Clinical trial results:
Tocilizumab SC in Patients with Active Rheumatoid Arthritis and Inadequate Response to DMARDs. A Single-Arm, Open-Label Study to Evaluate Safety, Tolerability and Efficacy. In a Subgroup of Patients Inflammation Will Be Measured by Ultrasound.

Summary

EudraCT number	2013-002007-34
Trial protocol	FI DK SE
Global end of trial date	13 September 2016

Results information

Result version number	v1 (current)
This version publication date	14 September 2017
First version publication date	14 September 2017

Trial information

Trial identification

Sponsor protocol code	ML28691

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02046616
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This open-label, single-arm study was designed to evaluate the safety, efficacy, and tolerability of subcutaneous (SC) tocilizumab (RoActemra/Actemra) as monotherapy or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs) in participants with active rheumatoid arthritis (RA) who are naive to tocilizumab. Participants received tocilizumab 162 milligrams (mg) subcutaneously weekly (QW) for 24 weeks.

Protection of trial subjects:

This study was conducted in full conformance with the International Council for Harmonisation (ICH)-E6 (Guideline for Good Clinical Practice) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study was designed to comply with the requirements of the ICH-E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) and the European Union Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 44
Country: Number of subjects enrolled	Finland: 37
Country: Number of subjects enrolled	Sweden: 25
Country: Number of subjects enrolled	Norway: 27
Worldwide total number of subjects	133
EEA total number of subjects	133

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	103
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One hundred thirty-three participants entered the 24-week Treatment Period. Those who completed treatment entered the Follow-Up (FU) Period for an additional 8 weeks.

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 Alone or Combined with Methotrexate or Other DMARD

Arm description:

All participants received tocilizumab as a single fixed dose (monotherapy) or in combination with methotrexate or other non-biologic DMARDs at a dose of 162 milligrams (mg), irrespective of body weight, administered subcutaneously weekly (QW) for 24 weeks. An additional 8 weeks were allotted for post-treatment evaluation of safety/immunogenicity.

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

Dosage and administration details:

Tocilizumab 162 mg was administered subcutaneously QW.

Number of subjects in period 1	Tocilizumab Alone or Combined with Methotrexate or Other DMARD
Started	133
Completed	114
Not completed	19
Physician decision	3
Not Specified	1
Insufficient Therapeutic Response	1
Any Other Adverse Event	13
Anaphylaxis/Serious Hypersensitivity	1

Period 2

Period 2 title	8-Week FU Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tocilizumab Alone or Combined with Methotrexate or Other DMARD

Arm description:

All participants received tocilizumab as a single fixed dose (monotherapy) or in combination with methotrexate or other non-biologic DMARDs at a dose of 162 mg, irrespective of body weight, administered subcutaneously QW for 24 weeks. An additional 8 weeks were allotted for post-treatment evaluation of safety/immunogenicity.

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

Dosage and administration details:

Tocilizumab 162 mg was administered subcutaneously QW.

Number of subjects in period 2	Tocilizumab Alone or Combined with Methotrexate or Other DMARD
Started	114
Completed	113
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab Alone or Combined with Methotrexate or Other DMARD

Reporting group description:

All participants received tocilizumab as a single fixed dose (monotherapy) or in combination with methotrexate or other non-biologic DMARDs at a dose of 162 milligrams (mg), irrespective of body weight, administered subcutaneously weekly (QW) for 24 weeks. An additional 8 weeks were allotted for post-treatment evaluation of safety/immunogenicity.

Reporting group values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD	Total	
Number of subjects	133	133	
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	55.9		
standard deviation	± 12	-	
Gender Categorical Units: Subjects			
Female	108	108	
Male	25	25	

Subject analysis sets	
Subject analysis set title	Tocilizumab Alone or Combined with Methotrexate or Other DMARD
Subject analysis set type	Full analysis

Subject analysis set description:

All participants received tocilizumab as a single fixed dose (monotherapy) or in combination with methotrexate or other non-biologic DMARDs at a dose of 162 mg, irrespective of body weight, administered subcutaneously QW for 24 weeks. An additional 8 weeks were allotted for post-treatment evaluation of safety/immunogenicity.

Reporting group values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD		
Number of subjects	133		
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	55.9		
standard deviation	± 12		

Gender Categorical Units: Subjects			
Female	108		
Male	25		

End points

End points reporting groups

Reporting group title	Tocilizumab Alone or Combined with Methotrexate or Other DMARD

Reporting group description:

All participants received tocilizumab as a single fixed dose (monotherapy) or in combination with methotrexate or other non-biologic DMARDs at a dose of 162 milligrams (mg), irrespective of body weight, administered subcutaneously weekly (QW) for 24 weeks. An additional 8 weeks were allotted for post-treatment evaluation of safety/immunogenicity.

Reporting group title	Tocilizumab Alone or Combined with Methotrexate or Other DMARD

Reporting group description:

All participants received tocilizumab as a single fixed dose (monotherapy) or in combination with methotrexate or other non-biologic DMARDs at a dose of 162 mg, irrespective of body weight, administered subcutaneously QW for 24 weeks. An additional 8 weeks were allotted for post-treatment evaluation of safety/immunogenicity.

Subject analysis set title	Tocilizumab Alone or Combined with Methotrexate or Other DMARD
Subject analysis set type	Full analysis

Subject analysis set description:

All participants received tocilizumab as a single fixed dose (monotherapy) or in combination with methotrexate or other non-biologic DMARDs at a dose of 162 mg, irrespective of body weight, administered subcutaneously QW for 24 weeks. An additional 8 weeks were allotted for post-treatment evaluation of safety/immunogenicity.

Primary: Change from Baseline in Clinical Disease Activity Index (CDAI) at Week 12

End point title	Change from Baseline in Clinical Disease Activity Index (CDAI) at Week 12[1]

End point description:

CDAI was derived as the sum of the following: tender joint count (TJC), swollen joint count (SJC), participant global assessment (PGA) of disease activity, and physician assessment of disease activity. TJC and SJC were taken as the number of tender and swollen joints, respectively, out of 28 assessed joints. PGA and physician assessment of disease activity were scored 0-100 millimeters (mm) and rounded to the nearest centimeter (cm) on a visual analog scale (VAS), where higher scores indicate greater perceived disease activity. The total CDAI score range was 0-76, where higher scores indicate increased disease activity. Change from baseline was averaged among all participants. Negative values indicate improvement/reduction in RA disease activity. Intent-to-Treat (ITT) Set: all participants who were treated with at least one dose of SC tocilizumab. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Primary

End point timeframe:

Baseline, Week 12

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: Statistical analyses were exploratory and hence, are not reported here.

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: units on a scale				
arithmetic mean (standard deviation)				

Baseline (n=133)	24.9 (± 10.5)			
Change at Week 12 (n=119)	-16.6 (± 12.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Disease Activity Score 28 (DAS28)-Erythrocyte Sedimentation Rate (ESR) Score

End point title	Change from Baseline in Disease Activity Score 28 (DAS28)-Erythrocyte Sedimentation Rate (ESR) Score

End point description:

DAS28-ESR was based on TJC, SJC, PGA of disease activity, and laboratory-derived ESR. TJC and SJC were taken as the number of tender and swollen joints, respectively, out of 28 assessed joints. PGA of disease activity was scored 0-100 mm on a VAS, where higher scores indicate greater perceived disease activity. The total DAS28-ESR score was transformed to a single score range of 0-10, where higher scores indicate increased disease activity. Change from baseline was averaged among all participants. Negative values indicate improvement/reduction in RA disease activity. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=133)	5 (± 1.1)			
Change at Week 2 (n=127)	-1.4 (± 1)			
Change at Week 4 (n=129)	-2.1 (± 1.1)			
Change at Week 8 (n=125)	-2.8 (± 1.3)			
Change at Week 12 (n=119)	-2.9 (± 1.5)			
Change at Week 16 (n=120)	-3.2 (± 1.4)			
Change at Week 20 (n=113)	-3.3 (± 1.4)			
Change at Week 24 (n=114)	-3.3 (± 1.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with American College of Rheumatology (ACR) Response

End point title	Percentage of Participants with American College of Rheumatology (ACR) Response

End point description:

ACR response was assessed by percent improvement (20% for ACR20, 50% for ACR50, 70% for ACR70) in both TJC and SJC plus at least three of the following: physician assessment of disease activity, PGA of disease activity, PGA of pain, Health Assessment Questionnaire-Disability Index (HAQ-DI), and either ESR or C-reactive protein level. TJC and SJC were taken as the number of tender and swollen joints, out of 68 and 66 assessed joints, respectively. PGA and physician assessments were scored 0-100 mm on VAS, where higher scores indicate greater perceived disease activity (or pain). HAQ-DI was scored using participant responses to 20 questions assessing activities of daily living (ADLs), with total score scale of 0-3, where higher scores indicate increased functional disability. The percentage of participants meeting criteria for each level of ACR response was reported. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: percentage of participants				
number (not applicable)				
ACR20, Week 2 (n=127)	25.2			
ACR20, Week 4 (n=130)	51.5			
ACR20, Week 8 (n=125)	70.4			
ACR20, Week 12 (n=120)	70.8			
ACR20, Week 16 (n=120)	82.5			
ACR20, Week 20 (n=114)	77.2			
ACR20, Week 24 (n=114)	78.1			
ACR50, Week 2 (n=127)	8.7			
ACR50, Week 4 (n=130)	22.3			
ACR50, Week 8 (n=125)	46.4			
ACR50, Week 12 (n=120)	51.7			
ACR50, Week 16 (n=120)	65.8			
ACR50, Week 20 (n=114)	64.9			
ACR50, Week 24 (n=114)	63.2			
ACR70, Week 2 (n=127)	0.8			
ACR70, Week 4 (n=130)	8.5			
ACR70, Week 8 (n=125)	24			
ACR70, Week 12 (n=120)	30			
ACR70, Week 16 (n=120)	44.2			
ACR70, Week 20 (n=114)	42.1			
ACR70, Week 24 (n=114)	47.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with European League Against Rheumatism (EULAR) Response

End point title	Percentage of Participants with European League Against Rheumatism (EULAR) Response

End point description:

EULAR response was assessed by change from baseline and absolute DAS28-ESR score. EULAR response classification was as follows: Good (change >1.2 with absolute score </=3.2), Moderate (change >1.2 with absolute score >3.2 or change >0.6 with absolute score </=5.1), None (change </=0.6 or absolute score >5.1). DAS28-ESR was based on TJC, SJC, and PGA of disease activity, and laboratory-derived ESR. TJC and SJC were taken as the number of tender and swollen joints, respectively, out of 28 assessed joints. PGA of disease activity was scored 0-100 mm on a VAS, where higher scores indicate greater perceived disease activity. The total DAS28-ESR score was transformed to a single score range of 0-10, where higher scores indicate increased disease activity. The percentage of participants meeting criteria for each level of EULAR response was reported. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: percentage of participants				
number (not applicable)				
Week 2, Good (n=127)	29.1			
Week 2, Moderate (n=127)	47.2			
Week 2, None (n=127)	23.6			
Week 4, Good (n=129)	51.2			
Week 4, Moderate (n=129)	39.5			
Week 4, None (n=129)	9.3			
Week 8, Good (n=125)	78.4			
Week 8, Moderate (n=125)	16.8			
Week 8, None (n=125)	4.8			
Week 12, Good (n=119)	78.2			
Week 12, Moderate (n=119)	16			
Week 12, None (n=119)	5.9			
Week 16, Good (n=120)	87.5			
Week 16, Moderate (n=120)	9.2			

Week 16, None (n=120)	3.3			
Week 20, Good (n=113)	86.7			
Week 20, Moderate (n=113)	8.8			
Week 20, None (n=113)	4.4			
Week 24, Good (n=114)	87.7			
Week 24, Moderate (n=114)	9.6			
Week 24, None (n=114)	2.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CDAI at Weeks 2, 4, 8, 16, 20, and 24

End point title	Change from Baseline in CDAI at Weeks 2, 4, 8, 16, 20, and 24

End point description:

CDAI was derived as the sum of the following: TJC, SJC, PGA of disease activity, and physician assessment of disease activity. TJC and SJC were taken as the number of tender and swollen joints, respectively, out of 28 assessed joints. PGA and physician assessment of disease activity were scored 0-100 mm and rounded to the nearest cm on a VAS, where higher scores indicate greater perceived disease activity. The total CDAI score range was 0-76, where higher scores indicate increased disease activity. Change from baseline was averaged among all participants. Negative values indicate improvement/reduction in RA disease activity. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Week 2 (n=126)	-6.2 (± 8.4)			
Change at Week 4 (n=127)	-10.5 (± 9.8)			
Change at Week 8 (n=125)	-15.7 (± 11)			
Change at Week 16 (n=120)	-18.8 (± 11.5)			
Change at Week 20 (n=113)	-18.9 (± 11.7)			
Change at Week 24 (n=114)	-19 (± 11.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Simplified Disease Activity Index (SDAI)

End point title	Change from Baseline in Simplified Disease Activity Index (SDAI)

End point description:

SDAI was derived as the sum of the following: TJC, SJC, PGA of disease activity, physician assessment of disease activity, and laboratory-derived C-reactive protein level. TJC and SJC were taken as the number of tender and swollen joints, respectively, out of 28 assessed joints. PGA and physician assessment of disease activity were scored 0-100 mm and rounded to the nearest cm on a VAS, where higher scores indicate greater perceived disease activity. The total SDAI score range was 0-86, where higher scores indicate increased disease activity. Change from baseline was averaged among all participants. Negative values indicate improvement/reduction in RA disease activity. ITT Set; only those who provided data at baseline and at least one post-baseline assessment were analyzed. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	132			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=132)	35.76 (± 20.71)			
Change at Week 2 (n=124)	-15.37 (± 16.71)			
Change at Week 4 (n=125)	-20.32 (± 19.24)			
Change at Week 8 (n=124)	-25.89 (± 20.88)			
Change at Week 12 (n=119)	-26.19 (± 23.21)			
Change at Week 16 (n=119)	-29.03 (± 21.15)			
Change at Week 20 (n=112)	-28.47 (± 21.26)			
Change at Week 24 (n=113)	-28.93 (± 20.93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in TJC

End point title	Change from Baseline in TJC

End point description:

TJC was taken as the number of tender joints out of 28 assessed joints. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: tender joints				
arithmetic mean (standard deviation)				
Baseline (n=133)	8.8 (± 5.2)			
Change at Week 2 (n=127)	-2.1 (± 5.8)			
Change at Week 4 (n=130)	-3.5 (± 6.1)			
Change at Week 8 (n=125)	-5.8 (± 6.3)			
Change at Week 12 (n=120)	-5.5 (± 7.1)			
Change at Week 16 (n=120)	-6.7 (± 6.9)			
Change at Week 20 (n=114)	-6.7 (± 6.5)			
Change at Week 24 (n=114)	-7.1 (± 5.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SJC

End point title	Change from Baseline in SJC

End point description:

SJC was taken as the number of swollen joints out of 28 assessed joints. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			

Units: swollen joints				
arithmetic mean (standard deviation)				
Baseline (n=133)	6.8 (± 5.5)			
Change at Week 2 (n=127)	-2.3 (± 4.3)			
Change at Week 4 (n=130)	-3.1 (± 4.7)			
Change at Week 8 (n=125)	-4.8 (± 5.1)			
Change at Week 12 (n=120)	-5.3 (± 5.3)			
Change at Week 16 (n=120)	-5.9 (± 5.2)			
Change at Week 20 (n=114)	-6 (± 5.4)			
Change at Week 24 (n=114)	-5.4 (± 5.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with At Least One Adverse Event Leading to Dosage Modification

End point title	Percentage of Participants with At Least One Adverse Event Leading to Dosage Modification

End point description:

The percentage of participants with at least one adverse event leading to dose/frequency reduction or temporary dose hold was reported. ITT Set.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: percentage of participants				
number (not applicable)				
Dose/Frequency Reduced Due to Adverse Event	18.8			
Dose Held Due to Adverse Event	27.07			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Neutralizing Anti-Tocilizumab Antibodies

End point title	Number of Participants with Neutralizing Anti-Tocilizumab Antibodies

End point description:

Participants were evaluated for the presence of anti-tocilizumab antibodies. Confirmatory assays were performed in the case of a positive screen assay result. ITT Set; only those who provided data for at least one assessment were analyzed.

End point type	Secondary

End point timeframe:

Baseline to FU Week 8 (up to 32 weeks overall)

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	132			
Units: participants				
number (not applicable)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Tocilizumab Concentration

End point title	Tocilizumab Concentration

End point description:

Tocilizumab concentration was determined, averaged among all participants, and expressed in micrograms per milliliter (mcg/mL). ITT Set. Here "n" refers to number of participants with quantifiable tocilizumab concentration at the specified assessment.

End point type	Secondary

End point timeframe:

Predose (30 minutes) at baseline; Weeks 12, 24; and FU Week 8 (up to 32 weeks overall)

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Baseline (n=3)	0.6 (± 0.3)			
Week 12 (n=117)	47.4 (± 28.1)			
Week 24 (n=112)	48 (± 27.2)			
FU Week 8 (n=11)	32.8 (± 19.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Soluble Interleukin-6 Receptor (sIL-6R) Concentration

End point title	Soluble Interleukin-6 Receptor (sIL-6R) Concentration

End point description:

sIL-6R concentration was determined, averaged among all participants, and expressed in nanograms per milliliter (ng/mL). ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Predose (30 minutes) at baseline; Weeks 12, 24; and FU Week 8 (up to 32 weeks overall)

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=132)	37 (± 12.7)			
Week 12 (n=120)	509.4 (± 138.7)			
Week 24 (n=113)	520.2 (± 156.4)			
FU Week 8 (n=36)	166 (± 203.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient Global Assessment of Disease Activity According to VAS

End point title	Change from Baseline in Patient Global Assessment of Disease Activity According to VAS

End point description:

PGA of disease activity was scored 0-100 mm on a VAS, where higher scores indicate greater perceived disease activity. Change from baseline was averaged among all participants. Negative values indicate improvement/reduction in RA disease activity. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=133)	53.2 (± 21.1)			
Change at Week 2 (n=128)	-6.8 (± 18.6)			
Change at Week 4 (n=129)	-20.3 (± 21.3)			
Change at Week 8 (n=125)	-24.6 (± 25.8)			
Change at Week 12 (n=119)	-30.3 (± 25.5)			
Change at Week 16 (n=120)	-32.3 (± 23.9)			
Change at Week 20 (n=113)	-32.2 (± 27.1)			
Change at Week 24 (n=114)	-34.3 (± 24.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient Global Assessment of RA-Related Pain According to VAS

End point title	Change from Baseline in Patient Global Assessment of RA-Related Pain According to VAS

End point description:

PGA of RA-related pain was scored 0-100 mm on a VAS, where higher scores indicate greater perceived pain. Change from baseline was averaged among all participants. Negative values indicate improvement/reduction in RA-related pain. ITT Set; only those who provided data at baseline and at least one post-baseline assessment were analyzed. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	132			
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=132)	54.8 (± 22.1)			
Change at Week 2 (n=126)	-9.1 (± 20.8)			
Change at Week 4 (n=128)	-22.5 (± 24.4)			
Change at Week 8 (n=123)	-28.9 (± 26.6)			
Change at Week 12 (n=117)	-32.8 (± 27.5)			
Change at Week 16 (n=118)	-35.6 (± 25.9)			
Change at Week 20 (n=113)	-35 (± 26.7)			
Change at Week 24 (n=113)	-37.8 (± 26.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in HAQ-DI Score

End point title	Change from Baseline in HAQ-DI Score

End point description:

HAQ-DI consisted of 20 questions assessing ADLs in 8 domains (dress/groom, arise, eat, walk, reach, grip, hygiene) with each item rated 0 (no difficulty) to 3 (unable to do). The highest score recorded for any question in a domain determined the score for that domain, unless assistance was required. The total HAQ-DI score was the sum of domain scores divided by the number of domains answered/scored, for a single score range of 0-3, where higher scores indicate increased functional disability. Change from baseline was averaged among all participants. Negative values indicate improvement in ability to perform ADLs. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=133)	1.2 (± 0.6)			
Change at Week 2 (n=128)	-0.1 (± 0.4)			
Change at Week 4 (n=130)	-0.3 (± 0.5)			
Change at Week 8 (n=124)	-0.5 (± 0.5)			

Change at Week 12 (n=119)	-0.5 (± 0.6)			
Change at Week 16 (n=120)	-0.6 (± 0.6)			
Change at Week 20 (n=114)	-0.6 (± 0.6)			
Change at Week 24 (n=114)	-0.6 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance with Treatment According to Percentage of Injections Administered

End point title	Compliance with Treatment According to Percentage of Injections Administered

End point description:

Participants were provided with diary cards to record home injections. Compliance with treatment was calculated individually for each participant as the actual number of injections as a percentage of the planned number of injections (up to the point of discontinuation for those who discontinued study treatment prematurely) and then averaged among all participants. ITT Set.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: percentage of injections				
arithmetic mean (standard deviation)	86.78 (± 23.04)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

FACIT-F consisted of 40 questions/statements assessing chronic illness therapy with special emphasis on fatigue over the past 7 days, with each item rated 0 (not at all) to 4 (very much). During score calculations, negatively-worded item scales (e.g., "I have a lack of energy") were reversed so that higher scores indicated more favorable conditions. The total FACIT-F score was the sum of all item scores and ranged 0-160, and the brief FACIT-F score was the sum of 13 item scores and ranged 0-52, where higher scores indicate greater well-being. Change from baseline was averaged among all

participants. Positive values indicate improvement in well-being. ITT Set. Here "n" refers to number of participants evaluable at the specified assessment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8, 12, 16, 20, 24

End point values	Tocilizumab Alone or Combined with Methotrexate or Other DMARD			
Subject group type	Subject analysis set			
Number of subjects analysed	133			
Units: units on a scale				
arithmetic mean (standard deviation)				
Brief Score, Baseline (n=133)	32.9 (± 11.1)			
Brief Score, Change at Week 2 (n=128)	3.4 (± 6.9)			
Brief Score, Change at Week 4 (n=130)	5.7 (± 8.3)			
Brief Score, Change at Week 8 (n=124)	6.6 (± 8)			
Brief Score, Change at Week 12 (n=118)	7.6 (± 7.8)			
Brief Score, Change at Week 16 (n=120)	7.9 (± 9.7)			
Brief Score, Change at Week 20 (n=114)	8 (± 9.1)			
Brief Score, Change at Week 24 (n=113)	8.4 (± 8.5)			
Total Score, Baseline (n=133)	106.8 (± 23.6)			
Total Score, Change at Week 2 (n=128)	6.9 (± 14)			
Total Score, Change at Week 4 (n=129)	13 (± 16.6)			
Total Score, Change at Week 8 (n=124)	15.1 (± 16.2)			
Total Score, Change at Week 12 (n=118)	17.1 (± 16.2)			
Total Score, Change at Week 16 (n=118)	18 (± 20.1)			
Total Score, Change at Week 20 (n=114)	18.6 (± 19.8)			
Total Score, Change at Week 24 (n=111)	20.1 (± 19.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to FU Week 8 (up to 32 weeks overall)

Adverse event reporting additional description:

ITT Set

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Tocilizumab Alone or Combined with Methotrexate or Other DMARD

Reporting group description:

All participants received tocilizumab as a single fixed dose (monotherapy) or in combination with methotrexate or other non-biologic DMARDs at a dose of 162 mg, irrespective of body weight, administered subcutaneously QW for 24 weeks. An additional 8 weeks were allotted for post-treatment evaluation of safety/immunogenicity.

Serious adverse events	Tocilizumab Alone or Combined with Methotrexate or Other DMARD		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 133 (9.02%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal cancer			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			

subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infectious pleural effusion			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tocilizumab Alone or Combined with Methotrexate or Other DMARD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 133 (90.23%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	9		
Neutrophil count decreased			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	7		
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 133 (12.78%)		
occurrences (all)	17		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	10		
Headache			

subjects affected / exposed occurrences (all)	9 / 133 (6.77%) 10		
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	 7 / 133 (5.26%) 11		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 11 / 133 (8.27%) 12		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 8 / 133 (6.02%) 9 10 / 133 (7.52%) 15		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 7 / 133 (5.26%) 7		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 20 / 133 (15.04%) 25 10 / 133 (7.52%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2015	The planned sample size was changed.
12 April 2016	The period for post-study follow-up of adverse events was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported