Clinical trial results:
Randomized, Phase IV, Placebo-controlled, Comparative Study to Evaluate the Efficacy and Safety of Tapering Methotrexate (MTX) Dosage Versus Maintaining the Dosage in Patients with Severe Active Rheumatoid Arthritis (RA) Who Have Demonstrated an Inadequate Response (IR) to Prior Disease-modifying Anti-rheumatic Drugs (DMARDs) Treatment and Have Initiated RoActemra (RoActemra, TCZ) in Combination with MTX

Summary

EudraCT number	2011-005260-20
Trial protocol	GB
Global end of trial date	05 February 2015

Results information

Result version number	v1 (current)
This version publication date	04 September 2016
First version publication date	04 September 2016

Trial information

Trial identification

Sponsor protocol code	ML28096

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01661140
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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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	05 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2015
Global end of trial reached?	Yes
Global end of trial date	05 February 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the percentage of subjects who maintain good/moderate European League Against Rheumatism (EULAR) response between subjects receiving RoActemra in combination with a tapering dose of MTX and subjects receiving RoActemra in combination with a stable dose of MTX from Week 24 to Week 60.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 427
Worldwide total number of subjects	427
EEA total number of subjects	427

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)	335
From 65 to 84 years	90
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The initial open label phase of the study consisted of one group of 427 subjects. After completion of the open label phase only subjects, who achieved a good/moderate disease response, were randomised into the double blind phase of the study. 272 subjects were randomised into the two groups entering the main phase of the study.

Period 1

Period 1 title	Open-Label Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Initial Phase

Arm description:

At Week 0 subjects started open-label tocilizumab and open-label methotrexate (MTX) for 24 weeks, which was the initial phase of the study.

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

Dosage and administration details:

8 milligrams per kilogram (mg/kg) intravenously every 4 weeks, 24 weeks

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

Dosage and administration details:

Methotrexate (MTX) was administered weekly according to the subject's pre-study MTX dose.

Number of subjects in period 1	Initial Phase
Started	427
Completed	351
Not completed	76
Adverse event, non-fatal	44
Protocol violation	3
Death	1
Administrative/other	1

Investigator decision	3
Lost to follow-up	2
Withdrew consent	5
Sponsor termination	16
Did not meet EULAR criteria	1

Period 2

Period 2 title	Double-Blind Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Methotrexate (MTX) Tapering Group

Arm description:

After the open-label period ended at Week 24, subjects achieving a good/moderate European League Against Rheumatism (EULAR) disease response were randomised to the MTX Tapering Group or MTX Maintenance Group. In the MTX Tapering Group subjects received a double-blind MTX dose according to the MTX tapering scheme between Week 24 and Week 56. In addition, subjects continued to receive open-label tocilizumab between Week 24 and Week 56. From Week 56 to Week 72 subjects received tocilizumab monotherapy.

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

Dosage and administration details:

8 milligrams per kilogram (mg/kg) intravenously every 4 weeks, 72 weeks.

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

Dosage and administration details:

Tapering doses of methotrexate (MTX) were administered weekly from Week 24 to Week 56. Tapering doses depended on dose administered to the subject during the open label period. First tapering occured at randomisation (Week 24), second tapering at Week 32, third tapering at Week 40 and final tapering at Week 48.

Arm title	Methotrexate (MTX) Maintenance Group

Arm description:

After the open-label period ended at Week 24, subjects achieving a good/moderate European League Against Rheumatism (EULAR) disease response were randomised to the MTX Tapering Group or MTX Maintenance Group. In the MTX Maintenance Group subjects continued to be administered the same dose of MTX in a double-blind fashion from Week 25 to Week 56. In addition, subjects continued to receive open-label tocilizumab from Week 25 to Week 56. From Week 56 to Week 72 subjects received tocilizumab monotherapy.

Arm type	Experimental

Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra, Actemra
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 milligrams per kilogram (mg/kg) intravenously every 4 weeks, 72 weeks

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

Dosage and administration details:

Stable doses of methotrexate (MTX) were administered weekly from Week 24 to Week 56. MTX was dosed according to the subject's open-label MTX dose.

Number of subjects in period 2[1]	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group
Started	136	136
Completed	95	86
Not completed	41	50
Adverse event, non-fatal	16	18
Protocol violation	2	3
Administrative/other	7	6
Refused treatment	-	1
Investigator decision	1	2
Withdrew consent	1	3
Sponsor termination	14	17

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Of the 351 subjects who completed the open-label period, 79 did not continue to the double-blind period. The remaining 272 subjects were randomised to double blind treatment groups.

Baseline characteristics

Reporting groups	
Reporting group title	Initial Phase
Reporting group description:	
At Week 0 subjects started open-label tocilizumab and open-label methotrexate (MTX) for 24 weeks, which was the initial phase of the study.	

Reporting group values	Initial Phase	Total	
Number of subjects	427	427	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	55		
standard deviation	± 12.03	-	
Gender categorical			
Units: Subjects			
Female	326	326	
Male	101	101	

End points

End points reporting groups

Reporting group title	Initial Phase

Reporting group description:

At Week 0 subjects started open-label tocilizumab and open-label methotrexate (MTX) for 24 weeks, which was the initial phase of the study.

Reporting group title	Methotrexate (MTX) Tapering Group

Reporting group description:

After the open-label period ended at Week 24, subjects achieving a good/moderate European League Against Rheumatism (EULAR) disease response were randomised to the MTX Tapering Group or MTX Maintenance Group. In the MTX Tapering Group subjects received a double-blind MTX dose according to the MTX tapering scheme between Week 24 and Week 56. In addition, subjects continued to receive open-label tocilizumab between Week 24 and Week 56. From Week 56 to Week 72 subjects received tocilizumab monotherapy.

Reporting group title	Methotrexate (MTX) Maintenance Group

Reporting group description:

After the open-label period ended at Week 24, subjects achieving a good/moderate European League Against Rheumatism (EULAR) disease response were randomised to the MTX Tapering Group or MTX Maintenance Group. In the MTX Maintenance Group subjects continued to be administered the same dose of MTX in a double-blind fashion from Week 25 to Week 56. In addition, subjects continued to receive open-label tocilizumab from Week 25 to Week 56. From Week 56 to Week 72 subjects received tocilizumab monotherapy.

Primary: Percentage of Subjects Maintaining Previous Disease Activity (European League Against Rheumatism [EULAR] Response) From Week 24 (Time of Randomisation) to Week 60

End point title	Percentage of Subjects Maintaining Previous Disease Activity (European League Against Rheumatism [EULAR] Response) From Week 24 (Time of Randomisation) to Week 60

End point description:

Response was determined using EULAR criteria based upon (Disease Activity Score In 28 Joints) DAS28 absolute scores at the assessment visit and the DAS28 reduction from the reference visit. Subjects with a score lesser than or equal to (<=) 3.2 and reduction of greater than (>) 1.2 points were assessed as having a 'good' response. Subjects with a score >3.2 with reduction of >1.2 points, or a score <=5.1 with reduction of >0.6 to <=1.2 points, were assessed as having a 'moderate' response. Subjects with a score >5.1 with reduction of >0.6 to <=1.2 points, or any score with reduction <=0.6 points, were assessed as non-responders with response recorded as 'none.'

Intention to treat (ITT) population included all randomised participants.

End point type	Primary

End point timeframe:

From randomisation (Week 24) to Week 60

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)	76.5	65.4		

Statistical analyses

Statistical analysis title	Difference in percentage
Statistical analysis description:	
Comparison was Tapering MTX : MTX maintenance. Last post-baseline EULAR response recorded used for subjects with a missing result at Week 60.	
Comparison groups	Methotrexate (MTX) Tapering Group v Methotrexate (MTX) Maintenance Group
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.036
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.803
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.037
upper limit	3.133

Notes:

[1] - Non-inferiority if the difference between treatments is statistically significant and the lower limit of the 95% confidence interval (CI) is greater than 0.9.

Secondary: Change From Week 24 in Disease Activity Score In 28 Joints (DAS28) Score at Week 60

End point title	Change From Week 24 in Disease Activity Score In 28 Joints (DAS28) Score at Week 60

End point description:

The DAS28 defined as a combined index for measuring disease activity in rheumatoid arthritis (RA). The index included swollen (range 0-28) and tender joint counts (TJC) (range 0-28), acute phase response Erythrocyte Sedimentation Rate (ESR), and general health status (range 1-100). The index was calculated using the following formula: The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x patient global assessment of disease activity]. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity.

ITT population included all randomised subjects. Here, number of subjects analysed signifies those subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

From randomisation (Week 24) to Week 60

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 135, 136)	2.572 (± 1.3218)	2.573 (± 1.3017)		
Change at Week 60 (n= 134, 135)	-0.179 (± 1.1702)	-0.233 (± 1.5156)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Disease Activity Score In 28 Joints (DAS28) Score at Week 72

End point title	Change From Week 24 in Disease Activity Score In 28 Joints (DAS28) Score at Week 72

End point description:

The DAS28 defined as a combined index for measuring disease activity in rheumatoid arthritis (RA). The index included swollen (range 0-28) and tender joint counts (TJC) (range 0-28), acute phase response Erythrocyte Sedimentation Rate (ESR), and general health status (range 1-100). The index was calculated using the following formula: The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x patient global assessment of disease activity]. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity.

ITT population included all randomised subjects. Here, number of subjects analysed signifies those subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

From randomisation (Week 24) to Week 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	135		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.105 (± 1.2262)	-0.224 (± 1.4961)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Score of <=1 in Tender Joint Count (TJC) and Swollen Joint Count (SJC) at Week 60 and 72

End point title	Percentage of Subjects Who Achieved Score of <=1 in Tender Joint Count (TJC) and Swollen Joint Count (SJC) at Week 60 and 72

End point description:

Percentage of subjects who achieve score of <=1 in TJC and SJC at week 60 and 72 were reported. The number of swollen joints was recorded on the joint assessment form at each visit, no swelling = 0, swelling =1; total was calculated by adding all the joints for a maximum score of 28. The number of tender joints was recorded on the joint assessment form at each visit, no tenderness = 0, tenderness = 1; total was calculated by adding all the joints for a maximum score of 28.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
TJC <=1, Week 60	39	39		
SJC <=1, Week 60	44.1	58.1		
TJC <=1, Week 72	37.5	40.4		
SJC <=1, Week 72	55.9	60.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved a Disease Activity Score In 28 Joints (DAS28) <= 3.2

End point title	Percentage of Subjects Who Achieved a Disease Activity Score In 28 Joints (DAS28) <= 3.2

End point description:

The DAS28 index was calculated using the following formula: The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x patient global assessment of disease activity]. Subjects who achieved score <=3.2 at weeks 60 and 72 were reported.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
Week 60	59.6	62.5		
Week 72	61	60.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved DAS28 Remission (DAS28 < 2.6)

End point title	Percentage of Subjects Who Achieved DAS28 Remission (DAS28 < 2.6)

End point description:

The DAS28 index was calculated using the following formula: The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x patient global assessment of disease activity]. Participants who achieve DAS28 remission score <2.6 at weeks 60 and 72 were reported.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
Week 60	51.5	47.1		
Week 72	50	51.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Change in Disease Activity Score (cDAS) >=1.2

End point title	Percentage of Subjects Who Achieved Change in Disease Activity Score (cDAS) >=1.2

End point description:

The DAS28 index was calculated using the following formula: The DAS28 was calculated as [0.28 x the square root of number of swollen joints] + [0.56 x the square root of number of tender joints] + [0.7 x the natural log of ESR] + [0.014 x patient global assessment of disease activity]. Participants who achieve cDAS28 >=1.2 score at weeks 60 and 72 were reported.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
Week 60	9.6	16.2		
Week 72	9.6	15.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Clinical Disease Activity Index (CDAI) Remission (CDAI < 2.8) at Week 60 and 72

End point title	Percentage of Subjects Who Achieved Clinical Disease Activity Index (CDAI) Remission (CDAI < 2.8) at Week 60 and 72

End point description:

Clinical Disease Activity Index (CDAI) was an index for measuring disease activity in RA. The index was calculated using the following formula: CDAI: SJC28 + TJC28 + patient global assessment of disease (PGA) 10 centimeter [cm] Visual Analog Scale [VAS] + physician global assessment of disease (PhGA) 10 cm VAS. VAS assessments involved a 10 cm horizontal scale from 'no disease activity' to 'maximum disease activity.' CDAI scores ranged from 0 to 76, with higher scores indicating increased disease activity.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Randomisation (Week 24), Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
Week 60	2.9	1.5		
Week 72	1.5	3.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Simplified Disease Activity Index (SDAI) Remission (SDAI < 3.3) at Week 60 and 72

End point title	Percentage of Subjects Who Achieved Simplified Disease Activity Index (SDAI) Remission (SDAI < 3.3) at Week 60 and 72

End point description:

Simplified Disease Activity Index (SDAI) was an index for measuring disease activity in RA. The index was calculated using the following formula: CDAI: SJC28 + TJC28 + PGA (10 cm VAS) + PhGA (10 cm VAS + C-Reactive Protein (CRP). VAS assessments involved a 10-cm horizontal scale from 'no disease activity' to 'maximum disease activity. Scores ranged from 0 to 86, with higher scores also indicating increased disease activity.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Randomisation (Week 24), Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
Week 60	2.9	0.7		
Week 72	2.9	0.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement in Physical Function Using

Health Assessment Questionnaire [HAQ] at Week 60 and 72

End point title	Percentage of Subjects With Improvement in Physical Function Using Health Assessment Questionnaire [HAQ] at Week 60 and 72

End point description:

The HAQ-disability index (DI) evaluates subject-reported quality of life using 8 categories: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other common activities such as running errands and performing household chores and 20 questions. Each category contains multiple questions, which were answered using a 4-point scale from 0 to 3. The overall index score was an average of the individual item responses and may range from 0 to 3, where higher scores indicate more difficulty in daily living activities. Improvement was defined as a decrease from Week 24 to Week 60 and 72. Reported is the percentage of subjects with an improvement in HAQ-DI score.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Randomisation (Week 24), Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
Improvement at Week 60	27	39.6		
Improvement at Week 72	40.5	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement in Physical Function Using Functional Assessment of Chronic Illness Therapy - Fatigue [FACIT-F] at Week 60 and 72

End point title	Percentage of Subjects With Improvement in Physical Function Using Functional Assessment of Chronic Illness Therapy - Fatigue [FACIT-F] at Week 60 and 72

End point description:

The FACIT-fatigue assessment was a 13-item questionnaire with subjects scoring each item on a 5-point scale (not at all; a little bit; somewhat; quite a bit and very much). The total score ranges from 0 to 65 and higher scores indicate more fatigue. Improvement was defined as a decrease from Week 24 to Week 60 and 72. Reported is the percentage of subjects with an improvement in total FACIT score.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Randomisation (Week 24), Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
Improvement at Week 60	54	50		
Improvement at Week 72	45.2	56.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement in Physical Function Using 12-item Short Form Health Survey [SF-12]) at Week 60 and 72

End point title	Percentage of Subjects With Improvement in Physical Function Using 12-item Short Form Health Survey [SF-12]) at Week 60 and 72

End point description:

Quality of life questionnaire (SF-12) scores were computed using the scores of 12 questions and ranged from 0 to 100, where a 0 score indicated the lowest level of health measured by the scales and 100 indicated the highest level of health. Improvement was defined as a decrease from Week 24 to Week 60 and 72. Reported is the percentage of subjects with an improvement in SF-12 score.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Randomisation (Week 24), Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)				
Improvement at Week 60	22.2	10.4		
Improvement at Week 72	23.8	15.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anaemia

End point title	Percentage of Subjects With Anaemia

End point description:

Safety population included all the randomised subjects.

End point type	Secondary

End point timeframe:

Week 0 up to Week 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: percentage of subjects				
number (not applicable)	1.5	0.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE was any adverse event that can be fatal, life threatening, requires long or prolonged hospitalisation, results in persistent or significant disability/incapacity, congenital anomaly or significant medical event in the investigator's judgment.

Safety population included all the randomised subjects.

End point type	Secondary

End point timeframe:

Week 0 up to Week 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: subjects				
number (not applicable)				

AEs	98	98		
SAEs	9	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Able to Discontinue Methotrexate

End point title	Percentage of Subjects Able to Discontinue Methotrexate

End point description:

End point type	Secondary

End point timeframe:

Week 0 up to Week 60

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: percentage of subjects				
number (not applicable)				

Notes:

[2] - Data were not collected for this end point.

[3] - Data were not collected for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Employed Assessed Using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP)

End point title	Number of Subjects Employed Assessed Using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP)

End point description:

The WPAI-SHP questionnaire assesses work productivity and activity impairment. It is a patient-reported assessment regarding hours missed and hours worked at employment and degree to which a specified health problem affected work productivity and regular activities. It consists of 6 questions to assess the impact of a specific health problem on work productivity and on regular daily activities.

ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: participants				
Week 60	33	17		
Week 72	23	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Hours Actually Worked and Work Hours Missed Assessed Using the WPAI-SHP

End point title	Hours Actually Worked and Work Hours Missed Assessed Using the WPAI-SHP

End point description:

The WPAI-SHP questionnaire assesses work productivity and activity impairment. It is a patient-reported assessment regarding hours missed and hours worked at employment and degree to which a specified health problem affected work productivity and regular activities. It consists of 6 questions to assess the impact of a specific health problem on work productivity and on regular daily activities. Reported here are hours actually worked, work hours missed due to rheumatoid arthritis (RA), work hours missed due to other reasons and the change from Week 24 for each of these parameters reported at Week 60 and Week 72.

Subjects in the ITT population with available data were analysed.

End point type	Secondary

End point timeframe:

Randomisation (Week 24), Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: hours				
median (full range (min-max))				
Hours actually worked (HAW), Week 60 (n=33, 17)	25 (0 to 58)	28 (0 to 40)		
Change from Week 24 in HAW, Week 60 (n=29, 17)	-1 (-47 to 40)	2 (-43 to 38)		
Work hours missed (WHM) to RA, Week 60 (n=33, 17)	0 (0 to 15)	0 (0 to 35)		
Change from Week 24 in WHM RA, Week 60 (n=30, 16)	0 (-30 to 15)	0 (-7 to 21)		

WHM other, Week 60 (n=33, 17)	0 (0 to 46)	0 (0 to 35)		
Change from Week 24 WHM other, Week 60 (n=30, 16)	0 (-56 to 46)	0 (-38 to 35)		
HAW, Week 72 (n=23, 13)	30 (0 to 48)	16 (0 to 40)		
Change from Week 24 in HAW, Week 72, (n=20, 12)	0 (-37 to 23)	2.5 (-30 to 40)		
WHM to RA, Week 72 (n=23, 13)	0 (0 to 37)	0 (0 to 35)		
Change from Week 24 in WHM RA, Week 72 (n=21, 11)	0 (-30 to 37)	0 (-7 to 21)		
WHM other, Week 72 (n=23, 13)	0 (0 to 30)	0 (0 to 8)		
Change from Week 24 WHM other, Week 72 (n=21, 11)	0 (-56 to 30)	0 (-38 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Productivity and Regular Daily Activities Affected by Rheumatoid Arthritis Assessed Using the WPAI-SHP

End point title	Change in Productivity and Regular Daily Activities Affected by Rheumatoid Arthritis Assessed Using the WPAI-SHP

End point description:

The WPAI-SHP questionnaire assesses work productivity and activity impairment. It is a patient-reported assessment regarding hours missed and hours worked at employment and degree to which a specified health problem affected work productivity and regular activities. It consists of 6 questions to assess the impact of a specific health problem on work productivity and on regular daily activities. Assessments were made using a visual analogue scale ranging from 0 to 10 where 0 = minimum impact and 10 = maximum impact.

Subjects in the ITT population with available data at the respective time points were analysed.

End point type	Secondary

End point timeframe:

Randomisation (Week 24), Week 60, 72

End point values	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: units on a scale				
median (full range (min-max))				
Productivity (P), Week 60 (n=34, 18)	2 (0 to 8)	2 (0 to 10)		
Change in P from Week 24 at Week 60 (n=30, 16)	1 (-6 to 8)	0 (-5 to 7)		
Regular Daily Activities (RDA), Week 60 (n=60, 45)	3 (0 to 9)	3 (0 to 9)		
Change in RDA from Week 24 at Week 60 (n=59, 44)	0 (-5 to 7)	0 (-6 to 6)		
Productivity (P), Week 72 (n=24, 12)	3 (0 to 8)	3 (0 to 9)		
Change in P from Week 24 at Week 72 (n=21, 11)	0 (-3 to 4)	0 (-5 to 7)		

Regular Daily Activities (RDA), Week 72 (n=42, 31)	3 (0 to 10)	3 (0 to 9)		
Change in RDA from Week 24 at Week 72 (n=41, 29)	0 (-5 to 4)	-1 (-5 to 7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment to unscheduled visit (up to Week 72)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Initial Phase

Reporting group description:

At Week 0 participants started open-label tocilizumab and open-label MTX for 24 weeks, which was the initial phase of the study.

Adverse events in this reporting group are those occurring in the open-label phase only.

Reporting group title	Methotrexate (MTX) Tapering Group

Reporting group description:

After the open-label period ended at Week 24, subjects achieving a good/moderate European League Against Rheumatism (EULAR) disease response were randomised to the MTX Tapering Group or MTX Maintenance Group. In the MTX Tapering Group subjects received a double-blind MTX dose according to the MTX tapering scheme between Week 24 and Week 56. In addition, subjects continued to receive open-label tocilizumab between Week 24 and Week 56. From Week 56 to Week 72 subjects received tocilizumab monotherapy.

Adverse events in this reporting group are those occurring in the double-blind phase only.

Reporting group title	Methotrexate (MTX) Maintenance Group

Reporting group description:

After the open-label period ended at Week 24, subjects achieving a good/moderate European League Against Rheumatism (EULAR) disease response were randomised to the MTX Tapering Group or MTX Maintenance Group. In the MTX Maintenance Group subjects continued to be administered the same dose of MTX in a double-blind fashion from Week 25 to Week 56. In addition, subjects continued to receive open-label tocilizumab from Week 25 to Week 56. From Week 56 to Week 72 subjects received tocilizumab monotherapy.

Adverse events in this reporting group are those occurring in the double-blind phase only.

Serious adverse events	Initial Phase	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 427 (4.92%)	9 / 136 (6.62%)	3 / 136 (2.21%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon neoplasm			
subjects affected / exposed	0 / 427 (0.00%)	1 / 136 (0.74%)	0 / 136 (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

Carcinoid tumour of the gastrointestinal tract			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 427 (0.47%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 136 (0.74%)	0 / 136 (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
Joint dislocation			
subjects affected / exposed	0 / 427 (0.00%)	1 / 136 (0.74%)	0 / 136 (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
Fall			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Multiple fractures			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Nervous system disorders			
Carotid artery dissection			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Migraine			

subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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 dislocation			
subjects affected / exposed	0 / 427 (0.00%)	1 / 136 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 427 (0.47%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterovesical fistula			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 2	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	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Interstitial lung disease			

subjects affected / exposed	2 / 427 (0.47%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Pneumonitis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Pulmonary fibrosis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Telangiectasia			
subjects affected / exposed	0 / 427 (0.00%)	0 / 136 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 427 (0.00%)	1 / 136 (0.74%)	0 / 136 (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
Arthralgia			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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

Costochondritis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Pain in extremity			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 427 (0.00%)	2 / 136 (1.47%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 427 (0.47%)	2 / 136 (1.47%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Abdominal sepsis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 136 (0.74%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 427 (0.00%)	0 / 136 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node tuberculosis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 136 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 136 (0.74%)	0 / 136 (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
Arthritis infective			

subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Bronchitis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Cellulitis			
subjects affected / exposed	2 / 427 (0.47%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Tooth infection			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Urinary tract infection			

subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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
Viral labyrinthitis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 136 (0.00%)	0 / 136 (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

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

Non-serious adverse events	Initial Phase	Methotrexate (MTX) Tapering Group	Methotrexate (MTX) Maintenance Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 427 (61.59%)	62 / 136 (45.59%)	70 / 136 (51.47%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	51 / 427 (11.94%)	6 / 136 (4.41%)	7 / 136 (5.15%)
occurrences (all)	59	7	8
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	16 / 427 (3.75%)	7 / 136 (5.15%)	6 / 136 (4.41%)
occurrences (all)	20	7	7
Fall			
subjects affected / exposed	15 / 427 (3.51%)	8 / 136 (5.88%)	4 / 136 (2.94%)
occurrences (all)	15	10	4
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 427 (8.90%)	8 / 136 (5.88%)	6 / 136 (4.41%)
occurrences (all)	58	10	12
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	54 / 427 (12.65%)	7 / 136 (5.15%)	11 / 136 (8.09%)
occurrences (all)	67	14	12
Mouth ulceration			
subjects affected / exposed	48 / 427 (11.24%)	5 / 136 (3.68%)	9 / 136 (6.62%)
occurrences (all)	56	6	10
Nausea			

subjects affected / exposed	28 / 427 (6.56%)	5 / 136 (3.68%)	8 / 136 (5.88%)
occurrences (all)	36	7	11
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	23 / 427 (5.39%)	9 / 136 (6.62%)	8 / 136 (5.88%)
occurrences (all)	26	12	9
Cough			
subjects affected / exposed	29 / 427 (6.79%)	8 / 136 (5.88%)	6 / 136 (4.41%)
occurrences (all)	30	9	6
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	32 / 427 (7.49%)	3 / 136 (2.21%)	7 / 136 (5.15%)
occurrences (all)	36	3	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 427 (3.75%)	8 / 136 (5.88%)	9 / 136 (6.62%)
occurrences (all)	21	9	10
Musculoskeletal pain			
subjects affected / exposed	13 / 427 (3.04%)	7 / 136 (5.15%)	6 / 136 (4.41%)
occurrences (all)	15	8	6
Back pain			
subjects affected / exposed	16 / 427 (3.75%)	2 / 136 (1.47%)	7 / 136 (5.15%)
occurrences (all)	18	2	7
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	61 / 427 (14.29%)	16 / 136 (11.76%)	17 / 136 (12.50%)
occurrences (all)	68	17	22
Lower respiratory tract infection			
subjects affected / exposed	41 / 427 (9.60%)	11 / 136 (8.09%)	12 / 136 (8.82%)
occurrences (all)	46	12	13
Upper respiratory tract infection			
subjects affected / exposed	23 / 427 (5.39%)	12 / 136 (8.82%)	7 / 136 (5.15%)
occurrences (all)	25	13	8
Urinary tract infection			
subjects affected / exposed	19 / 427 (4.45%)	9 / 136 (6.62%)	6 / 136 (4.41%)
occurrences (all)	21	12	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2012	- Information added to include pregnancy report and study drug compliance information. - Information removed for immunogenicity as it was confirmed that the sites would not receive results.
09 July 2013	- Modification of the time-point for the primary endpoint analysis changed from Week 56 to Week 60 in order to obtain data on 12 weeks monotherapy, versus 8 weeks, after completion of tapering, as this represents more clinically meaningful and robust data to support the expected success of the tapering strategy. - Total study treatment duration changed to 72 weeks to ensure patient access to the drug and to have data on 24 weeks after the completion of tapering. - Change in the definition of disease flare, as during the conduct of the study, it was identified that the previous disease flare definition (based on the increase in the combined number of tender and swollen joints from the previous study visit) could classify patients as having disease flare even if they were in remission. - Modification of inclusion criterion number 3 to further clarify that patients had to qualify for biologic therapy according to National Institute for Health and Clinical Excellence (NICE) in order to be eligible to participate in the study. - Modification of exclusion criterion number 2 to align with the current version of the summary of product characteristics (SmPC). Also addition of exclusion criterion number 40 for consistency in the clinical trial program. - Length of study changed to 42 months and recruitment period changed to 23 months to ensure sufficient time for completion of patient enrollment into the study.
13 September 2013	- Text added to permitted therapy to provide clarification of the use of DMARDs at Week 0. - Text rewritten on MTX/Placebo to avoid changing MTX dose to handle neutropenia, as it should be dealt with as per RoActemra (tocilizumab) SmPC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 February 2015	The study was terminated early due to difficulty with recruitment and a higher than expected withdrawal rate.	-

Notes:

Limitations and caveats

None reported