Clinical trial results:
TOSCARA: An open-label, single-arm study to evaluate the efficacy, safety and tolerability of tocilizumab (TCZ) subcutaneous in TCZ-naïve patients with active rheumatoid arthritis

Summary

EudraCT number	2013-002150-79
Trial protocol	BE
Global end of trial date	04 September 2015

Results information

Result version number	v1
This version publication date	17 November 2016
First version publication date	17 November 2016

Trial information

Trial identification

Sponsor protocol code	ML28701

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02031471
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: TOSCARA

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
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of subcutaneous (SC) tocilizumab (TCZ) monotherapy and/or in combination with methotrexate (MTX) or other non-biologic disease modifying antirheumatic drugs (DMARDs) using change of Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 24.

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	28 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 52
Country: Number of subjects enrolled	Luxembourg: 5
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	45

From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 62 subjects were screened, 57 subjects were enrolled. Subjects who completed the 24 Week Treatment Period achieving at least a moderate European League Against Rheumatism (EULAR) response at Week 24 were allowed to enter the Long Term Extension (LTE) Period.

Period 1

Period 1 title	24 Week Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tocilizumab

Arm description:

Adults with rheumatoid arthritis received a fixed dose of tocilizumab during the 24-week open-label core study and those entering the long term extension (LTE) period further received a fixed dose up to a maximum of 28 weeks or until tocilizumab was commercially available and/or reimbursed whichever came first. A fixed dose of 162 milligram (mg) tocilizumab was administered subcutaneously once weekly.

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

Dosage and administration details:

Subjects received fixed dose of 162 mg SC weekly.

Number of subjects in period 1	Tocilizumab
Started	57
Completed	46
Not completed	11
Hypersensitivity reaction	1
Insufficient therapeutic response	1
Protocol violation	1
Adverse event, non-fatal	6
Subject decision to withdraw	2

Period 2

Period 2 title	Long Term Extension (LTE) Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tocilizumab

Arm description:

Adults with rheumatoid arthritis received a fixed dose of tocilizumab during the 24-week open-label core study and those entering the long term extension (LTE) period further received a fixed dose up to a maximum of 28 weeks or until tocilizumab was commercially available and/or reimbursed whichever came first. A fixed dose of 162 milligram (mg) tocilizumab was administered subcutaneously once weekly.

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

Dosage and administration details:

Subjects received fixed dose of 162 mg SC weekly.

Number of subjects in period 2[1]	Tocilizumab
Started	39
Completed	37
Not completed	2
Insufficient therapeutic response	1
Adverse event, non-fatal	1

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: Only subjects who achieved at least a moderate EULAR response at Week 24 entered the LTE Period.

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab

Reporting group description:

Adults with rheumatoid arthritis received a fixed dose of tocilizumab during the 24-week open-label core study and those entering the long term extension (LTE) period further received a fixed dose up to a maximum of 28 weeks or until tocilizumab was commercially available and/or reimbursed whichever came first. A fixed dose of 162 milligram (mg) tocilizumab was administered subcutaneously once weekly.

Reporting group values	Tocilizumab	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 54.49 ± 11.08	 -	
Gender categorical Units: Subjects			
Female	44	44	
Male	13	13	

End points

End points reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Adults with rheumatoid arthritis received a fixed dose of tocilizumab during the 24-week open-label core study and those entering the long term extension (LTE) period further received a fixed dose up to a maximum of 28 weeks or until tocilizumab was commercially available and/or reimbursed whichever came first. A fixed dose of 162 milligram (mg) tocilizumab was administered subcutaneously once weekly.

Reporting group title	Tocilizumab

Reporting group description:

Adults with rheumatoid arthritis received a fixed dose of tocilizumab during the 24-week open-label core study and those entering the long term extension (LTE) period further received a fixed dose up to a maximum of 28 weeks or until tocilizumab was commercially available and/or reimbursed whichever came first. A fixed dose of 162 milligram (mg) tocilizumab was administered subcutaneously once weekly.

Primary: Change From Baseline in Disease Activity Score 28 - Erythrocyte Sedimentation Rate (DAS28-ESR) Score in the Full Analysis Set (FAS)

End point title	Change From Baseline in Disease Activity Score 28 - Erythrocyte Sedimentation Rate (DAS28-ESR) Score in the Full Analysis Set (FAS)[1]

End point description:

The DAS28 score is a measure of the subject's disease activity calculated using the tender joint count of 28 joints (TJC28), swollen joint count of 28 joints (SJC28), patient's global assessment of disease activity visual analog scale (PGA VAS) with 0=no disease activity to 100=maximum disease activity displayed on the 100-millimeter (mm) horizontal VAS and acute phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) for a total possible score of 0 to 10. For this study ESR was used to calculate the DAS28 score. The index is calculated using the following formula: DAS28 = (0.56*√[TJC28]) + (0.28*√[SJC28]) + (0.70*ln[ESR]) + (0.014*VAS). Higher scores represent higher disease activity. A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Primary

End point timeframe:

From baseline to Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=56)	5.55 (± 1.17)			
Change at Week 24 (n=42)	-3.24 (± 1.47)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Disease Activity Score 28 - Erythrocyte Sedimentation Rate (DAS28-ESR) Score in the Per Protocol Set (PPS)

End point title	Change From Baseline in Disease Activity Score 28 - Erythrocyte Sedimentation Rate (DAS28-ESR) Score in the Per Protocol Set (PPS)[2]

End point description:

The DAS28 score is a measure of the subject's disease activity calculated using the TJC28, SJC28, PGA VAS with 0=no disease activity to 100=maximum disease activity displayed on the 100-mm horizontal VAS and acute phase reactant (ESR or CRP) for a total possible score of 0 to 10. For this study ESR was used to calculate the DAS28 score. The index is calculated using the following formula: DAS28 = (0.56*√[TJC28]) + (0.28*√[SJC28]) + (0.70*ln[ESR]) + (0.014*VAS). Higher scores represent higher disease activity. A negative change from baseline indicates an improvement. The PPS consisted of all subjects of the FAS having a value at baseline and at Week 24 for the endpoint DAS28-ESR, excluding sponsor defined deviation(s) which could have affected the evaluation of the primary endpoint (DAS28-ESR). Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Primary

End point timeframe:

From baseline to Week 24

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 27)	5.73 (± 1.33)			
Change at Week 24 (n= 20)	3.21 (± 1.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Positive American College of Rheumatology (ACR) Response Scores

End point title	Percentage of Subjects With Positive American College of Rheumatology (ACR) Response Scores

End point description:

The ACR core set of outcome measures and their definition of improvement includes a >= 20% improvement (ACR20) compared to Baseline in both SJC and TJC as well as in three out of five additional parameters: Physician's Global Assessment of disease activity VAS, PGA VAS, patient's assessment of pain VAS, Health Assessment Questionnaire-Disability Index (HAQ-DI), and acute phase reactant (CRP or ESR). VAS range for all assessments was 0=no disease activity to 100=maximum disease activity displayed on the 100-mm horizontal VAS. Achievement of an ACR50 requires a >= 50% improvement in the same parameters and an ACR70 requires a >= 70% improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24, and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percentage of subjects				
number (not applicable)				
Baseline: ACR 20 (n=55)	0			
Week 2: ACR 20 (n=51)	21.6			
Week 24: ACR 20 (n=39)	84.6			
Week 52: ACR 20 (n=8)	100			
Baseline: ACR 50 (n=55)	0			
Week 2: ACR 50 (n=52)	1.9			
Week 24: ACR 50 (n=39)	66.7			
Week 52: ACR 50 (n=8)	62.5			
Baseline: ACR 70 (n=55)	0			
Week 2: ACR 70 (n=52)	0			
Week 24: ACR 70 (n=39)	38.5			
Week 52: ACR 70 (n=8)	25			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Responses According to European League Against Rheumatism (EULAR) Criteria

End point title	Percentage of Subjects With Responses According to European League Against Rheumatism (EULAR) Criteria

End point description:

EULAR response was calculated as the difference between DAS28-ESR scores at baseline and Week 24, and reported as the percentage of subjects with good, moderate, or no response. Good responders = decrease from baseline >1.2 with a DAS28 score of <=3.2; moderate responders = decrease from baseline >1.2 with a DAS28 score of >3.2, or decrease from baseline >0.6 to <=1.2 with a DAS28 score of <=5.1; non-responders = decrease from baseline <=0.6 or decrease from baseline >0.6 and <=1.2 with a DAS28 score of >5.1. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percentage of subjects				
number (not applicable)				
Week 2: Good response (n=56)	17.9			
Week 24: Good response (n=42)	76.2			
Week 2: Moderate response (n=56)	50			
Week 24: Moderate response (n=42)	19			
Week 2: No response (n=56)	32.1			
Week 24: No response (n=42)	4.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simplified Disease Activity Index (SDAI)/Clinical Disease Activity Index (CDAI)

End point title	Change From Baseline in Simplified Disease Activity Index (SDAI)/Clinical Disease Activity Index (CDAI)

End point description:

SDAI is a similar index to DAS28 but has the advantage of not needing a complicated mathematical formula for its determination, but a simple arithmetical addition of TJC28 and SJC28, PGA VAS and Physician Global Assessment of disease activity VAS, and CRP concentration in mg/L. CDAI does not incorporate an acute response, therefore it can be used to evaluate disease activity in the absence of laboratory testing of CRP and ESR. VAS range for all assessments was 0=no disease activity to 100=maximum disease activity displayed on the 100-mm horizontal VAS. SDAI scores ranged from 0 to 86, CDAI from 0 to 76 with higher scores indicating increased disease activity. A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=53)	33.26 (± 13.5)			
Change at Week 2: SDAI (n=52)	-9 (± 11.89)			
Change at Week 24: SDAI (n=38)	-25.33 (± 13.63)			
Change at Week 52: SDAI (n=7)	-34.04 (± 16.01)			
Baseline: CDAI (n= 55)	31.86 (± 12.6)			
Change at Week 2: CDAI (n=55)	-7.61 (± 11.51)			

Change at Week 24: CDAI (n=42)	-23.55 (± 13.03)			
Change at Week 52: CDAI (n=8)	-29.99 (± 13.89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Tender/Swollen Joint Counts (TJC/SJC)

End point title	Change in Total Tender/Swollen Joint Counts (TJC/SJC)

End point description:

An assessment of 66 joints for swelling and 68 joints for tenderness was made. Joints were assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis or fused joints were not taken into consideration for swelling or tenderness. A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Joint Counts				
arithmetic mean (standard deviation)				
Baseline: TJC (n=53)	16.02 (± 11.77)			
Change at Week 2: TJC (n=53)	-3.58 (± 8.91)			
Change at Week 24: TJC (n=41)	-12.1 (± 11.07)			
Change at Week 52: TJC (n=8)	-17.25 (± 13.02)			
Baseline: SJC (n=55)	10.2 (± 7.14)			
Change at Week 2: SJC (n=55)	-3.93 (± 7.33)			
Change at Week 24: SJC (n=42)	-9.81 (± 7.84)			
Change at Week 52: SJC (n=8)	-11.75 (± 7.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Corticosteroid Dose Reduction/Discontinuation

End point title	Percentage of Subjects With Corticosteroid Dose

	Reduction/Discontinuation

End point description:

The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	26[3]			
Units: Percentage of subjects				
number (not applicable)	50			

Notes:

[3] - Number of subjects analysed signifies those subjects who were evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving CDAI Remission, CDAI Low Disease Activity, Moderate Disease Activity and High Disease Activity

End point title	Percentage of Subjects Achieving CDAI Remission, CDAI Low Disease Activity, Moderate Disease Activity and High Disease Activity

End point description:

CDAI is calculated by simple arithmetical addition of TJC28 and SJC28, PGA VAS and Physician Global Assessment of disease activity VAS. VAS range was 0=no disease activity to 100=maximum disease activity displayed on the 100-mm horizontal VAS. Total CDAI score ranges from 0 to 76 with higher scores indicating increased disease activity. Clinical remission = score ≤ 2.8; Low disease activity = score > 2.8 and ≤ 10.0; Moderate disease activity = score > 10.0 and ≤ 22.0; High disease activity = score > 22.0. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Baseline: Clinical remission (n=55)	0			
Week 2: Clinical remission (n=56)	1.8			
Week 24: Clinical remission (n=43)	30.2			
Week 52: Clinical remission (n=8)	37.5			
Baseline: Low disease activity (n=55)	0			
Week 2: Low disease activity (n=56)	7.1			

Week 24: Low disease activity (n=43)	34.9			
Week 52: Low disease activity (n=8)	25			
Baseline: Moderate disease activity (n=55)	21.8			
Week 2: Moderate disease activity (n=56)	48.2			
Week 24: Moderate disease activity (n=43)	30.2			
Week 52: Moderate disease activity (n=8)	37.5			
Baseline: High disease activity (n=55)	78.2			
Week 2: High disease activity (n=56)	42.9			
Week 24: High disease activity (n=43)	4.7			
Week 52: High disease activity (n=8)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving SDAI Remission, SDAI LDA, Moderate Disease Activity and High Disease Activity

End point title	Percentage of Subjects Achieving SDAI Remission, SDAI LDA, Moderate Disease Activity and High Disease Activity

End point description:

SDAI is calculated by simple arithmetical addition of TJC28 and SJC28, PGA VAS and Physician Global Assessment of disease activity VAS, and CRP concentration in mg/L. VAS range was 0=no disease activity to 100=maximum disease activity displayed on the 100-mm horizontal VAS. Total SDAI score ranges from 0 to 86 with higher scores indicating increased disease activity. Clinical remission = score ≤ 3.3; Low disease activity = score > 3.3 and ≤ 11.0; Moderate disease activity = score > 11.0 and ≤ 26.0; high disease activity = score > 26.0. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Baseline: Clinical remission (n=53)	0			
Week 2: Clinical remission (n=55)	1.8			
Week 24: Clinical remission (n=40)	30			
Week 52: Clinical remission (n=7)	42.9			
Baseline: Low disease activity (n=53)	0			
Week 2: Low disease activity (n=55)	7.3			
Week 24: Low disease activity (n=40)	40			
Week 52: Low disease activity (n=7)	14.3			

Baseline: Moderate disease activity (n=53)	30.2			
Week 2: Moderate disease activity (n=55)	54.5			
Week 24: Moderate disease activity (n=40)	25			
Week 52: Moderate disease activity (n=7)	42.9			
Baseline: High disease activity (n=53)	69.8			
Week 2: High disease activity (n=55)	36.4			
Week 24: High disease activity (n=40)	5			
Week 52: High disease activity (n=7)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving DAS28-ESR Remission, DAS28-ESR LDA, Moderate Disease Activity and High Disease Activity

End point title	Percentage of Subjects Achieving DAS28-ESR Remission, DAS28-ESR LDA, Moderate Disease Activity and High Disease Activity

End point description:

The DAS28 score is a measure of the subject's disease activity calculated using TJC28, SJC28, PGA VAS with 0=no disease activity to 100=maximum disease activity displayed on the 100-millimeter (mm) horizontal VAS and acute phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) for a total possible score of 0 to 10. For this study ESR was used to calculate the DAS28 score. The index is calculated using the following formula: DAS28 = (0.56*√[TJC28]) + (0.28*√[SJC28]) + (0.70*ln[ESR]) + (0.014*VAS). Higher scores represent higher disease activity. Clinical remission = score <2.6; Low disease activity = score ≥2.6 and ≤3.2; Moderate disease activity = score > 3.2 and ≤5.1; High disease activity = score >5.1. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Baseline: Clinical remission (n=56)	0			
Week 2: Clinical remission (n=56)	7.1			
Week 24: Clinical remission (n=42)	64.3			
Week 52: Clinical remission (n=8)	87.5			
Baseline: Low disease activity (n=56)	1.8			
Week 2: Low disease activity (n=56)	16.1			
Week 24: Low disease activity (n=42)	16.7			
Week 52: Low disease activity (n=8)	0			

Baseline: Moderate disease activity (n=56)	35.7			
Week 2: Moderate disease activity (n=56)	53.6			
Week 24: Moderate disease activity (n=42)	19			
Week 52: Moderate disease activity (n=8)	12.5			
Baseline: High disease activity (n=56)	62.5			
Week 2: High disease activity (n=56)	23.2			
Week 24: High disease activity (n=42)	0			
Week 52: High disease activity (n=8)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving a Clinically Significant Improvement in DAS28

End point title	Percentage of Subjects Achieving a Clinically Significant Improvement in DAS28

End point description:

The DAS28 score is a measure of the subject's disease activity calculated using TJC28, SJC28, PGA VAS with 0=no disease activity to 100=maximum disease activity displayed on the 100-millimeter (mm) horizontal VAS and acute phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) for a total possible score of 0 to 10. For this study ESR was used to calculate the DAS28 score. The index is calculated using the following formula: DAS28 = (0.56*√[TJC28]) + (0.28*√[SJC28]) + (0.70*ln[ESR]) + (0.014*VAS). Higher scores represent higher disease activity. DAS28 Clinically Significant Improvement was defined as a DAS28 score reduction of at least 1.2 units from Baseline. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Week 2 (n=56)	66.1			
Week 24 (n=42)	90.5			
Week 52 (n=8)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physician’s Global Assessment of Disease Activity VAS

End point title	Change From Baseline in Physician’s Global Assessment of Disease Activity VAS

End point description:

Physician's Global Assessment of disease activity VAS represents the physician's assessment of the subject's current disease activity on a 100 mm horizontal VAS. The extreme left end of the line represents 0= "no disease activity" (symptom-free and no arthritis symptoms) and the extreme right end 100= "maximum disease activity". This was completed by the Treating Physician (or designee). A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=56)	64.93 (± 17.73)			
Change at Week 2 (n=56)	-16.34 (± 16.88)			
Change at Week 24 (n=45)	-48.93 (± 25.06)			
Change at Week 52 (n=9)	-57.44 (± 23.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient’s Global Assessment of Disease Activity VAS

End point title	Change From Baseline in Patient’s Global Assessment of Disease Activity VAS

End point description:

PGA VAS represents the subject's overall assessment of their current disease activity on a 100 mm horizontal VAS. The extreme left end of the line represents 0= "no disease activity" (symptom-free and no arthritis symptoms) and the extreme right end 100="maximum disease activity" (maximum arthritis disease activity). A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57)	67.28 (± 22.25)			
Change at Week 2 (n=57)	-11.82 (± 23.23)			
Change at Week 24 (n=46)	-36.02 (± 29.38)			
Change at Week 52 (n=9)	-44.78 (± 35.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient’s Assessment of Pain VAS

End point title	Change From Baseline in Patient’s Assessment of Pain VAS

End point description:

Patient's Assessment of Pain VAS represents the subject's assessment of his/her current level of pain on a 100 mm horizontal VAS. The extreme left end of the line represents 0="no pain" and the extreme right end 100="unbearable pain". A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2 and Week 24

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57)	66.77 (± 21.43)			
Change at Week 2 (n=57)	-11.32 (± 19.74)			
Change at Week 24 (n=46)	-35.37 (± 27.03)			
Change at Week 52 (n=9)	-49.33 (± 39.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acute Phase Reactants: Change From Baseline in CRP

End point title	Acute Phase Reactants: Change From Baseline in CRP

End point description:

A negative change from baseline in CRP level indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: milligrams per litre (mg/L)				
arithmetic mean (standard deviation)				
Baseline (n=55)	13.79 (± 20.78)			
Change at Week 2 (n=54)	-13.19 (± 20.64)			
Change at Week 24 (n=42)	-10.12 (± 14.5)			
Change at Week 52 (n=8)	-25.07 (± 23.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acute Phase Reactants: Change From Baseline in ESR

End point title	Acute Phase Reactants: Change From Baseline in ESR

End point description:

A negative change from baseline in ESR indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: millimetres per hour (mm/hr)				
arithmetic mean (standard deviation)				
Baseline (n=56)	33.75 (± 28.9)			
Change at Week 2 (n=55)	-19.95 (± 18.22)			
Change at Week 24 (n=44)	-22.8 (± 24.88)			
Change at Week 52 (n=9)	-27.78 (± 23.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

End point title	Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

End point description:

The Stanford HAQ-DI is a patient-oriented outcome assessment questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other common activities. 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. A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57)	1.44 (± 0.68)			
Change at Week 2 (n=57)	-0.08 (± 0.43)			
Change at Week 24 (n=46)	-0.54 (± 0.68)			
Change at Week 52 (n=9)	-1.33 (± 0.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)

End point description:

The symptom-specific measure FACIT-F was developed to assess chronic illness therapy with special emphasis on fatigue in the past 7 days. In this study, only the FACIT-F short questionnaire, which is a shorter version of the initial FACIT-F questionnaire, was used. Each of the questions is categorically answered using the scales 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much. The figures are reversed during score calculations, so that higher score values indicate more favorable conditions. The 13 items included in the FACIT-F short can be used to calculate the brief score for FACIT-F scale (score range: 0-52). A positive change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57)	26.09 (± 10.75)			
Change at Week 2 (n=57)	2.32 (± 9.58)			
Change at Week 24 (n=45)	10.53 (± 12.06)			
Change at Week 52 (n=9)	20.89 (± 12.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pittsburgh Sleep Quality Index (PSQI)

End point title	Change From Baseline in Pittsburgh Sleep Quality Index (PSQI)

End point description:

The PSQI is a self-rated questionnaire which assesses sleep quality and disturbances over 1-month time

interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The subject self-rates each of these seven areas of sleep. Scoring of answers is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert Scale. Global scores range from 0 to 21 and a global sum of "5" or greater indicates a "poor" sleeper. Although there are several questions that request the evaluation of the subject's bedmate or roommate, these are not scored. A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 4, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57)	8.81 (± 4.39)			
Change at Week 4 (n=54)	-1.24 (± 3.53)			
Change at Week 24 (n=46)	-2.63 (± 4.14)			
Change at Week 52 (n=9)	-4.56 (± 5.88)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Quality of Sleep VAS

End point title	Change From Baseline in Patient Quality of Sleep VAS

End point description:

The Patient Quality of Sleep VAS assessment represents the subject's assessment of his/her current quality of sleep on a 100 mm horizontal VAS. The extreme left end of the line represents 0="no difficulty to sleep" and the extreme right end 100="extreme sleeping difficulties". A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57)	54.95 (± 31.23)			

Change at Week 2 (n=57)	-8.4 (± 23.72)			
Change at Week 24 (n=46)	-21.93 (± 30.87)			
Change at Week 52 (n=9)	-34.22 (± 37.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Arthritis Impact Measurement Scale-Short Form (AIMS-SF)

End point title	Change From Baseline in Arthritis Impact Measurement Scale-Short Form (AIMS-SF)

End point description:

The AIMS-SF is a reduced version of the validated AIMS2 questionnaire. The Short Form has been developed using a comprehensive expert-based approach and supported by psychometric testing. The AIMS-SF is a self-administered questionnaire to measure changes in global health, pain, mobility and social function in adult subjects with arthritis and reports scores for physical, symptoms, affect, social and work assessments. Scores range from 0 to 10, higher scores indicating higher impact of arthritis on the assessments. A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint. Here, 99999 indicates standard deviation as it was not estimable for 1 subject.

End point type	Secondary

End point timeframe:

From Baseline to Week 4, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57[4]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline: Physical (n=49)	3.57 (± 1.92)			
Change at Week 4: Physical (n= 47)	-0.57 (± 1.36)			
Change at Week 24: Physical (n=39)	-1.41 (± 1.83)			
Change at Week 52: Physical (n=3)	-3.62 (± 2.23)			
Baseline: Symptom (n= 50)	6.33 (± 2.59)			
Change at Week 4: Symptom (n= 48)	-1.15 (± 2.46)			
Change at Week 24: Symptom (n=40)	-2.69 (± 2.8)			
Change at Week 52: Symptom (n=3)	-3.89 (± 5.91)			
Baseline: Affect (n=50)	5.07 (± 2.22)			
Change at Week 4: Affect (n= 48)	-0.66 (± 1.56)			
Change at Week 24: Affect (n=40)	-1.74 (± 2.22)			
Change at Week 52: Affect (n=3)	-4.5 (± 2.22)			
Baseline: Social (n=50)	5.36 (± 1.73)			
Change at Week 4: Social (n=48)	0.18 (± 1.41)			
Change at Week 24: Social (n=40)	-0.56 (± 1.61)			
Change at Week 52: Social (n=3)	-1.46 (± 2.37)			

Baseline: Work (n=26)	3.17 (± 2.46)			
Change at Week 4: Work (n= 23)	-0.92 (± 2.53)			
Change at Week 24: Work (n=21)	-0.65 (± 2.87)			
Change at Week 52: Work (n=1)	3.75 (± 99999)			

Notes:

[4] - 99999 = Standard deviation not estimable for one subject.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Fatigue VAS

End point title	Change From Baseline in Patient Fatigue VAS

End point description:

The patient fatigue VAS assessment represents the subject's assessment of his/her current level of fatigue on a 100 mm horizontal VAS. The extreme left end of the line represents 0="no fatigue" and the extreme right end 100="extreme fatigue". A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=57)	60.19 (± 24.79)			
Change at Week 2 (n=57)	-3.74 (± 20.68)			
Change at Week 24 (n=46)	-21.48 (± 28.07)			
Change at Week 52 (n=9)	-50.89 (± 26.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Satisfaction VAS

End point title	Change From Baseline in Patient Satisfaction VAS

End point description:

The Patient Satisfaction VAS assessment represents the subject's assessment of his/her current satisfaction with treatment on a 100 mm horizontal VAS. The extreme left end of the line represents 0="no satisfaction" and the extreme right end 100="extremely satisfied". A positive change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for

endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 2, Week 24 and Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=53)	39.66 (± 28.63)			
Change at Week 2 (n=53)	9.49 (± 33.97)			
Change at Week 24 (n=43)	33.07 (± 35.5)			
Change at Week 52 (n=8)	49.38 (± 35.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Instability Scale for Rheumatoid Arthritis (RA-WIS)

End point title	Change From Baseline in Work Instability Scale for Rheumatoid Arthritis (RA-WIS)

End point description:

The 23-item RA-WIS is a simple, validated screening tool for work instability, i.e., the consequences of a mismatch between an individual's functional ability and their work tasks. This self-administered questionnaire covers a broad range of specific work-related issues and enables monitoring the risk of work disability in rheumatoid arthritis patients. The RA-WIS is scored by summing responses from all 23 scale items. The scale ranges from 0 to 23. Cut points have been established to differentiate levels of work instability: low < 10, moderate 10-17 and high > 17. A negative change from baseline indicates an improvement. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=26)	13.15 (± 6.05)			
Change at Week 24 (n=22)	-3.55 (± 6.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Satisfaction Questionnaire for Medication (TSQM) Scores

End point title	Treatment Satisfaction Questionnaire for Medication (TSQM) Scores

End point description:

The abbreviated 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) derived from the TSQM Version 1.4 but without the five items of the side effects domain, is a reliable and valid measure to assess subjects' satisfaction with treatment. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain. Domains included are effectiveness, convenience and global satisfaction. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Effectiveness (n=46)	66.7 (± 19.07)			
Convenience (n=46)	76.09 (± 15.66)			
Global Satisfaction (n=46)	65.06 (± 15.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Percentage of Subjects With Adverse Events

End point title	Safety: Percentage of Subjects With Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a subject 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 (including an abnormal laboratory finding, for example), 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. The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)	96.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Percentage of Subjects With Anti-tocilizumab Antibodies

End point title	Safety: Percentage of Subjects With Anti-tocilizumab Antibodies

End point description:

The FAS consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab. Here, n is the number of subjects with evaluable data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Baseline (n= 55)	0			
Week 24 (n= 43)	1.7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 52 weeks

Adverse event reporting additional description:

The safety population consisted of all subjects included in the study who received at least one dose of subcutaneous tocilizumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Adults with rheumatoid arthritis received a fixed dose of tocilizumab during the 24-week open-label core study and those entering the LTE period further received a fixed dose up to a maximum of 28 weeks or until tocilizumab was commercially available and/or reimbursed whichever came first. A fixed dose of 162 mg tocilizumab was administered subcutaneously once weekly.

Serious adverse events	Tocilizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 57 (8.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur Fracture			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Atrial Flutter			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Arthritis Infective			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tocilizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 57 (63.16%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			

subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Injection site erythema			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	7		
Oropharyngeal pain			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			

subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Rheumatoid arthritis			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	6		
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	8		
Urinary tract infection			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2014	Change to inclusion criterion to allow the previous use of more than one biologic DMARD therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported