Clinical trial results:
A randomised, double-blind, parallel-group study of safety and the effect on clinical outcome of tocilizumab subcutaneous (SC) versus placebo SC in combination with traditional disease modifying anti-rheumatic drugs (DMARDs), in patients with moderate to severe active rheumatoid arthritis.

Summary

EudraCT number	2010-019912-18
Trial protocol	ES GR HU BG
Global end of trial date	27 November 2013

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	08 August 2015

Trial information

Trial identification

Sponsor protocol code	NA25220

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01232569
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2012
Global end of trial reached?	Yes
Global end of trial date	27 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomised, parallel-group, placebo-controlled, multicenter study will evaluate the reduction in disease activity and the safety of tocilizumab (RoActemra/Actemra) in combination with traditional disease-modifying anti-rheumatic drugs (DMARDs) in patients with active, moderate to severe rheumatoid arthritis. In the double-blind part of the study, patients will be randomised to receive either 162 mg tocilizumab or placebo subcutaneously every 2 weeks for 24 weeks using a pre-filled syringe. In the open-label part of the study, patients who reach Week 24 on their randomised treatment will be rerandomised to receive 162 mg tocilizumab subcutaneously every 2 weeks from Week 24 to Week 96 using a pre-filled syringe or an auto-injector. Patients with inadequate efficacy had the option to escape to treatment with tocilizumab 162 mg subcutaneously once weekly.
The analysis of the endpoints occurred at Week 24. No analyses were planned at Week 96, so none are presented.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 99
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Bulgaria: 27
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Argentina: 29
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Brazil: 98
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Colombia: 17
Country: Number of subjects enrolled	Guatemala: 9
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Malaysia: 7
Country: Number of subjects enrolled	Mexico: 106
Country: Number of subjects enrolled	Panama: 6

Country: Number of subjects enrolled	Philippines: 11
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	United States: 114
Worldwide total number of subjects	656
EEA total number of subjects	149

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)	575
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 656 patients randomised into the study (437 to the tocilizumab arm and 219 to the placebo arm), 438 patients received tocilizumab as their first dose and 218 received placebo as their first dose because of a dose administration error with 1 patient.

Pre-assignment

Screening details:

The target population for this study was patients with moderate to severe rheumatoid arthritis who were inadequate responders to disease-modifying anti-rheumatic drugs that may include one or more anti−tumor necrosis factor-α agents.

Period 1

Period 1 title	Double-blind treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Tocilizumab 162 mg sc

Arm description:

Patients received tocilizumab 162 mg subcutaneously (sc) every 2 weeks for 24 weeks.

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

Dosage and administration details:

Tocilizumab was supplied in a ready-to-use, single-use, pre-filled syringe. Patients and/or caregivers were trained to administer the injection.

Arm title	Placebo sc

Arm description:

Patients received placebo sc every 2 weeks for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was supplied in a ready-to-use, single-use, pre-filled syringe. Patients and/or caregivers were trained to administer the injection.

Number of subjects in period 1	Tocilizumab 162 mg sc	Placebo sc
Started	438	218
Completed	410	209
Not completed	28	9
Physician decision	1	-
Death	2	-
Withdrawal by Subject	9	2
Escape	2	2
Lost to follow-up	4	-
Adverse Event (Except Anaphylaxis)	9	3
Lack of efficacy	1	2

Period 2

Period 2 title	Open-label extension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tocilizumab pre-filled syringe

Arm description:

Patients received tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 72 weeks.

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

Dosage and administration details:

Tocilizumab was supplied in a ready-to-use, single-use, pre-filled syringe. Patients and/or caregivers were trained to administer the injection.

Arm title	Tocilizumab auto-injector

Arm description:

Patients received tocilizumab 162 mg sc via auto-injector every 2 weeks for 72 weeks.

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

Dosage and administration details:

Tocilizumab was supplied in a ready-to-use, single-use, auto-injector. Patients and/or caregivers were trained to administer the injection.

Number of subjects in period 2[1]	Tocilizumab pre-filled syringe	Tocilizumab auto-injector
Started	230	227
Completed	203	200
Not completed	27	27
Reason not specified	27	27

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: Some participants who completed the double-blind treatment period did not enter the open-label period. Only participants who reached week 24 on their randomised treatment were rerandomised into the open-label period.

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab 162 mg sc
Reporting group description:	
Patients received tocilizumab 162 mg subcutaneously (sc) every 2 weeks for 24 weeks.	
Reporting group title	Placebo sc
Reporting group description:	
Patients received placebo sc every 2 weeks for 24 weeks.	

Reporting group values	Tocilizumab 162 mg sc	Placebo sc	Total
Number of subjects	438	218	656
Age categorical Units: Subjects			
Adults (18-64 years)	383	192	575
From 65-84 years	55	26	81
Age continuous			
Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population.			
Units: years			
arithmetic mean	120	120	
standard deviation	± 60	± 60	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	0	0	0
Not recorded	438	218	656

Subject analysis sets	
Subject analysis set title	Tocilizumab 162 mg sc
Subject analysis set type	Safety analysis
Subject analysis set description:	
Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population.	
Subject analysis set title	Placebo sc
Subject analysis set type	Safety analysis
Subject analysis set description:	
Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population.	

Reporting group values	Tocilizumab 162 mg sc	Placebo sc	
Number of subjects	437	218	
Age categorical Units: Subjects			
Adults (18-64 years)			

From 65-84 years			

Age continuous			
Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population.			
Units: years			
arithmetic mean	52.1	52	
standard deviation	± 11.49	± 11.67	
Gender categorical			
Units: Subjects			
Female	375	180	
Male	62	38	
Not recorded	0	0	

End points

End points reporting groups

Reporting group title	Tocilizumab 162 mg sc
Reporting group description:	
Patients received tocilizumab 162 mg subcutaneously (sc) every 2 weeks for 24 weeks.	
Reporting group title	Placebo sc
Reporting group description:	
Patients received placebo sc every 2 weeks for 24 weeks.	
Reporting group title	Tocilizumab pre-filled syringe
Reporting group description:	
Patients received tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 72 weeks.	
Reporting group title	Tocilizumab auto-injector
Reporting group description:	
Patients received tocilizumab 162 mg sc via auto-injector every 2 weeks for 72 weeks.	
Subject analysis set title	Tocilizumab 162 mg sc
Subject analysis set type	Safety analysis
Subject analysis set description:	
Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population.	
Subject analysis set title	Placebo sc
Subject analysis set type	Safety analysis
Subject analysis set description:	
Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population.	

Primary: Percentage of patients with an American College of Rheumatology 20 (ACR20) response at Week 24

End point title	Percentage of patients with an American College of Rheumatology 20 (ACR20) response at Week 24
End point description:	
A patient had an ACR20 response if there was at least a 20% improvement, ie, reduction from baseline, in tender and swollen joint counts (28 assessed joints) and in at least 3 of the following 5 parameters: Separate patient and physician assessments of patient disease activity in the previous 24 hours on a visual analog scale (VAS, left end=no disease activity [symptom-free and no arthritis symptoms], right end=maximum disease activity; patient assessment of pain in previous 24 hours on a VAS (left end=no pain and right end=unbearable pain); Health Assessment Questionnaire-Disability Index (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do); and acute-phase reactant (either C-reactive protein or erythrocyte sedimentation rate).	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	437	219		
Units: Percentage of patients				
number (confidence interval 95%)	60.9 (56.3 to 65.4)	31.5 (25.4 to 37.7)		

Statistical analyses

Statistical analysis title	Tocilizumab vs placebo
Comparison groups	Tocilizumab 162 mg sc v Placebo sc
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	29.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	22
upper limit	37

Secondary: Percentage of patients with ACR50 and ACR70 responses at Week 24

End point title	Percentage of patients with ACR50 and ACR70 responses at Week 24

End point description:

A patient had an ACR50 response if there was at least a 50% improvement in the ACR scores. A patient had an ACR70 response if there was at least a 70% improvement in the ACR scores.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	437	219		
Units: Percentage of patients				
number (confidence interval 95%)				
ACR50	39.8 (35.2 to 44.4)	12.3 (8 to 16.7)		
ACR70	19.7 (16 to 23.4)	5 (2.1 to 7.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of ACR20, ACR50, and ACR70 responses

End point title	Time to onset of ACR20, ACR50, and ACR70 responses

End point description:

Time to first ACR response was calculated as the number of days between the date of the first ACR response minus the date of the first dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	437[1]	219[2]		
Units: Days				
median (confidence interval 95%)				
ACR20	57 (57 to 58)	86 (85 to 113)		
ACR50	115 (113 to 141)	999 (999 to 999)		
ACR70	174 (172 to 999)	999 (999 to 999)		

Notes:

[1] - Only patients with available data were included in the analysis. 999.0 = NA due to too few events

[2] - 999.0 = Not calculable due to too few events.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in tender joint count (TJC) and swollen joint count (SJC) at Week 24

End point title	Change from baseline in tender joint count (TJC) and swollen joint count (SJC) at Week 24

End point description:

Joints (28 joints) will be assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	432[3]	219		
Units: Joint count				
arithmetic mean (standard deviation)				
Tender joint count	-14.8 (± 15)	-8.1 (± 14.2)		
Swollen joint count	-9.6 (± 9.7)	-5.9 (± 10.2)		

Notes:

[3] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in C-reactive protein at Week 24

End point title	Change from baseline in C-reactive protein at Week 24

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345[4]	124[5]		
Units: mg/dL				
arithmetic mean (standard deviation)	-1.7 (± 2.6)	-0.1 (± 1.8)		

Notes:

[4] - Only patients with available data were included in the analysis.

[5] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in erythrocyte sedimentation rate at Week 24

End point title	Change from baseline in erythrocyte sedimentation rate at Week 24

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347[6]	124[7]		
Units: mm/hrmm/hr				
arithmetic mean (standard deviation)	-36.4 (± 23.6)	-9.5 (± 22.7)		

Notes:

[6] - Only patients with available data were included in the analysis.

[7] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the patient’s and the physician’s global assessment of disease activity visual analog score

End point title	Change from baseline in the patient’s and the physician’s global assessment of disease activity visual analog score

End point description:

Patients and physicians assessed the patient’s disease activity in the previous 24 hours on a 100 mm visual analog scale, where the extreme left end of the line represented “no disease activity” (symptom-free and no arthritis symptoms) and the extreme right end represented “maximum disease activity”. Scores ranged from 0 to 100 with a higher score indicating more disease activity. A negative change score indicated less disease activity.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348[8]	124[9]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Patient's Global Assessment VAS, N=346, 123	-32 (± 27.6)	-20.9 (± 25.2)		
Physician's Global Assessment VAS, N=348, 124	-36.9 (± 22.5)	-30.7 (± 25.8)		

Notes:

[8] - Only patients with available data were included in the analysis.

[9] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the patient’s pain visual analog score

End point title	Change from baseline in the patient’s pain visual analog score

End point description:

Patients assessed their pain in the previous 24 hours on a visual analog scale, where the extreme left end of the line represented "no pain" and the extreme right end represented "unbearable pain". Scores ranged from 0 to 100 with a higher score indicating more pain. A negative change score indicated less pain.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346[10]	123[11]		
Units: Units on a scale				
arithmetic mean (standard deviation)	-28.1 (± 27.2)	-15 (± 28.3)		

Notes:

[10] - Only patients with available data were included in the analysis.

[11] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24

End point title	Change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24

End point description:

The HAQ-DI is a questionnaire specific for rheumatoid arthritis and consists of 20 questions referring to 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Patients completed the questionnaire by answering the 20 questions on a scale of 0 (without difficulty) to 3 (unable to do). The total score ranges from 0 (no disability) to 3 (completely disabled). A negative change score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348[12]	124[13]		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.5 (± 0.6)	-0.3 (± 0.6)		

Notes:

[12] - Only patients with available data were included in the analysis.

[13] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with an improvement of ≥ 0.3 units from baseline in the HAQ-DI score at Week 24

End point title	Percentage of patients with an improvement of ≥ 0.3 units from baseline in the HAQ-DI score at Week 24

End point description:

The HAQ-DI is a questionnaire specific for rheumatoid arthritis and consists of 20 questions referring to 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Patients completed the questionnaire by answering the 20 questions on a scale of 0 (without difficulty) to 3 (unable to do). The total score ranges from 0 (no disability) to 3 (completely disabled). A negative change score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348[14]	124[15]		
Units: Percentage of patients				
number (confidence interval 95%)	58 (52.9 to 63.2)	46.8 (38 to 55.6)		

Notes:

[14] - Only patients with available data were included in the analysis.

[15] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Disease Activity Score 28 (DAS28) at Week 24

End point title	Change from baseline in Disease Activity Score 28 (DAS28) at Week 24

End point description:

The DAS28 is a combined index for measuring disease activity in rheumatic arthritis (RA) and includes swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and general health (GH) status. The index is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(ESR)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints. GH = a patient's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]). When ESR equaled 0 mm/hr, it was set to 1 mm/hr. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. A negative change score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344[16]	123[17]		
Units: Units on a scale				
arithmetic mean (standard deviation)	-3.3 (± 1.4)	-1.8 (± 1.3)		

Notes:

[16] - Only patients with available data were included in the analysis.

[17] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with a DAS28 score ≤ 3.2 (DAS28 low disease activity) at Week 24

End point title	Percentage of patients with a DAS28 score ≤ 3.2 (DAS28 low disease activity) at Week 24

End point description:

The DAS28 is a combined index for measuring disease activity in rheumatic arthritis (RA) and includes swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and general health (GH) status. The index is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(ESR)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints. GH = a patient's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]). When ESR equaled 0 mm/hr, it was set to 1 mm/hr. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. A negative change score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347[18]	124[19]		
Units: Percentage of patients				
number (confidence interval 95%)	45.2 (40 to 50.5)	15.3 (9 to 21.7)		

Notes:

[18] - Only patients with available data were included in the analysis.

[19] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with a DAS28 score < 2.6 (DAS28 remission) at Week 24

End point title	Percentage of patients with a DAS28 score < 2.6 (DAS28 remission) at Week 24

End point description:

The DAS28 is a combined index for measuring disease activity in rheumatic arthritis (RA) and includes swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and general health (GH) status.

The index is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(ESR)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints. GH = a patient's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]). When ESR equaled 0 mm/hr, it was set to 1 mm/hr. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. A negative change score indicates improvement.

End point type	Secondary

End point timeframe:

Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347[20]	124[21]		
Units: Percentage of patients				
number (confidence interval 95%)	32 (27.1 to 36.9)	4 (0.6 to 7.5)		

Notes:

[20] - Only patients with available data were included in the analysis.

[21] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with good, moderate, or no European League Against Rheumatism (EULAR) responses at Week 24

End point title	Percentage of patients with good, moderate, or no European League Against Rheumatism (EULAR) responses at Week 24

End point description:

Change of the Disease Activity Score 28 score from baseline was used to determine EULAR responses of good, moderate, or no response. For a post-baseline score ≤ 3.2, a change from baseline of < -1.2 was a good response, < -0.6 to ≥ -1.2 was a moderate response, and ≥ -0.6 was no response. For a post-baseline score > 3.2 to ≤ 5.1, a change from baseline of < -0.6 was a moderate response and ≥ -0.6 was no response. For a post-baseline score > 5.1, a change from baseline < -1.2 was a moderate response and ≥ -1.2 was no response. A good response could not be achieved for post-baseline scores > 3.2.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374[22]	138[23]		
Units: Percentage of patients				
number (not applicable)				
Good Response	41.7	13.8		
Moderate Response	44.9	54.3		
No Response	13.4	31.9		

Notes:

[22] - Only patients with available data were included in the analysis.

[23] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the van der Heijde modified Sharp radiographic score at Week 24

End point title	Change from baseline in the van der Heijde modified Sharp radiographic score at Week 24

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	391[24]	186[25]		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.62 (± 2.692)	1.23 (± 2.816)		

Notes:

[24] - Only patients with available data were included in the analysis.

[25] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Physical and Mental Component Scores of the Short Form 36 (SF-36) Health Survey at Week 24

End point title	Change from baseline in the Physical and Mental Component Scores of the Short Form 36 (SF-36) Health Survey at Week 24

End point description:

The SF-36 Health Survey uses patient-reported symptoms on 8 subscales to assess health-related quality of life (HRQoL). The Physical Component Summary (PCS) score summarizes the subscales Physical Functioning, Role−Physical, Bodily Pain, and General Health. The Mental Component Summary (MCS) score summarizes the subscales Vitality, Social Functioning, Role−Emotional, and Mental Health. Each score was scaled from 0 to 100 with a higher score indicating better HRQoL. A positive change score indicates an improvement in HRQoL.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347[26]	123[27]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Physical Component Mental Component	7.2 (± 8) 6.1 (± 10.8)	4.3 (± 5.9) 3 (± 9.7)		

Notes:

[26] - Only patients with available data were included in the analysis.

[27] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in haemoglobin at Week 24

End point title	Change from baseline in haemoglobin at Week 24

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab 162 mg sc	Placebo sc		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	343[28]	123[29]		
Units: g/L				
arithmetic mean (standard deviation)	11 (± 12.6)	0 (± 7.1)		

Notes:

[28] - Only patients with available data were included in the analysis.

[29] - Only patients with available data were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of each patient's randomization into the study until their last visit (up to 96 weeks).

Adverse event reporting additional description:

Safety population: All patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population.
Due to the study design, some participants received tocilizumab throughout the study, others not.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Tocilizumab pre-filled syringe

Reporting group description:

Patients received tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 24 weeks. In addition, this reporting group includes participants rerandomised at Week 24 to tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 72 weeks (Weeks 25-96).

Reporting group title	Placebo pre-filled syringe

Reporting group description:

Patients received placebo subcutaneously (sc) via a pre-filled syringe every 2 weeks for 24 weeks.

Reporting group title	Tocilizumab pre-filled syringe to tocilizumab auto-injector

Reporting group description:

Patients received tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 24 weeks followed by tocilizumab162 mg sc via an autoinjector every 2 weeks for 72 weeks.

Reporting group title	Placebo pre-filled syringe to tocilizumab pre-filled syringe

Reporting group description:

Patients received placebo sc via a pre-filled syringe every 2 weeks for 24 weeks followed by tocilizumab162 mg sc via a pre-filled syringe every 2 weeks for 72 weeks.

Reporting group title	Placebo pre-filled syringe to tocilizumab autoinjector

Reporting group description:

Patients received placebo sc via a pre-filled syringe every 2 weeks for 24 weeks followed by tocilizumab162 mg sc via an autoinjector every 2 weeks for 72 weeks.

Serious adverse events	Tocilizumab pre-filled syringe	Placebo pre-filled syringe	Tocilizumab pre-filled syringe to tocilizumab auto-injector
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 437 (8.24%)	8 / 218 (3.67%)	17 / 168 (10.12%)
number of deaths (all causes)	4	0	3
number of deaths resulting from adverse events	3	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			

subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Rectal cancer			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Schwannoma			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Myelodysplastic syndrome			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian epithelial cancer			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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			

Pyrexia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	2 / 437 (0.46%)	0 / 218 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hypertrophy			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst torsion			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 437 (0.46%)	0 / 218 (0.00%)	0 / 168 (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
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Injury, poisoning and procedural complications			

Cervical vertebral fracture			
subjects affected / exposed	0 / 437 (0.00%)	1 / 218 (0.46%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Angina pectoris			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atrial fibrillation			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Myocardial infarction			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Supraventricular tachycardia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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			
Grand mal convulsion			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Syncope			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 437 (0.46%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal adhesions			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Constipation			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Inguinal hernia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 437 (0.23%)	1 / 218 (0.46%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 437 (0.00%)	1 / 218 (0.46%)	0 / 168 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	0 / 437 (0.00%)	1 / 218 (0.46%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Osteoarthritis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 218 (0.46%)	0 / 168 (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
Spinal column stenosis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 218 (0.46%)	0 / 168 (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
Synovial cyst			
subjects affected / exposed	0 / 437 (0.00%)	1 / 218 (0.46%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 437 (0.46%)	2 / 218 (0.92%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 437 (0.46%)	1 / 218 (0.46%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	2 / 437 (0.46%)	0 / 218 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	2 / 437 (0.46%)	0 / 218 (0.00%)	0 / 168 (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
Abscess			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Bronchitis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Bronchopneumonia			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Coccidioidomycosis			
subjects affected / exposed	0 / 437 (0.00%)	1 / 218 (0.46%)	0 / 168 (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
Erysipelas			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Joint abscess			

subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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
Ludwig angina			
subjects affected / exposed	0 / 437 (0.00%)	0 / 218 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 437 (0.00%)	1 / 218 (0.46%)	0 / 168 (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
Septic shock			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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	0 / 437 (0.00%)	0 / 218 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 437 (0.23%)	0 / 218 (0.00%)	0 / 168 (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

Serious adverse events	Placebo pre-filled syringe to tocilizumab pre-filled syringe	Placebo pre-filled syringe to tocilizumab autoinjector	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 61 (3.28%)	0 / 59 (0.00%)	
number of deaths (all causes)	1	0	

number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schwannoma			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian epithelial cancer			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hypertrophy			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst torsion			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			

subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar radiculopathy			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocortical insufficiency acute			

subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis bacterial			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coccidioidomycosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ludwig angina			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tocilizumab pre-filled syringe	Placebo pre-filled syringe	Tocilizumab pre-filled syringe to tocilizumab auto-injector
Total subjects affected by non-serious adverse events			
subjects affected / exposed	212 / 437 (48.51%)	65 / 218 (29.82%)	89 / 168 (52.98%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	67 / 437 (15.33%)	13 / 218 (5.96%)	24 / 168 (14.29%)
occurrences (all)	85	14	29
Aspartate aminotransferase increased			
subjects affected / exposed	40 / 437 (9.15%)	10 / 218 (4.59%)	14 / 168 (8.33%)
occurrences (all)	53	10	21
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 437 (5.95%)	8 / 218 (3.67%)	9 / 168 (5.36%)
occurrences (all)	30	9	11
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 437 (6.41%)	13 / 218 (5.96%)	8 / 168 (4.76%)
occurrences (all)	35	15	9
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	25 / 437 (5.72%)	1 / 218 (0.46%)	8 / 168 (4.76%)
occurrences (all)	33	1	14
Leukopenia			
subjects affected / exposed	13 / 437 (2.97%)	1 / 218 (0.46%)	5 / 168 (2.98%)
occurrences (all)	17	1	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	21 / 437 (4.81%)	3 / 218 (1.38%)	6 / 168 (3.57%)
occurrences (all)	23	3	6
Gastritis			
subjects affected / exposed	6 / 437 (1.37%)	3 / 218 (1.38%)	1 / 168 (0.60%)
occurrences (all)	6	3	1
Musculoskeletal and connective tissue disorders			

Rheumatoid arthritis			
subjects affected / exposed	14 / 437 (3.20%)	4 / 218 (1.83%)	12 / 168 (7.14%)
occurrences (all)	16	4	14
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	52 / 437 (11.90%)	14 / 218 (6.42%)	21 / 168 (12.50%)
occurrences (all)	66	14	32
Nasopharyngitis			
subjects affected / exposed	35 / 437 (8.01%)	5 / 218 (2.29%)	16 / 168 (9.52%)
occurrences (all)	40	5	19
Urinary tract infection			
subjects affected / exposed	26 / 437 (5.95%)	7 / 218 (3.21%)	15 / 168 (8.93%)
occurrences (all)	30	8	19
Sinusitis			
subjects affected / exposed	13 / 437 (2.97%)	1 / 218 (0.46%)	8 / 168 (4.76%)
occurrences (all)	16	3	12
Bronchitis			
subjects affected / exposed	13 / 437 (2.97%)	2 / 218 (0.92%)	4 / 168 (2.38%)
occurrences (all)	15	2	4
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	13 / 437 (2.97%)	2 / 218 (0.92%)	5 / 168 (2.98%)
occurrences (all)	15	2	5
Dyslipidaemia			
subjects affected / exposed	6 / 437 (1.37%)	2 / 218 (0.92%)	2 / 168 (1.19%)
occurrences (all)	7	2	2

Non-serious adverse events	Placebo pre-filled syringe to tocilizumab pre-filled syringe	Placebo pre-filled syringe to tocilizumab autoinjector	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 61 (57.38%)	33 / 59 (55.93%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 61 (9.84%)	10 / 59 (16.95%)	
occurrences (all)	7	13	
Aspartate aminotransferase increased			

subjects affected / exposed	4 / 61 (6.56%)	6 / 59 (10.17%)	
occurrences (all)	5	9	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 61 (3.28%)	2 / 59 (3.39%)	
occurrences (all)	2	2	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 61 (8.20%)	2 / 59 (3.39%)	
occurrences (all)	5	2	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 61 (8.20%)	7 / 59 (11.86%)	
occurrences (all)	5	7	
Leukopenia			
subjects affected / exposed	0 / 61 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 61 (4.92%)	5 / 59 (8.47%)	
occurrences (all)	3	6	
Gastritis			
subjects affected / exposed	2 / 61 (3.28%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	1 / 61 (1.64%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 61 (19.67%)	6 / 59 (10.17%)	
occurrences (all)	20	7	
Nasopharyngitis			
subjects affected / exposed	5 / 61 (8.20%)	4 / 59 (6.78%)	
occurrences (all)	7	4	
Urinary tract infection			

subjects affected / exposed	2 / 61 (3.28%)	4 / 59 (6.78%)	
occurrences (all)	2	5	
Sinusitis			
subjects affected / exposed	5 / 61 (8.20%)	1 / 59 (1.69%)	
occurrences (all)	5	1	
Bronchitis			
subjects affected / exposed	1 / 61 (1.64%)	3 / 59 (5.08%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	2 / 61 (3.28%)	4 / 59 (6.78%)	
occurrences (all)	2	5	
Dyslipidaemia			
subjects affected / exposed	6 / 61 (9.84%)	1 / 59 (1.69%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2011	Amendment B • Tocilizumab autoinjector, as a new investigational product, was made available for use in the open−label portion of the study. • Additional details for the analyses of the radiographic endpoint were included. • The required tests for the liver profile were clarified, liver profile testing was added at Week 36, and vital sign measurements were added at Weeks 10 and 36. • The adjustment of the random element used to ensure a baseline randomization ratio of 2:1 was clarified. • To prevent any potential unblinding, a dual assessor approach was used until the completion of Week 48 data analysis. • The reporting period for adverse events, including non-serious adverse events to Roche Drug Safety was clarified (ie, within 24 hours of learning of the event). • The requirement for an X−ray image at the initiation of escape therapy was clarified.
26 April 2011	Amendment C • An optional ease-of-use substudy was added to the open-label period for the sites in Canada and the United States in order to evaluate the ability of patients, caregivers and healthcare professionals to handle and use the pre-filled syringe or autoinjector.
12 September 2012	Amendments D and E • In response to cases of fatal infections in patients participating in the trial, Protocol versions D (rest of world sites) and E (US sites) implemented an increase in the frequency of study visits for safety monitoring. Starting at Week 44, the frequency of study visits was changed from every 12 weeks to every 4 weeks. Vital signs, concomitant medications, and adverse events were required at these additional visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported