Clinical trial results:
A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Remission in DMARD- and Biological-Naive Early Rheumatoid Arthritis (RA) Subjects Treated With Tocilizumab (TCZ) Plus Tight Control Methotrexate (MTX) Treatment, TCZ Monotherapy or Tight Control MTX Monotherapy

Summary

EudraCT number	2009-013316-12
Trial protocol	NL
Global end of trial date	10 September 2014

Results information

Result version number	v1 (current)
This version publication date	14 April 2016
First version publication date	14 April 2016

Trial information

Trial identification

Sponsor protocol code	ML22497

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01034137
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2014
Global end of trial reached?	Yes
Global end of trial date	10 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the number of participants with early rheumatoid arthritis (RA) who achieve sustained remission with three different regimens: tocilizumab (TCZ) combined with tightly controlled methotrexate (MTX), tightly controlled MTX as monotherapy and tocilizumab as monotherapy. The main focus is the contrast between the combination therapy and the MTX monotherapy followed by the contrast between the two monotherapy treatments.

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. The participants were provided an Emergency Medical Call Center Help Desk in the case of emergency during the study to ensure the safety. An Independent Ethics Committee supervised the participant's safety.

Background therapy:

No

Evidence for comparator:

No

Actual start date of recruitment	13 January 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 317
Worldwide total number of subjects	317
EEA total number of subjects	317

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)	251
From 65 to 84 years	66
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 360 participants were enrolled at 21 centers in the Netherlands from 04 JAN 2010 to 30 JUL 2012.

Pre-assignment

Screening details:

Of 360 participants, 43 failed screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tocilizumab + Methotrexate

Arm description:

Participants received intravenous (IV) Tocilizumab (TCZ) 8 milligram (mg)/kilogram (kg) every four weeks for a maximum of 26 infusions + oral capsules of Methotrexate (MTX) 10–30 mg/week in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week. The weekly dose of MTX was taken on one particular day of the week.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RO4877533, RoActemra, ACTEMRA
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received a IV infusion of TCZ 8 mg/kg every 4 weeks for a maximum of 26 infusions

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Lederle, Methotrexate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received weekly oral MTX in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week. The weekly dose was taken on one particular day of the week.

Arm title	Tocilizumab+ Placebo Methotrexate

Arm description:

Participants received IV TCZ 8 mg/kg every four weeks for a maximum of 26 infusions + weekly oral matching placebo MTX capsules in climbing dosages. The weekly dose of placebo MTX was taken on one particular day of the week.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RO4877533, RoActemra, ACTEMRA
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received a IV infusion of TCZ 8 mg/kg every 4 weeks for a maximum of 26 infusions

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

Dosage and administration details:

Participants received weekly oral matching placebo MTX in climbing dosages. The weekly dose was taken on one particular day of the week.

Arm title	Methotrexate+ Placebo Tocilizumab

Arm description:

Participants received weekly oral MTX in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week + matching placebo TCZ IV 8 mg/kg every four week for a maximum of 26 infusions. The weekly dose of MTX was taken on one particular day of the week.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Lederle, Methotrexate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received weekly oral MTX in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week. The weekly dose was taken on one particular day of the week.

Investigational medicinal product name	Matching Tocilizumab Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received IV infusion of matching placebo TCZ 8 mg/kg every four weeks for a maximum of 26 infusions.

Number of subjects in period 1	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab
Started	106	103	108
Completed	78	81	78
Not completed	28	22	30
Consent withdrawn by subject	4	3	3
Refused treatment or did not cooperate	2	-	1
Administrative or other	2	3	4
Adverse event, non-fatal	9	10	8
Lack of efficacy	9	4	13
Protocol deviation	2	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab + Methotrexate
Reporting group description:	
Participants received intravenous (IV) Tocilizumab (TCZ) 8 milligram (mg)/kilogram (kg) every four weeks for a maximum of 26 infusions + oral capsules of Methotrexate (MTX) 10–30 mg/week in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week. The weekly dose of MTX was taken on one particular day of the week.	
Reporting group title	Tocilizumab+ Placebo Methotrexate
Reporting group description:	
Participants received IV TCZ 8 mg/kg every four weeks for a maximum of 26 infusions + weekly oral matching placebo MTX capsules in climbing dosages. The weekly dose of placebo MTX was taken on one particular day of the week.	
Reporting group title	Methotrexate+ Placebo Tocilizumab
Reporting group description:	
Participants received weekly oral MTX in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week + matching placebo TCZ IV 8 mg/kg every four week for a maximum of 26 infusions. The weekly dose of MTX was taken on one particular day of the week.	

Reporting group values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab
Number of subjects	106	103	108
Age categorical Units: Subjects			
Adults (18-64 years)	85	79	87
From 65-84 years	21	24	21
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.1	55	52.2
standard deviation	± 11.8	± 12.9	± 13.7
Gender categorical Units: Subjects			
Female	65	78	69
Male	41	25	39

Reporting group values	Total		
Number of subjects	317		
Age categorical Units: Subjects			
Adults (18-64 years)	251		
From 65-84 years	66		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	212		
Male	105		

End points

End points reporting groups

Reporting group title	Tocilizumab + Methotrexate

Reporting group description:

Participants received intravenous (IV) Tocilizumab (TCZ) 8 milligram (mg)/kilogram (kg) every four weeks for a maximum of 26 infusions + oral capsules of Methotrexate (MTX) 10–30 mg/week in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week. The weekly dose of MTX was taken on one particular day of the week.

Reporting group title	Tocilizumab+ Placebo Methotrexate

Reporting group description:

Participants received IV TCZ 8 mg/kg every four weeks for a maximum of 26 infusions + weekly oral matching placebo MTX capsules in climbing dosages. The weekly dose of placebo MTX was taken on one particular day of the week.

Reporting group title	Methotrexate+ Placebo Tocilizumab

Reporting group description:

Participants received weekly oral MTX in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week + matching placebo TCZ IV 8 mg/kg every four week for a maximum of 26 infusions. The weekly dose of MTX was taken on one particular day of the week.

Subject analysis set title	Overall trial
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent to treat (ITT) population consisted of all participants who were randomized and received at least one dose of TCZ/placebo infusion or MTX/placebo capsules and performed at least one post-baseline efficacy measurement like achieving sustained disease activity score, scoring 28 joints remission, clinical disease activity index, simplified disease activity index, or american college of rheumatology 20/50/70/90 etc.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all participants who received at least one dose of TCZ/placebo infusion or MTX/placebo capsule and have at least one post-baseline safety assessment like achieving sustained disease activity score, scoring 28 joints remission, clinical disease activity index, simplified disease activity index, or american college of rheumatology 20/50/70/90 etc.

Primary: Percentage of Participants Achieving Sustained Remission Rate At Week 104

End point title	Percentage of Participants Achieving Sustained Remission Rate At Week 104

End point description:

Sustained remission rate (SRR) is defined as disease activity score 28 (DAS28) <2.6 during ≥ 23 weeks and no more than 4 swollen joints (28 joint count) due to RA at Week 24 of remission, with the exception of up to 2 in-between DAS28 values which could be between 2.6 and 3.2. The DAS28 is a combined index for measuring disease activity in RA. The index includes swollen (range 0-28) and tender (range 0-28) joint counts, acute phase response (ESR in millimeters per hour [mm/hr]), and general health status (participant global assessment of disease activity using VAS, range 1-100 mm). DAS28, which uses a 28-joint count, is derived from the original DAS, which includes a 44-swollen joint count. The DAS28 scale ranges from 0 to 10, where higher scores indicate worsening. DAS28 <2.6 equals (=) remission. The ITT population set was used for analysis.

End point type	Primary

End point timeframe:

Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Percentage of Participants				
number (not applicable)	85.8	83.5	44.4	

Statistical analyses

Statistical analysis title	SRR in TCZ + MTX vs. MTX + Placebo
Comparison groups	Tocilizumab + Methotrexate v Methotrexate+ Placebo Tocilizumab
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.996
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.589
upper limit	2.506

Statistical analysis title	SRR in TCZ + Placebo vs. MTX + Placebo
Comparison groups	Tocilizumab+ Placebo Methotrexate v Methotrexate+ Placebo Tocilizumab
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.481
upper limit	2.323

Statistical analysis title	SRR in TCZ + MTX vs. TCZ + placebo
Comparison groups	Tocilizumab + Methotrexate v Tocilizumab+ Placebo Methotrexate

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.616
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.915
upper limit	1.16

Secondary: Median Time to First Sustained Remission

End point title	Median Time to First Sustained Remission

End point description:

It is the time to event analysis for the first period of SR. Sustained remission is defined as DAS28 <2.6 during >=23 weeks and no more than 4 swollen joints due to RA at Week 24 of remission, with the exception of up to 2 in-between DAS28 values which could be between 2.6 and 3.2. The index includes swollen and tender joint counts (range 0-28), acute phase response (ESR in mm/hr), and general health status (participant global assessment of disease activity using VAS, range 1-100 mm). DAS28, which uses a 28-joint count, is derived from the original DAS, which includes a 44-swollen joint count. The DAS28 scale ranges from 0 to 10, where higher scores indicate worsening. DAS28 <2.6 equals (=) remission. The ITT population was used for analysis. Median time and upper limit of confidence interval could not be calculated as there was not that much SR in the MTX + PBO group. As the system does not accept 'Not evaluable', we have presented an arbitrary value (99999) for the same.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Days				
median (confidence interval 95%)	69 (57 to 85)	89 (58 to 116)	99999 (243 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Duration of First Sustained Remission

End point title	Mean Duration of First Sustained Remission

End point description:

It is the duration of the first period of sustained DAS28 remission. Participants who switch treatment strategy before reaching sustained remission considered failures. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	86	48	
Units: Weeks				
arithmetic mean (standard deviation)	65.85 (± 26.7)	65 (± 24.75)	52.9 (± 25.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving Disease Activity Score 28 Remission at Weeks 12, 24, 52, and 104

End point title	Number of Participants Achieving Disease Activity Score 28 Remission at Weeks 12, 24, 52, and 104

End point description:

The DAS28 is a combined index for measuring disease activity in RA. The index includes swollen (range 0-28) and tender (range 0-28) joint counts, acute phase response (ESR in mm/hr), and general health status (participant global assessment of disease activity using VAS, range 1-100 mm). DAS28, which uses a 28-joint count, is derived from the original DAS, which includes a 44-swollen joint count. The DAS28 scale ranges from 0 to 10, where higher scores indicate worsening. DAS28 <2.6 equals (=) remission. Participants with missing data at visits before early study termination or who stopped the study prematurely because of insufficient therapeutic response or safety reasons considered non-responders or who stopped the study for other reasons, response set to missing after early withdrawal. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	102	106	
Units: Number of Participants				
number (not applicable)				
Week 12 n=105, 102, 106	76	66	23	

Week 24 n=105, 102, 106	84	77	42	
Week 52 n=100, 99, 103	71	80	63	
Week 104 n=96, 95, 99	71	67	58	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to First Disease Activity Score 28 Remission

End point title	Median Time to First Disease Activity Score 28 Remission

End point description:

It is the time to event analysis for the first DAS28 remission. The ITT population set was used for analysis.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Days				
median (confidence interval 95%)	56 (54 to 58)	57 (49 to 60)	167 (138 to 195)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Cumulative Remission Rate at Weeks 12, 24, 52, and 104

End point title	Percentage of Participants With Cumulative Remission Rate at Weeks 12, 24, 52, and 104

End point description:

The DAS28 score is a measure of the subject's disease activity. DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline (Week 0) indicated improvement. Participants with missing data at visits before early study termination or who stopped the study prematurely because of insufficient therapeutic response or safety reasons considered non-responders or who stopped the study for other reasons, response set to missing after early withdrawal. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	102	106	
Units: Percentage of Participants				
number (not applicable)				
Week 12 n=105,102,106	72.4	64.7	21.7	
Week 24 n=105,102,106	80	75.5	39.6	
Week 52 n=100,99,103	71	80.8	61.2	
Week 104 n=96,95,99	63.5	70.5	58.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Duration of First Disease Activity Score 28 Remission

End point title	Mean Duration of First Disease Activity Score 28 Remission

End point description:

It is the duration of the first period of DAS28 remission. The ITT population set was used for analysis.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Weeks				
arithmetic mean (standard deviation)	42.99 (± 31.79)	37.01 (± 30.89)	20.49 (± 23.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Change From Baseline in Clinical Disease Activity Index Score at Weeks 24, 52, and 104

End point title	Median Change From Baseline in Clinical Disease Activity Index Score at Weeks 24, 52, and 104

End point description:

The clinical disease activity Index (CDAI) are continuous measures of RA disease activity. The CDAI is the numerical sum of four outcome parameters: tender joint count (TJC), swollen joint count (SJC) based on a 28-joint assessment; and patient's global assessment (PtGA) and physician's global assessment (PhGA) assessed on 0-10 cm visual analog scale (VAS). CDAI total score ranges from 0 to 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.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Scores on a scale				
median (full range (min-max))				
Week 24	-20 (-66.5 to -1.5)	-20 (-62.5 to 13)	-14.8 (-42 to 13)	
Week 52	-19.5 (-67 to 3)	-21 (-62.5 to 2)	-18 (-47.5 to -0.5)	
Week 104	-19 (-39 to 6)	-21.5 (-62.5 to -1)	-18 (-51 to 12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Change From Baseline in Simplified Disease Activity Index Scores at Weeks 24, 52, and 104

End point title	Median Change From Baseline in Simplified Disease Activity Index Scores at Weeks 24, 52, and 104

End point description:

The simplified disease activity index (SDAI) are continuous measures of RA disease activity. The SDAI is the numerical sum of five outcome parameters: TJC and SJC (based on a 28-joint assessment), PtGA and PhGA (assessed on 0-10 cm VAS), and C-reactive protein (CRP) (mg/dL). SDAI total score ranges from 0-86. SDAI <=3.3 indicates disease remission, >3.4 to 11 = low disease activity, >11 to 26 = moderate disease activity, and >26 = high disease activity.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Scores on a scale				
median (full range (min-max))				
Week 24	-31 (-282 to 6.4)	-32.8 (-290 to 12.1)	-21.5 (-186 to 45.5)	
Week 52	-26.3 (-272.5 to 30)	-33.5 (-288 to 1.2)	-27.9 (-189 to -1.5)	
Week 104	-25.6 (-98.9 to 11)	-32.8 (-293.5 to 6.5)	-28 (-188.4 to 14.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Good European League Against Rheumatism Response Rate at Weeks 24, 52, and 104

End point title	Number of Participants With Good European League Against Rheumatism Response Rate at Weeks 24, 52, and 104

End point description:

European league against rheumatism (EULAR) response criteria classify each participant as a good, moderate or non-responder to treatment based on the degree of improvement from baseline and the level of disease activity at the endpoint. EULAR response is derived using the individual participant's DAS28 as the measure of severity of disease. Good or moderate response is defined as follows: Good response : DAS28 at the time point =<3.2 and improvement from baseline > 1.2. Moderate response : DAS28 at the time point > 3.2 and improvement from baseline > 1.2, or DAS28 at the time point ≤ 5.1 and improvement from baseline > 0.6 and =<1.2. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Weeks 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	97	103	
Units: Number of participants				
number (not applicable)				
Week 24 n=105, 97, 103	93	84	50	
Week 52 n=100, 96, 99	75	85	71	
Week 104 n=96, 95, 96	63	72	65	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to First European League Against Rheumatism Response

End point title	Median Time to First European League Against Rheumatism Response

End point description:

It is the time to first EULAR response. EULAR response criteria classify each participant as a good, moderate or non-responder to treatment based on the degree of improvement from baseline and the level of disease activity at the endpoint. EULAR response is derived using the individual participant's DAS28 as the measure of severity of disease. Good or moderate response is defined as follows: Good response : DAS28 at the time point =<3.2 and improvement from baseline > 1.2. Moderate response : DAS28 at the time point > 3.2 and improvement from baseline > 1.2, or DAS28 at the time point ≤ 5.1 and improvement from baseline > 0.6 and =<1.2. Response 1 is defined as yes (good) versus no (moderate or no response). Response 2 is defined as yes (good or moderate) versus no (no response). The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: days				
median (inter-quartile range (Q1-Q3))				
EULAR response 1	35.5 (29 to 58)	47 (29 to 60)	132 (84 to 195)	
EULAR response 2	29 (28 to 30)	29 (27 to 31)	57 (29 to 85)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With American College of Rheumatology 20 Response Rate at Weeks 12, 24, 52 and 104

End point title	Percentage of Participants With American College of Rheumatology 20 Response Rate at Weeks 12, 24, 52 and 104

End point description:

American College of Rheumatology (ACR) 20 response is defined as a >= 20% improvement (reduction) compared with baseline for both tender joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: patient's assessment of pain over the previous 24 hours: using a Visual Analog Scale (VAS) with left end of the line 0=no pain to right end of the line 100=unbearable pain; patient's global assessment of disease activity and physician's global assessment of disease activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant, either C-reactive protein or Erythrocyte Sedimentation Rate. The ITT population was analysed.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Percentage of Participants				
number (not applicable)				
Weeks 12	63.8	67.6	41.5	
Weeks 24	75.2	75.5	59.4	
Weeks 52	74.7	71.7	68.9	
Weeks 104	63.5	65.3	60.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With American College of Rheumatology 50 Response Rate at Weeks 12, 24, 52 and 104

End point title	Percentage of Participants With American College of Rheumatology 50 Response Rate at Weeks 12, 24, 52 and 104

End point description:

ACR50 response is defined as a >=50% improvement (reduction) compared with baseline for both TJC68 and SJC66, as well as for three of the additional five ACR core set variables: patient's assessment of pain over the previous 24 hours: using a VAS with left end of the line 0=no pain to right end of the line 100=unbearable pain; patient's Global assessment of disease activity and physician's global assessment of disease activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant, either C-reactive protein or Erythrocyte Sedimentation Rate. The ITT population set was used for analysis.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Percentage of Participants				
number (not applicable)				
Week 12	47.6	44.1	21.7	
Week 24	63.8	58.8	34	
Week 52	61.6	58.6	51.5	

Week 104	49	54.7	48.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With American College of Rheumatology 70 Response Rate at Weeks 12, 24, 52 and 104

End point title	Percentage of Participants With American College of Rheumatology 70 Response Rate at Weeks 12, 24, 52 and 104

End point description:

ACR70 response is defined as a >=70% improvement (reduction) compared with baseline for both TJC68 and SJC66, as well as for three of the additional five ACR core set variables: patient's Assessment of pain over the previous 24 hours: using a VAS with left end of the line 0=no pain to right end of the line 100=unbearable pain; patient's global assessment of disease activity and physician's global assessment of disease activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; health assessment questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant, either C-reactive protein or Erythrocyte Sedimentation Rate. The ITT population set was used for analysis.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Percentage of Participants				
number (not applicable)				
Week 12	30.5	23.5	7.5	
Week 24	43.8	37.3	15.1	
Week 52	44.4	44.4	33	
Week 104	36.5	38.9	35.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With American College of Rheumatology 90 Response Rate at Weeks 12, 24, 52 and 104

End point title	Percentage of Participants With American College of Rheumatology 90 Response Rate at Weeks 12, 24, 52 and 104

End point description:

ACR90 response is defined as a >=90% improvement (reduction) compared with baseline for both tender joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a VAS with left end of the line 0=no pain to right end of the line 100=unbearable pain; patient's global assessment of disease activity and physician's global assessment of disease activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; health assessment questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant, either C-reactive protein or erythrocyte sedimentation rate. The ITT population set was used for analysis.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Percentage of Participants				
number (not applicable)				
Weeks 12	9.5	3.9	0	
Weeks 24	18.1	11.8	4.7	
Weeks 52	19.2	21.2	6.8	
Weeks 104	20.8	20	14.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Change From Baseline in the Swollen Joint Count (SJC) at Weeks 12, 24, 52, and 104

End point title	Mean Percent Change From Baseline in the Swollen Joint Count (SJC) at Weeks 12, 24, 52, and 104

End point description:

The number of swollen joints among 22 anatomical joints for both the right and left side of the body were assessed by a joint evaluator where the presence of a swollen joint was scored as 1 and absence as 0. The total SJC was derived by the sum of the scores for a range of SJC from 0 (best possible score; no swollen joints) to 44 (worse possible score; all joints swollen). The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	100	98	
Units: Percent change				
arithmetic mean (standard deviation)				
Week 12 n=104, 100, 98	-69.2 (± 91.1)	-68.2 (± 45.1)	-44.9 (± 73.9)	
Week 24 n=100, 100, 97	-91.7 (± 18.5)	-86.9 (± 24.3)	-69.3 (± 37.8)	
Week 52 n=86, 91, 87	-93.3 (± 19.6)	-89 (± 24.1)	-91.3 (± 20)	
Week 104 n=78, 80, 77	-85.7 (± 44.7)	-91.6 (± 31.3)	-87.9 (± 23.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Change From Baseline in the Tender Joint Count (TJC) at Weeks 12, 24, 52, and 104

End point title	Mean Percent Change From Baseline in the Tender Joint Count (TJC) at Weeks 12, 24, 52, and 104

End point description:

The number of tender joints among 22 anatomical joints for both the right and left side of the body were assessed by a joint evaluator where the presence of a tender joint was scored as 1 and absence as 0. The total TJC was derived by the sum of the scores for a range of TJC from 0 (best possible score; no tender joints) to 44 (worse possible score; all tender joints). The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	98	99	
Units: Percent change				
arithmetic mean (standard deviation)				
Week 12 n=102, 98, 99	-68 (± 44.6)	-53.7 (± 84.1)	-36.9 (± 65.9)	
Week 24 n=98, 98, 97	-81.9 (± 28.8)	-66.1 (± 83.8)	-66.6 (± 34)	
Week 52 n=84, 89, 87	-77.8 (± 49.8)	-80.4 (± 33.1)	-77.7 (± 33.6)	
Week 104 n=76, 79, 77	-84.5 (± 26.4)	-82.5 (± 30.7)	-79.9 (± 31.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Change From Baseline in Patient Health Visual Analog

Scale at Weeks 12, 24, 52, and 104

End point title	Mean Percent Change From Baseline in Patient Health Visual Analog Scale at Weeks 12, 24, 52, and 104

End point description:

Patient health visual analog scale is a component of ACR. It is measured using a visual analogue scale with scores ranging from 0 to 100 (higher scores indicate worse disease activity). An improvement (decrease) in the patient's global assessment based on disease activity relative to respective baseline values was analyzed.The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	97	97	
Units: Percent change				
arithmetic mean (standard deviation)				
Week 12 n =96, 97, 97	-43.8 (± 75.2)	-40.8 (± 74.7)	-25.3 (± 69)	
Week 24 n=92, 96, 93	-66.5 (± 36.5)	-54.8 (± 41.8)	-41.5 (± 62.4)	
Week 52 n=79, 82, 84	-66.5 (± 37.7)	-63.4 (± 36.8)	-58.4 (± 69.6)	
Week 104 n=72, 72, 72	-64 (± 39.7)	-67.4 (± 36.3)	-64.7 (± 39.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Change From Baseline in The Physician Health Visual Analog Scale at Weeks 12, 24, 52, and 104

End point title	Mean Percent Change From Baseline in The Physician Health Visual Analog Scale at Weeks 12, 24, 52, and 104

End point description:

Physician health visual analog scale is a component of ACR. It is measured using a visual analogue scale with scores ranging from 0 to 100 (higher scores indicate worse disease activity).An improvement (decrease) in the physician's global assessment based on disease activity parameter relative to respective baseline values was analyzed. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	101	100	
Units: Percent change				
arithmetic mean (standard deviation)				
Week 12 n =104, 101, 100	-41.6 (± 47.2)	-36.5 (± 42.7)	-18.2 (± 52.5)	
Week 24 n =100, 101, 98	-61 (± 37.7)	-46.7 (± 40.9)	-26.1 (± 57.9)	
Week 52 n =86, 92, 88	-56.9 (± 42.8)	-56.2 (± 45.7)	-48.2 (± 50.1)	
Week 104 n =78, 81, 78	-63.2 (± 37)	-60.2 (± 38.9)	-53.9 (± 54.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Change From Baseline in Pain Visual Analog Scale at Weeks 12, 24, 52, and 104

End point title	Mean Percent Change From Baseline in Pain Visual Analog Scale at Weeks 12, 24, 52, and 104

End point description:

Pain VAS is a component of ACR. VAS pain score calculated as 0 to 10 cm; where 0 = no pain, and 10 = worst possible pain. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	83	77	
Units: Percent change				
arithmetic mean (standard deviation)				
Week 12 n=82, 83, 77	-59.3 (± 37.6)	-55.8 (± 34.7)	-39.1 (± 43.5)	
Week 24 n=76, 77, 78	-74.9 (± 31.4)	-70.3 (± 25.4)	-48.6 (± 52.6)	
Week 52 n=76, 72, 72	-77 (± 30.9)	-72.4 (± 41.1)	-66.4 (± 35.9)	
Week 104 n=58, 61, 63	-76.5 (± 35)	-78.8 (± 27.7)	-74.9 (± 27.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Change From Baseline in C-Reactive Protein at Weeks 12, 24, 52, and 104

End point title	Mean Percent Change From Baseline in C-Reactive Protein at Weeks 12, 24, 52, and 104

End point description:

C-reactive protein (CRP) is a component of ACR. CRP is a marker of inflammation. The ITT population set was used for analysis.n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103	101	100	
Units: Percent change				
arithmetic mean (standard deviation)				
Week 12 n=103, 101, 100	-47.4 (± 216.5)	-69.8 (± 39.4)	-28.5 (± 65.9)	
Week 24 n=99, 101, 98	-64.4 (± 72.1)	-69.1 (± 47.1)	-16.8 (± 127.7)	
Week 52 n=85, 92, 88	-47.1 (± 107.2)	-51.9 (± 72)	-52.1 (± 100.4)	
Week 104 n=77, 81, 78	-45.5 (± 105.8)	-12.7 (± 256.5)	-46.7 (± 65.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Modified Sharp/van der Heijde Score at Weeks 52 and 104

End point title	Mean Change From Baseline in Modified Sharp/van der Heijde Score at Weeks 52 and 104

End point description:

The degree of joint damage was assessed using the van der Heijde modified total Sharp score (mTSS). The methodology quantifies the extent of bone erosions for 44 joints and joint space narrowing (JSN) for 42 joints, with higher scores representing greater damage. The independent read of X-ray images was performed by 2 primary readers. In case of discrepancy between the 2 primary readers, an adjudicator was involved. The mTSS can range from 0 to 448 with a higher score indicating more joint damage. A negative change score indicates improvement. The ITT population set was used for analysis.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 52	0.5 (± 1.495)	0.79 (± 3.242)	0.96 (± 2.87)	
Week 104	1.18 (± 3.919)	1.45 (± 4.272)	1.53 (± 2.421)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Withdraw Due to Lack of Sufficient Therapeutic Response

End point title	Percentage of Participants Who Withdraw Due to Lack of Sufficient Therapeutic Response

End point description:

Insufficient therapeutic response (participants not responding to the drug as assessed by the physician) was selected by the investigator as a reason for the participant to withdraw from the study. The ITT population set was used for analysis.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Percentage of Participants				
number (not applicable)	32.1	18.2	43.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Change in The Therapy Strategy During The Study

End point title	Number of Participants With Change in The Therapy Strategy During The Study

End point description:

Participants who switched treatment strategy from monotherapy (TCZ+ placebo MTX or MTX+ placebo TCZ treatment) to combination therapy (TCZ+MTX treatment) was reported. Also, participants who switched from verum therapy to standard of care was reported in the below table. The ITT population set was used for analysis.

End point type	Secondary
End point timeframe:	
From Baseline to Week 104	

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Number of participants				
number (not applicable)				
Treatment strategy switch	0	13	50	
Switch from verum to standard of care	9	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in The Dutch Consensus Health Assessment Questionnaire of Quality of Life at Weeks 12, 24, 52, and 104

End point title	Mean Change from Baseline in The Dutch Consensus Health Assessment Questionnaire of Quality of Life at Weeks 12, 24, 52, and 104

End point description:

The Dutch Consensus Health Assessment Questionnaire disability index is a self-completed participant questionnaire with 8 domains specific for RA. It assesses a participant functional ability, with scores ranging from 0 (without any difficulty) to 3 (unable to do). A change from baseline of –0.22 is considered to be the minimal clinically important difference. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary
End point timeframe:	
From Baseline (Week 0) to Weeks 12, 24, 52 and 104	

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	95	91	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 12 n=95, 95, 91	-0.5 (± 0.6)	-0.5 (± 0.5)	-0.2 (± 0.5)	
Week 24 n=92, 94, 87	-0.7 (± 0.6)	-0.6 (± 0.6)	-0.4 (± 0.5)	
Week 52 n=81, 81, 82	-0.7 (± 0.7)	-0.7 (± 0.6)	-0.5 (± 0.6)	
Weeks 104 n=68, 75, 71	-0.6 (± 0.7)	-0.6 (± 0.6)	-0.4 (± 0.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in The EuroQol score of Quality of Life at Weeks 12, 24, 52 and 104

End point title	Mean Change from Baseline in The EuroQol score of Quality of Life at Weeks 12, 24, 52 and 104

End point description:

EuroQol (EQ-5D) is a standard self-completed participant questionnaire that measures health outcome. The EQ-5D questionnaire consists of 2 parts: 1) EQ-5D with 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension is rated on a 3-point response scale as 1 = no problems, 2 = some/moderate problems, 3 = extreme problems. 2) EQ-VAS on a scale of 0 to 100, where 0 = worst possible health status and 100 = best possible health status. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	78	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
EQ-5D Week 12 n=72, 72, 78	0.15 (± 0.25)	0.19 (± 0.25)	0.11 (± 0.28)	
EQ-VAS Week 12 n=69, 70, 73	11.94 (± 21.07)	9.31 (± 16.9)	2.92 (± 17.54)	
EQ-5D Week 24 n=69, 73, 73	0.19 (± 0.22)	0.15 (± 0.3)	0.15 (± 0.27)	
EQ-VAS Week 24 n=67, 69, 71	13.15 (± 21.93)	10.86 (± 21.46)	8.97 (± 20.17)	
EQ-5D Week 52 n=61, 61, 69	0.18 (± 0.25)	0.21 (± 0.24)	0.25 (± 0.29)	
EQ-VAS Week 52 n=58, 59, 67	12.52 (± 21.61)	13.71 (± 18.63)	13.4 (± 24.45)	
EQ-5D Week 104 n=50,57,54	0.14 (± 0.22)	0.2 (± 0.28)	0.21 (± 0.29)	
EQ-VAS Week 104 n=50,52,57	10.88 (± 20.43)	14.37 (± 20.49)	10.96 (± 23.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in 36-Item Short Form Health Survey of Quality of Life at Weeks 12, 24, 52, and 104

End point title	Mean Change From Baseline in 36-Item Short Form Health Survey of Quality of Life at Weeks 12, 24, 52, and 104

End point description:

The 36-Item Short Form Health Survey is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical Component Summary (PCS) and Mental Component Summary (MCS) measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	79	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
PCS, Week 12 n=72, 73, 79	11.2 (± 13.4)	14.2 (± 14)	6.8 (± 14.1)	
MCS, Week 12 n=72, 71, 76	6.2 (± 12.3)	10.9 (± 14.1)	3.9 (± 12.7)	
PCS, Week 24 n= 72, 74, 76	16.3 (± 15.4)	13.6 (± 16.4)	9.1 (± 15.1)	
MCS, Week 24 n=67, 72,75	9.5 (± 13.6)	9.3 (± 16.6)	5.7 (± 13.9)	
PCS, Week 52 n=62, 63, 68	18.9 (± 16)	20.1 (± 17.2)	15.7 (± 17)	
MCS, Week 52 n=61, 63, 69	10.1 (± 12.9)	13.6 (± 15.8)	10.3 (± 16.6)	
PCS, Week 104 n=52, 57, 60	15.2 (± 19.8)	15.1 (± 18.3)	13.9 (± 19.9)	
MCS, Week 104 n=51, 57, 60	9.4 (± 12.2)	9.7 (± 16.5)	8.6 (± 15.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Patient Global Health Visual Analog Scale Score of Quality of Life at Weeks 12, 24, 52, and 104

End point title	Mean Change from Baseline in Patient Global Health Visual Analog Scale Score of Quality of Life at Weeks 12, 24, 52, and 104

End point description:

Patient global health VAS score ranges from 0 to 100 and a higher score indicates worse QoL. Patient global health VAS is a component of DAS28. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	99	103	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 12 n=101, 99, 103	-25.8 (± 25.7)	-24.2 (± 24.7)	-14.8 (± 25.4)	
Week 24 n= 97, 95, 96	-33.9 (± 23.5)	-29.2 (± 26.1)	-20.4 (± 27.3)	
Week 52 n=84, 90, 84	-34.3 (± 26.1)	-34.9 (± 26.2)	-31.5 (± 28.3)	
Week 104 n=76, 83, 74	-33.2 (± 22.1)	-34.3 (± 27.4)	-36.2 (± 28.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Physician Global Health Visual Analog Scale score of Quality of Life at Weeks 12, 24, 52, and 104

End point title	Mean Change From Baseline in Physician Global Health Visual Analog Scale score of Quality of Life at Weeks 12, 24, 52, and 104

End point description:

Physician global health VAS score ranges from 0 to 100 and a higher score indicates worse QoL. Physician global health VAS is a component of DAS28. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	82	79	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 12 n=79, 82, 79	-35.4 (± 23)	-34.6 (± 23.1)	-23 (± 23.1)	
Week 24 n=74, 75, 78	-43.9 (± 25.1)	-43.8 (± 21.1)	-31 (± 25.7)	
Week 52 n=71, 71, 71	-45.4 (± 24.9)	-46.9 (± 23.3)	-37.7 (± 23.5)	
Week 104 n=61, 68, 64	-43.7 (± 26.6)	-50.7 (± 23.5)	-41.1 (± 22.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Patient Pain Visual Analog Scale Score of Quality of Life at Weeks 12, 24, 52, and 104

End point title	Mean Change from Baseline in Patient Pain Visual Analog Scale Score of Quality of Life at Weeks 12, 24, 52, and 104

End point description:

Participants assessed their pain using a 0 to 10 horizontal visual analogue scale (VAS). The left-hand extreme of the line equals 0 and is described as "no pain" and the right-hand extreme equals 10 as "unbearable pain" .The final VAS score will be derived by multiplying the original scores by 10. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	96	101	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 12 n=95, 96, 101	-28.7 (± 28.8)	-29.5 (± 31)	-19.7 (± 25.5)	
Week 24 n=92, 93, 92	-36.4 (± 28.3)	-33.5 (± 27.4)	-28 (± 26.9)	
Week 52 n=78, 83, 82	-37.9 (± 26.1)	-36.6 (± 27.2)	-38.1 (± 27.1)	
Week 104 n=73, 80, 72	-34 (± 26.8)	-36.4 (± 27)	-41 (± 24.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Patient General Wellbeing Visual Analog Scale Score of Quality of Life at Weeks 12, 24, 52, and 104

End point title	Mean Change from Baseline in Patient General Wellbeing Visual Analog Scale Score of Quality of Life at Weeks 12, 24, 52, and 104

End point description:

Participants assessed their general wellbeing using a 0 to 10 horizontal visual analogue scale (VAS). The left-hand extreme of the line equals 0 and is described as " not active at all " and the right-hand extreme equals 10 as " very active " .The final VAS score will be derived by multiplying the original scores by 10. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	19	19	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 12 n=30, 19, 19	-27.3 (± 24.2)	-31.1 (± 27)	-6.6 (± 27)	
Week 24 n=28, 18, 18	-36.1 (± 23.7)	-35.6 (± 34)	-16.1 (± 24.8)	
Week 52 n=23, 17, 15	-40.9 (± 22.5)	-45.6 (± 25.7)	-26 (± 23.1)	
Week 104 n=23, 16, 19	-31.1 (± 22.4)	-38.1 (± 31.7)	-34.7 (± 27.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Functional Assessment of Chronic Illness Therapy Fatigue Score of Quality of Life at Weeks 12, 24, 52, and 104

End point title	Mean Change From Baseline in Functional Assessment of Chronic Illness Therapy Fatigue Score of Quality of Life at Weeks 12, 24, 52, and 104

End point description:

Functional Assessment of Chronic Illness Therapy-Fatigue (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 participants response to the questions (with the exception of 2 negatively stated), the greater the participants 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). A higher score reflects an improvement in the participant's health status. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52 and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	98	99	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 12 n=98, 98, 99	4.3 (± 8.9)	6.5 (± 8.9)	3.4 (± 9.5)	
Week 24 n=98, 99, 94	7.3 (± 9.3)	6.7 (± 10.6)	4.4 (± 8.5)	
Week 52 n=84, 86, 85	6.9 (± 10.6)	7.9 (± 10.4)	6.4 (± 10.1)	
Week 104 n=74, 78, 74	6.3 (± 9.7)	5.8 (± 10.5)	7 (± 10.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Revised Illness Perception Questionnaire Score of Quality of Life at Week 12

End point title	Mean Change From Baseline in Revised Illness Perception Questionnaire Score of Quality of Life at Week 12

End point description:

The Revised Illness Perception Questionnaire (IPQ-R) assesses an illness quantitatively around 9 domains (identity, acute or chronic timeline, consequences, personal control, treatment control, illness coherence, timeline cyclical, emotional representations, and cause). It scores as: 1(strongly disagree), 2(disagree), 3(neither agree/disagree), 4(agree), and 5(strongly agree), except identity as 1(yes) and 0(no). The sum of scores for identity, timeline, consequences, and cyclical domains are ranged from 0-16. High score represent strongly held beliefs about number of symptoms attributed to RA, chronicity of the condition, negative consequences of the illness and cyclical nature of the condition. The sum of scores for personal control, treatment control, and coherence dimensions are ranged from 0-15. High score represent positive beliefs about the number of controllability of RA and a personal understanding of the condition. n = participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Week 12

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	98	99	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Identity n=98, 98, 99	-0.6 (± 2)	-0.8 (± 1.8)	-0.1 (± 2.3)	
Acute or Chronic Timeline n=95, 97, 92	-0.1 (± 0.7)	0 (± 0.6)	0 (± 0.5)	
Consequences n=95, 96, 95	-0.4 (± 0.7)	-0.4 (± 0.7)	-0.2 (± 0.5)	
Personal Control n=98, 98, 98	0.1 (± 0.5)	0.1 (± 0.6)	-0.1 (± 0.7)	
Treatment Control n=98, 96, 94	0.2 (± 0.5)	0.2 (± 0.5)	0.1 (± 0.5)	
Illness Coherence n=95, 96, 95	0.2 (± 0.7)	0.3 (± 0.7)	0.2 (± 0.7)	
Timeline Cyclical n=95, 98, 96	-0.2 (± 0.8)	0 (± 0.7)	-0.2 (± 0.6)	
Emotional Representation n=95, 98, 96	-0.4 (± 0.8)	-0.6 (± 0.9)	-0.2 (± 0.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in The Revised Illness Perception Questionnaire Score of Quality of Life at Week 24

End point title	Mean Change From Baseline in The Revised Illness Perception Questionnaire Score of Quality of Life at Week 24

End point description:

The IPQ-R assesses an illness quantitatively around 9 domains (identity, acute or chronic timeline, consequences, personal control, treatment control, illness coherence, timeline cyclical, emotional representations, and cause). It scores as: 1(strongly disagree), 2 (disagree), 3 (neither agree/disagree), 4 (agree), and 5 (strongly agree), except identity as 1 (yes) and 0 (no). The sum of scores for identity, timeline, consequences, and cyclical domains are ranged from 0-16. High score represent strongly held

beliefs about the number of symptoms attributed to RA, the chronicity of the condition, the negative consequences of the illness and the cyclical nature of the condition. The sum of scores for personal control, treatment control, and coherence dimensions are ranged from 0-15. High score represent positive beliefs about the number of controllability of RA and a personal understanding of the condition. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Week 24

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	99	94	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Identity n=98, 99, 94	-1.2 (± 2.1)	-1 (± 1.9)	-0.3 (± 2.1)	
Acute or Chronic Timeline n=97, 96, 87	0 (± 0.7)	0.1 (± 0.6)	0 (± 0.6)	
Consequences n=97, 96, 89	-0.5 (± 0.7)	-0.4 (± 0.8)	-0.3 (± 0.7)	
Personal Control n=98, 97, 94	0.1 (± 0.6)	0 (± 0.7)	-0.1 (± 0.8)	
Treatment Control n=98, 95, 91	0.1 (± 0.5)	0.1 (± 0.5)	0.2 (± 0.5)	
Illness Coherence n=96, 94, 89	0.3 (± 0.7)	0.3 (± 0.7)	0.2 (± 0.8)	
Timeline Cyclical n=96, 97,90	-0.3 (± 0.7)	-0.2 (± 0.8)	-0.2 (± 0.7)	
Emotional Representation n=96, 97, 90	-0.5 (± 0.9)	-0.5 (± 1)	-0.5 (± 1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in The Revised Illness Perception Questionnaire Score of Quality of Life at Week 52

End point title	Mean Change From Baseline in The Revised Illness Perception Questionnaire Score of Quality of Life at Week 52

End point description:

The IPQ-R assesses an illness quantitatively around 9 domains (identity, acute or chronic timeline, consequences, personal control, treatment control, illness coherence, timeline cyclical, emotional representations, and cause). It scores as: 1(strongly disagree), 2 (disagree), 3 (neither agree/disagree), 4 (agree), and 5 (strongly agree), except identity as 1 (yes) and 0 (no). The sum of scores for identity, timeline, consequences, and cyclical domains are ranged from 0-16. High score represent strongly held beliefs about the number of symptoms attributed to RA, the chronicity of the condition, the negative consequences of the illness and the cyclical nature of the condition. The sum of scores for personal control, treatment control, and coherence dimensions are ranged from 0-15. High score represent positive beliefs about the number of controllability of RA and a personal understanding of the condition. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Week 52

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	86	85	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Identity n=84, 86, 85	-0.1 (± 2.3)	-1.4 (± 2.5)	-1 (± 2)	
Acute or Chronic Timeline n=83, 82, 83	-0.1 (± 0.9)	0.1 (± 0.7)	0.1 (± 0.6)	
Consequences n=83, 82, 84	-0.7 (± 0.9)	-0.7 (± 0.7)	-0.5 (± 0.7)	
Personal Control n=84, 84, 84	0.1 (± 0.6)	0.1 (± 0.6)	0 (± 0.6)	
Treatment Control n=84, 84, 84	0.1 (± 0.6)	0.2 (± 0.6)	0.2 (± 0.5)	
Illness Coherence n=83, 80, 83	0.3 (± 0.7)	0.4 (± 0.7)	0.4 (± 0.7)	
Timeline Cyclical n=83, 83, 83	-0.2 (± 0.8)	-0.3 (± 0.8)	-0.3 (± 0.7)	
Emotional Representation n=83, 82, 83	-0.7 (± 1)	-0.7 (± 1.1)	-0.7 (± 1.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in The Revised Illness Perception Questionnaire Score of Quality of Life at Week 104

End point title	Mean Change From Baseline in The Revised Illness Perception Questionnaire Score of Quality of Life at Week 104

End point description:

The IPQ-R assesses an illness quantitatively around 9 domains (identity, acute or chronic timeline, consequences, personal control, treatment control, illness coherence, timeline cyclical, emotional representations, and cause). It scores as: 1(strongly disagree), 2 (disagree), 3 (neither agree/disagree), 4 (agree), and 5 (strongly agree), except identity as 1 (yes) and 0 (no). The sum of scores for identity, timeline, consequences, and cyclical domains are ranged from 0-16. High score represent strongly held beliefs about the number of symptoms attributed to RA, the chronicity of the condition, the negative consequences of the illness and the cyclical nature of the condition. The sum of scores for personal control, treatment control, and coherence dimensions are ranged from 0-15. High score represent positive beliefs about the number of controllability of RA and a personal understanding of the condition. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	78	74	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Identity n=74, 78, 74	-1 (± 2.3)	-1.3 (± 2.1)	-0.9 (± 2.3)	
Acute or Chronic Timeline n=69, 75, 72	0 (± 0.9)	0.3 (± 0.9)	0.3 (± 0.7)	
Consequences n=69, 76, 73	-0.6 (± 0.8)	-0.5 (± 0.8)	-0.5 (± 0.8)	
Personal Control n=74, 77, 74	0.1 (± 0.7)	0 (± 0.7)	0 (± 0.7)	

Treatment Control n=72, 76, 73	0.1 (± 0.6)	0.1 (± 0.7)	0 (± 0.7)	
Illness Coherence n=69, 75,72	-0.3 (± 0.7)	0.4 (± 0.7)	0.4 (± 0.8)	
Timeline Cyclical n=69, 77, 73	-0.1 (± 0.7)	-0.1 (± 1)	-0.1 (± 0.8)	
Emotional Representation n=69, 77, 73	-0.6 (± 1)	-0.7 (± 1.1)	-0.7 (± 1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With any Adverse Events, any Serious Adverse Events, and Adverse Events Leading to Discontinuation

End point title	Number of Participants With any Adverse Events, any Serious Adverse Events, and Adverse Events Leading to Discontinuation

End point description:

An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign , symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. A serious adverse event is defined as any event which was fatal (resulted in death), life-threatening (with immediate risk of death), resulted in a new or prolongation of a current hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, considered medically significant by the investigator, required intervention to prevent one or more of the outcomes listed above. Safety analysis set was analysed for this end point.

End point type	Secondary

End point timeframe:

Up to Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Number of participants				
number (not applicable)				
Any AE	105	99	108	
Any SAE	16	19	13	
AEs Leading to Discontinuation	23	16	19	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Laboratory Values at Week 12

End point title	Number of Participants With Clinically Significant Laboratory Values at Week 12

End point description:

Laboratory parameters included hematology, chemistry and lipids. Any treatment-emergent abnormal laboratory result accompanied by clinical symptoms or leading to a change in study medication or requiring a change in concomitant therapy was considered clinically significant. Participants with clinically significant laboratory values are reported in the below table. Safety analysis set was analysed for this end point. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Week 12

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	101	100	
Units: Number of participants				
number (not applicable)				
Absolute Neutrophil Count n=97, 94, 97	2	0	0	
Eosinophil n=93, 90, 93	0	0	0	
Hematocrit n=104,100,100	0	0	0	
Hemoglobin n=104, 101,100	0	0	1	
Red blood cells n=104,100,100	1	0	0	
Thrombocyte n=104, 101,100	0	0	0	
White blood cells n=104, 101,100	3	2	0	
Alkaline phosphatase n=104,101, 99	0	0	0	
Alanine transaminase (ALT) n=104, 101,100	4	2	2	
Aspartate aminotransferase (AST) n=104,100,100	1	1	1	
Creatinine n=104,101,100	1	0	0	
CRP n=103,100,100	3	0	2	
High-density lipoprotein (HDL)n=101,100,99	1	0	1	
Low-density lipoprotein (LDL) n=99,97,98	5	2	2	
Total cholesterol n=102,100,99	7	5	2	
Triglycerides n=102,100, 99	0	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Laboratory Values at Week 24

End point title	Number of Participants With Clinically Significant Laboratory Values at Week 24

End point description:

Laboratory parameters included hematology, chemistry and lipids. Any treatment-emergent abnormal laboratory result accompanied by clinical symptoms or leading to a change in study medication or requiring a change in concomitant therapy was considered clinically significant. Participants with clinically significant laboratory values are reported in the below table. Safety analysis set was analysed

for this end point. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Week 24

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	101	98	
Units: Number of Participants				
number (not applicable)				
Absolute Neutrophil Count n=96, 97 ,97	1	0	0	
Eosinophil n=91, 93, 93	0	0	0	
Hematocrit n=100, 99, 98	0	1	0	
Hemoglobin n=100, 100, 98	0	1	1	
RBC n=99, 100, 98	0	1	0	
Thrombocyte n=100, 100, 98	0	0	0	
WBC n=100, 101, 98	2	0	0	
Alkaline phosphatase n=100, 101, 98	0	0	0	
ALT n=100, 101, 98	2	2	5	
AST n=100, 101, 98	2	0	1	
Creatinine n=100, 101, 98	0	0	0	
CRP n=100, 101, 97	0	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Laboratory Values at Week 52

End point title	Number of Participants With Clinically Significant Laboratory Values at Week 52

End point description:

Laboratory parameters included hematology, chemistry and lipids. Any treatment-emergent abnormal laboratory result accompanied by clinical symptoms or leading to a change in study medication or requiring a change in concomitant therapy was considered clinically significant. Participants with clinically significant laboratory values are reported in the below table. Safety analysis set was analysed for this end point. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Week 52

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	92	88	
Units: Number of Participants				
number (not applicable)				
Absolute Neutrophil Count n=83, 90, 85	0	0	0	
Eosinophil n=81, 88, 82	0	0	4	
Hematocrit n=86, 92, 87	0	0	1	
Hemoglobin n=86, 92, 88	0	0	2	
RBC n=86, 91, 87	0	0	1	
Thrombocyte n=85, 92, 88	0	0	1	
WBC n=86, 92, 88	0	1	0	
Alkaline phosphatase n=86, 92, 87	0	0	0	
ALT n=86, 92, 88	0	0	7	
AST n=86, 91, 88	0	0	2	
Creatinine n=86, 92, 88	0	2	0	
CRP n=86, 91, 87	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Laboratory Values at Week 104

End point title	Number of Participants With Clinically Significant Laboratory Values at Week 104

End point description:

Laboratory parameters included hematology, chemistry and lipids. Any treatment-emergent abnormal laboratory result accompanied by clinical symptoms or leading to a change in study medication or requiring a change in concomitant therapy was considered clinically significant. Participants with clinically significant laboratory values are reported in the below table. Safety analysis set was analysed for this end point. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

Week 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	80	78	
Units: Number of Participants				
number (not applicable)				
Absolute Neutrophil Count n=75, 78, 77	0	0	1	
Eosinophil n=72, 77, 74	0	0	0	
Hematocrit n=75, 78, 77	1	0	1	
Hemoglobin n=78, 80, 78	1	0	1	

RBC n=76, 79, 77	1	0	0	
Thrombocyte n=78, 79, 78	0	1	1	
WBC n=78, 80, 78	1	0	1	
Alkaline phosphatase n=78, 79, 78	0	0	0	
Alanine transaminase n=78, 80, 78	0	0	2	
Aspartate aminotransferase n=78, 80, 78	0	0	2	
Creatinine n=78, 79, 78	1	1	0	
CRP n=78, 80, 78	1	0	0	
High-density lipoprotein n=76, 76, 72	1	0	1	
Low-density lipoprotein n=74, 74, 72	0	1	3	
Total cholesterol n=76, 76, 72	0	2	3	
Triglycerides n=76, 76, 72	1	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Disease Activity Score 28 at Weeks 12, 24, 52, and 104

End point title	Absolute Change From Baseline in Disease Activity Score 28 at Weeks 12, 24, 52, and 104

End point description:

The DAS28 score is a measure of the participant's disease activity. DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicated improvement. Participants with missing data at visits before early study termination or who stopped the study prematurely because of insufficient therapeutic response or safety reasons considered non-responders or who stopped the study for other reasons, response set to missing after early withdrawal. The ITT population set was used for analysis. n = number of participants evaluable at particular time of assessment.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) to Weeks 12, 24, 52, and 104

End point values	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate+ Placebo Tocilizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	103	108	
Units: Scores on a scale				
median (full range (min-max))				
Week 12	3.1 (-0.21 to 7.34)	3.3 (0.37 to 6.76)	1.4 (-1.53 to 3.91)	
Week 24	3.6 (0.75 to 7.48)	3.6 (0.45 to 7.64)	2.1 (-1.67 to 5.11)	
Week 52	3.3 (-1.02 to 7.48)	3.4 (0.28 to 7.66)	3.3 (-0.74 to 6.13)	
Week 104	3.3 (-0.7 to 6.07)	3.3 (0.1 to 6.8)	3.2 (-0.79 to 7.52)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 104

Adverse event reporting additional description:

Serious adverse events and non-serious adverse events are reported in Safety Analysis Population, which consists of all participants who received at least one dose of study medication and had a safety assessment performed post-baseline.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Tocilizumab + Methotrexate

Reporting group description:

Participants received IV TCZ 8 mg/ kg every four weeks for a maximum of 26 infusions + oral capsules of MTX 10–30 mg/week in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week. The weekly dose of MTX was taken on one particular day of the week.

Reporting group title	Tocilizumab+ Placebo Methotrexate

Reporting group description:

Participants received IV TCZ 8 mg/kg every four weeks for a maximum of 26 infusions + weekly oral matching placebo MTX capsules in climbing dosages. The weekly dose of placebo MTX was taken on one particular day of the week.

Reporting group title	Methotrexate + Placebo Tocilizumab

Reporting group description:

Participants received weekly oral MTX in climbing dosages of 5 mg starting at 10 mg up till a maximum dosage of 30 mg/week + matching placebo TCZ IV 8 mg/kg every four week for a maximum of 26 infusions. The weekly dose of MTX was taken on one particular day of the week.

Serious adverse events	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate + Placebo Tocilizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 106 (15.09%)	19 / 103 (18.45%)	13 / 108 (12.04%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of bladder			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			

subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid adenoma			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc operation			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Device malfunction			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	1 / 106 (0.94%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 106 (0.94%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Diplopia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid ptosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative keratitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal adhesions			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	3 / 106 (2.83%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 106 (0.94%)	2 / 103 (1.94%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone lesion			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 106 (0.00%)	2 / 103 (1.94%)	2 / 108 (1.85%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 103 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic infection			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral pericarditis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 103 (0.97%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 106 (0.00%)	0 / 103 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tocilizumab + Methotrexate	Tocilizumab+ Placebo Methotrexate	Methotrexate + Placebo Tocilizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 106 (99.06%)	99 / 103 (96.12%)	106 / 108 (98.15%)
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	25 / 106 (23.58%)	16 / 103 (15.53%)	28 / 108 (25.93%)
occurrences (all)	30	16	38
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 106 (8.49%)	6 / 103 (5.83%)	15 / 108 (13.89%)
occurrences (all)	13	6	22
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 106 (10.38%)	10 / 103 (9.71%)	4 / 108 (3.70%)
occurrences (all)	13	10	5
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 106 (18.87%)	15 / 103 (14.56%)	22 / 108 (20.37%)
occurrences (all)	28	22	25
Dizziness			
subjects affected / exposed	12 / 106 (11.32%)	12 / 103 (11.65%)	17 / 108 (15.74%)
occurrences (all)	14	14	20
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 106 (28.30%)	25 / 103 (24.27%)	34 / 108 (31.48%)
occurrences (all)	39	29	41
Influenza like illness			
subjects affected / exposed	6 / 106 (5.66%)	8 / 103 (7.77%)	11 / 108 (10.19%)
occurrences (all)	6	10	13
Malaise			
subjects affected / exposed	4 / 106 (3.77%)	8 / 103 (7.77%)	9 / 108 (8.33%)
occurrences (all)	6	8	10
Oedema peripheral			
subjects affected / exposed	8 / 106 (7.55%)	6 / 103 (5.83%)	2 / 108 (1.85%)
occurrences (all)	10	7	2
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	13 / 106 (12.26%)	12 / 103 (11.65%)	3 / 108 (2.78%)
occurrences (all)	17	17	6
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	27 / 106 (25.47%)	20 / 103 (19.42%)	48 / 108 (44.44%)
occurrences (all)	35	24	64
Diarrhoea			
subjects affected / exposed	19 / 106 (17.92%)	12 / 103 (11.65%)	20 / 108 (18.52%)
occurrences (all)	22	14	24
Mouth ulceration			
subjects affected / exposed	15 / 106 (14.15%)	12 / 103 (11.65%)	5 / 108 (4.63%)
occurrences (all)	17	14	5
Abdominal pain upper			
subjects affected / exposed	4 / 106 (3.77%)	12 / 103 (11.65%)	13 / 108 (12.04%)
occurrences (all)	5	14	15
Abdominal discomfort			
subjects affected / exposed	6 / 106 (5.66%)	5 / 103 (4.85%)	15 / 108 (13.89%)
occurrences (all)	8	5	16
Vomiting			
subjects affected / exposed	4 / 106 (3.77%)	6 / 103 (5.83%)	8 / 108 (7.41%)
occurrences (all)	5	6	9
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 106 (13.21%)	10 / 103 (9.71%)	18 / 108 (16.67%)
occurrences (all)	17	11	22
Oropharyngeal pain			
subjects affected / exposed	8 / 106 (7.55%)	11 / 103 (10.68%)	6 / 108 (5.56%)
occurrences (all)	9	13	8
Rhonchi			
subjects affected / exposed	3 / 106 (2.83%)	5 / 103 (4.85%)	8 / 108 (7.41%)
occurrences (all)	3	5	9
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 106 (6.60%)	9 / 103 (8.74%)	10 / 108 (9.26%)
occurrences (all)	7	9	12
Alopecia			
subjects affected / exposed	1 / 106 (0.94%)	12 / 103 (11.65%)	11 / 108 (10.19%)
occurrences (all)	1	13	11
Eczema			

subjects affected / exposed	8 / 106 (7.55%)	6 / 103 (5.83%)	6 / 108 (5.56%)
occurrences (all)	8	7	6
Pruritus			
subjects affected / exposed	7 / 106 (6.60%)	5 / 103 (4.85%)	7 / 108 (6.48%)
occurrences (all)	8	6	10
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 106 (5.66%)	12 / 103 (11.65%)	11 / 108 (10.19%)
occurrences (all)	8	16	13
Arthralgia			
subjects affected / exposed	4 / 106 (3.77%)	8 / 103 (7.77%)	12 / 108 (11.11%)
occurrences (all)	5	11	16
Bursitis			
subjects affected / exposed	7 / 106 (6.60%)	6 / 103 (5.83%)	6 / 108 (5.56%)
occurrences (all)	7	7	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	38 / 106 (35.85%)	40 / 103 (38.83%)	37 / 108 (34.26%)
occurrences (all)	67	64	69
Influenza			
subjects affected / exposed	18 / 106 (16.98%)	13 / 103 (12.62%)	10 / 108 (9.26%)
occurrences (all)	25	15	11
Cystitis			
subjects affected / exposed	6 / 106 (5.66%)	6 / 103 (5.83%)	11 / 108 (10.19%)
occurrences (all)	12	11	24
Oral herpes			
subjects affected / exposed	7 / 106 (6.60%)	7 / 103 (6.80%)	6 / 108 (5.56%)
occurrences (all)	7	7	8
Urinary tract infection			
subjects affected / exposed	6 / 106 (5.66%)	3 / 103 (2.91%)	8 / 108 (7.41%)
occurrences (all)	6	4	16
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	10 / 106 (9.43%)	7 / 103 (6.80%)	4 / 108 (3.70%)
occurrences (all)	10	8	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2010	Protocol Amendment A- Adverse events of special interest (AESIs) were included, which allowed for more systematic querying of safety information on AEs. The dose modification rules were updated. A change in dosing of TCZ was implemented. The schedule of collection of biomarker samples was updated according to latest scientific insights.
07 September 2010	Protocol Amendment B-In order to align with the latest TCZ program standards for safety data collection, the safety information with TCZ was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported