	9	2	
Migraine			
subjects affected / exposed	7 / 140 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	13	1	
Paraesthesia			
subjects affected / exposed	6 / 140 (4.29%)	2 / 21 (9.52%)	
occurrences (all)	6	2	
Lethargy			
subjects affected / exposed	7 / 140 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	7	0	
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	12 / 140 (8.57%)	3 / 21 (14.29%)	
occurrences (all)	14	5	
Fatigue			
subjects affected / exposed	12 / 140 (8.57%)	1 / 21 (4.76%)	
occurrences (all)	12	1	
Injection site erythema			

subjects affected / exposed	11 / 140 (7.86%)	1 / 21 (4.76%)	
occurrences (all)	49	4	
Influenza like illness			
subjects affected / exposed	8 / 140 (5.71%)	1 / 21 (4.76%)	
occurrences (all)	9	1	
Peripheral swelling			
subjects affected / exposed	8 / 140 (5.71%)	1 / 21 (4.76%)	
occurrences (all)	9	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	14 / 140 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	15	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	32 / 140 (22.86%)	2 / 21 (9.52%)	
occurrences (all)	41	2	
Nausea			
subjects affected / exposed	21 / 140 (15.00%)	0 / 21 (0.00%)	
occurrences (all)	26	0	
Mouth ulceration			
subjects affected / exposed	18 / 140 (12.86%)	1 / 21 (4.76%)	
occurrences (all)	23	3	
Vomiting			
subjects affected / exposed	16 / 140 (11.43%)	2 / 21 (9.52%)	
occurrences (all)	21	2	
Abdominal pain			
subjects affected / exposed	7 / 140 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	9	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	27 / 140 (19.29%)	3 / 21 (14.29%)	
occurrences (all)	33	4	
Cough			
subjects affected / exposed	21 / 140 (15.00%)	4 / 21 (19.05%)	
occurrences (all)	22	5	
Productive cough			

subjects affected / exposed	3 / 140 (2.14%)	2 / 21 (9.52%)	
occurrences (all)	6	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	18 / 140 (12.86%)	0 / 21 (0.00%)	
occurrences (all)	22	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 140 (8.57%)	1 / 21 (4.76%)	
occurrences (all)	13	1	
Back pain			
subjects affected / exposed	10 / 140 (7.14%)	3 / 21 (14.29%)	
occurrences (all)	10	4	
Pain in extremity			
subjects affected / exposed	11 / 140 (7.86%)	0 / 21 (0.00%)	
occurrences (all)	11	0	
Rheumatoid arthritis			
subjects affected / exposed	11 / 140 (7.86%)	0 / 21 (0.00%)	
occurrences (all)	13	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 140 (23.57%)	5 / 21 (23.81%)	
occurrences (all)	40	6	
Lower respiratory tract infection			
subjects affected / exposed	25 / 140 (17.86%)	6 / 21 (28.57%)	
occurrences (all)	27	11	
Upper respiratory tract infection			
subjects affected / exposed	20 / 140 (14.29%)	2 / 21 (9.52%)	
occurrences (all)	31	3	
Urinary tract infection			
subjects affected / exposed	16 / 140 (11.43%)	5 / 21 (23.81%)	
occurrences (all)	25	6	
Oral herpes			
subjects affected / exposed	10 / 140 (7.14%)	1 / 21 (4.76%)	
occurrences (all)	13	1	
Lower respiratory tract infection viral			

subjects affected / exposed occurrences (all)	0 / 140 (0.00%) 0	2 / 21 (9.52%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2013	The major changes were corrections to ensure consistent wording for participant withdrawal criteria throughout the protocol and clarification regarding post-study follow-up visits. Minor formatting changes were also made to improve clarity and consistency.
06 May 2014	The major changes were the reduction in sample size from 260 participants to 160 participants, expansion of the target population to include those participants who had not experienced an adequate response to their current non-biologic DMARD therapy or the first anti-TNF agent and clarification that eligible participants were required to have "active" (not severe) rheumatoid arthritis. The reduction in sample size only increased the 95% confidence interval (CI) width by 0.09 for ESR and by 0.8 for CDAI. The expected precision of the CI widths around the mean change from baseline for a sample of 160 participants was still deemed to be clinically sufficient and a reasonable target to be able to draw conclusions from the study. The addition of DMARD inadequate response participants was not expected to compromise the power of the study as data from other studies indicate their responses are no worse and not more variable than those of the original study population. Details regarding study treatment, concomitant medications and assessments were updated for clarification. Administrative changes and additional minor changes were made to improve clarity and consistency.
10 December 2014	The major change was amendment of the target participant population to remove the window (previously 12 to 32 weeks) during which a participant who was receiving their first anti-TNF therapy would have to be assessed for an inadequate response to anti-TNF treatment. The rationale for this change was based on the feedback received from the sites, which indicated that such a protocol requirement was extremely difficult to implement and not aligned with local hospital protocols for assessing inadequate response to anti-TNF treatment. It was also clarified that inadequate response to non-biologic DMARD therapy was to be assessed according to local guidelines and that participants needed to be eligible for biologic therapy according to local guidelines. Language regarding pregnancy testing was also clarified in this amendment and names of relevant Roche personnel were updated. Additional minor changes were made to improve clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported