

**Clinical trial results:****Multi-Center, Open Label, Single Arm Phase IIIB Study on Safety and Efficacy of Subcutaneous Tocilizumab in Monotherapy or in Combination With Methotrexate or Other Non-Biologic Disease Modifying Antirheumatic Drugs in Rheumatoid Arthritis Patients With an Inadequate Response to Non-Biologic DMARDs – OSCAR****Summary**

EudraCT number	2013-000342-19
Trial protocol	NL
Global end of trial date	26 May 2016

Results information

Result version number	v1 (current)
This version publication date	04 June 2017
First version publication date	04 June 2017

Trial information**Trial identification**

Sponsor protocol code	ML28702
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01987479
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	10 October 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This multi-center, open-label single arm Phase IIIb study evaluated the safety and efficacy of subcutaneous (SC) tocilizumab administered as monotherapy and/or in combination with methotrexate or other non-biologic disease modifying antirheumatic drugs (DMARDs) in participants with rheumatoid arthritis (RA) with an inadequate response to non-biologic DMARDs.

Protection of trial subjects:

This study was conducted in full conformance with the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice (GCP) 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 150
Worldwide total number of subjects	150
EEA total number of subjects	150

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)	122
From 65 to 84 years	27

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 174 participants were screened, out of which 150 participants met eligibility criteria and were enrolled into the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tocilizumab Alone or in Combination with Methotrexate or DMARD
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Arm description:

Participants received a weekly SC injection of tocilizumab 162 milligrams (mg) as monotherapy or in combination with methotrexate or other non-biologic DMARDs for 24 weeks.

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 once a week by SC injection and as a single fixed dose, irrespective of body weight, for the treatment duration of 24 weeks.

Number of subjects in period 1	Tocilizumab Alone or in Combination with Methotrexate or DMARD
Started	150
Completed	133
Not completed	17
Physician decision	2
Adverse event, non-fatal	7
Unspecified	5
Lost to follow-up	1
Protocol deviation	1
participant/legal guardian decision to withdraw	1

Baseline characteristics

Reporting groups

Reporting group title	Tocilizumab Alone or in Combination with Methotrexate or DMARD
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Reporting group description:

Participants received a weekly SC injection of tocilizumab 162 milligrams (mg) as monotherapy or in combination with methotrexate or other non-biologic DMARDs for 24 weeks.

Reporting group values	Tocilizumab Alone or in Combination with Methotrexate or DMARD	Total	
Number of subjects	150	150	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	55.85 ± 11.2	-	
Gender Categorical Units: Subjects			
Female	110	110	
Male	40	40	

End points

End points reporting groups

Reporting group title	Tocilizumab Alone or in Combination with Methotrexate or DMARD
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Reporting group description:

Participants received a weekly SC injection of tocilizumab 162 milligrams (mg) as monotherapy or in combination with methotrexate or other non-biologic DMARDs for 24 weeks.

Primary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events ^[1]
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End point description:

An adverse event was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Adverse events included serious as well as non-serious adverse events. Full Analysis Set (FAS) population included all participants who received at least one dose of SC tocilizumab.

End point type	Primary
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End point timeframe:

Baseline up to Week 32

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: No statistical analyses were planned for this endpoint but descriptive statistics only

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)	91.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) Score at Weeks 2, 4, 8, 12, 16, 20, 24, and Early Withdrawal

End point title	Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) Score at Weeks 2, 4, 8, 12, 16, 20, 24, and Early Withdrawal
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End point description:

DAS28 was calculated from swollen joint count (SJC) and tender joint count (TJC) using 28 joints count, erythrocyte sedimentation rate (ESR; millimeters per hour [mm/hour]), and patient's global assessment of disease activity (measured on a 0 to 100 mm Visual Analog Scale [VAS] where 0 mm=no disease activity and 100 mm=worst disease activity). DAS28 scores were calculated as $[0.56 \times \text{square root of TJC}] + [0.28 \times \text{square root of SJC}] + [0.70 \times \text{natural log (ESR)}] + [0.014 \times \text{VAS}]$. Total score range: 0-

10, higher score=higher disease activity. DAS28-ESR less than or equal to (\leq) 3.2 implied low disease activity and greater than ($>$) 3.2 to 5.1 implied moderate to high disease activity, and DAS28-ESR less than ($<$) 2.6 implied clinical remission. FAS population. Here, "n" = participants who were evaluable at the specified timepoint.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)	

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=150)	4.8 (\pm 1.3)			
Change at Week 2 (n=148)	1.337 (\pm 0.989)			
Change at Week 4 (n=144)	2.037 (\pm 0.991)			
Change at Week 8 (n=136)	2.635 (\pm 1.098)			
Change at Week 12 (n=133)	2.908 (\pm 1.135)			
Change at Week 16 (n=128)	3.014 (\pm 1.24)			
Change at Week 20 (n=122)	3.169 (\pm 1.17)			
Change at Week 24 (n=121)	3.232 (\pm 1.247)			
Change at early withdrawal visit (n=27)	1.653 (\pm 1.562)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an American College of Rheumatology Criteria 20 (ACR20) Response

End point title	Percentage of Participants Achieving an American College of Rheumatology Criteria 20 (ACR20) Response
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End point description:

A participant had an ACR20 response if there was at least a 20 percent (%) improvement, ie, reduction from Baseline, in TJC and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 2) Patient's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 3) Patient's Assessment of Pain [VAS: 0 mm=no pain to 100 mm=unbearable pain]; 4) Health Assessment Questionnaire [20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do] and 5) an acute-phase reactant (either C-reactive protein [CRP] or ESR). FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Week 2 (n=148)	20.3			
Week 4 (n=144)	40.3			
Week 8 (n=136)	58.1			
Week 12 (n=133)	69.9			
Week 16 (n=130)	71.5			
Week 20 (n=123)	78.9			
Week 24 (n=121)	82.6			
Early withdrawal visit (n=27)	37			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an ACR50 Response

End point title	Percentage of Participants Achieving an ACR50 Response
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End point description:

A participant had an ACR50 response if there was at least a 50% improvement, ie, reduction from Baseline, in TJC and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 2) Patient's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 3) Patient's Assessment of Pain [VAS: 0 mm=no pain to 100 mm=unbearable pain]; 4) Health Assessment Questionnaire [20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do] and 5) an acute-phase reactant (either CRP or ESR). FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Week 2 (n=148)	6.1			
Week 4 (n=144)	18.1			
Week 8 (n=136)	33.1			
Week 12 (n=133)	43.6			
Week 16 (n=130)	52.3			
Week 20 (n=123)	54.5			
Week 24 (n=121)	62			
Early withdrawal visit (n=27)	18.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an ACR70 Response

End point title	Percentage of Participants Achieving an ACR70 Response
End point description:	
<p>A participant had an ACR70 response if there was at least a 70% improvement, ie, reduction from Baseline, in TJC and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 2) Patient's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 3) Patient's Assessment of Pain [VAS: 0 mm=no pain to 100 mm=unbearable pain]; 4) Health Assessment Questionnaire [20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do] and 5) an acute-phase reactant (either CRP or ESR). FAS population. Here, "n" = participants who were evaluable at specified timepoint.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)	

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Week 2 (n=148)	1.4			
Week 4 (n=144)	6.9			

Week 8 (n=136)	14			
Week 12 (n=133)	21.1			
Week 16 (n=130)	29.2			
Week 20 (n=123)	38.2			
Week 24 (n=121)	35.5			
Early withdrawal visit (n=27)	14.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an ACR90 Response

End point title	Percentage of Participants Achieving an ACR90 Response
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End point description:

A participant had an ACR90 response if there was at least a 90% improvement, ie, reduction from Baseline, in TJC and SJC (28 assessed joints) and in at least 3 of the following 5 parameters: 1) Physician's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 2) Patient's Global Assessment of Disease Activity [VAS: 0 mm=no disease activity to 100 mm=maximum disease activity]; 3) Patient's Assessment of Pain [VAS: 0 mm=no pain to 100 mm=unbearable pain]; 4) Health Assessment Questionnaire [20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do] and 5) an acute-phase reactant (either CRP or ESR). FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Week 2 (n=148)	0			
Week 4 (n=144)	1.4			
Week 8 (n=136)	2.9			
Week 12 (n=133)	6.8			
Week 16 (n=130)	9.2			
Week 20 (n=123)	11.4			
Week 24 (n=121)	15.7			
Early withdrawal visit (n=27)	3.7			

Statistical analyses

Secondary: Percentage of Participants With European League Against Rheumatism (EULAR) Response (Good, Moderate or No Response) Based on DAS28-ESR

End point title	Percentage of Participants With European League Against Rheumatism (EULAR) Response (Good, Moderate or No Response) Based on DAS28-ESR
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End point description:

DAS28-ESR was calculated from SJC and TJC using 28 joints count, ESR (mm/hour), and patient's global assessment of disease activity (VAS: 0 mm=no disease activity to 100 mm=maximum disease activity). $DAS28-ESR = [0.56 \times \text{square root of TJC}] + [0.28 \times \text{square root of SJC}] + [0.70 \times \text{natural log (ESR)}] + [0.014 \times VAS]$. DAS28-ESR based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and level of disease activity reached. Good responders had a change from baseline >1.2 with a DAS28 score ≤ 3.2 ; moderate responders had a change from baseline >1.2 with a DAS28 score >3.2 or a change from baseline >0.6 to ≤ 1.2 with a DAS28 score ≤ 5.1 . Participants with change from baseline >0.6 to ≤ 1.2 with a DAS28 score >5.1 , or any score with change from baseline ≤ 0.6 , were assessed as non-responders. FAS population. "n"=participants who were evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Week 2: Good response (n=148)	34.5			
Week 2: Moderate response (n=148)	41.9			
Week 2: No response (n=148)	23.6			
Week 4: Good response (n=144)	59.7			
Week 4: Moderate response (n=144)	34			
Week 4: No response (n=144)	6.3			
Week 8: Good response (n=136)	78.7			
Week 8: Moderate response (n=136)	17.6			
Week 8: No response (n=136)	3.7			
Week 12: Good response (n=133)	85			
Week 12: Moderate response (n=133)	12			
Week 12: No response (n=133)	3			
Week 16: Good response (n=128)	89.1			
Week 16: Moderate response (n=128)	7			
Week 16: No response (n=128)	3.9			
Week 20: Good response (n=122)	91.8			
Week 20: Moderate response (n=122)	5.7			
Week 20: No response (n=122)	2.5			
Week 24: Good response (n=121)	92.6			
Week 24: Moderate response (n=121)	5			
Week 24: No response (n=121)	2.5			

Early withdrawal visit: Good response (n=27)	44.4			
Early withdrawal visit: Moderate response (n=27)	29.6			
Early withdrawal visit: No response (n=27)	25.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simplified Disease Activity Index (SDAI) at Weeks 2, 4, 8, 12, 16, 20, 24, and Early Withdrawal

End point title	Change From Baseline in Simplified Disease Activity Index (SDAI) at Weeks 2, 4, 8, 12, 16, 20, 24, and Early Withdrawal
End point description:	The SDAI is the numerical sum of five outcome parameters: TJC and SJC based on a 28-joint assessment, patient and physician global assessment of disease The SDAI is the numerical sum of five outcome parameters: TJC and SJC based on a 28-joint assessment, patient and physician global assessment of disease activity assessed on 0-10 centimeter (cm) VAS (0 cm= no disease activity and 10 cm= worst disease activity), and CRP in milligrams per liter (mg/L). SDAI total score = 0-86. SDAI ≤ 3.3 indicates clinical remission, >3.4 to 11 = low disease activity, >11 to 26 = moderate disease activity, and >26 = high (or severe) disease activity. FAS population. Here, "Number of subjects analysed" = participants who were evaluable for this outcome. "n" = participants who were evaluable at specified timepoint.
End point type	Secondary
End point timeframe:	Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	145			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=145)	26.03 (\pm 12.55)			
Change at Week 2 (n=97)	-6.2 (\pm 7.4)			
Change at Week 4 (n=78)	-11.3 (\pm 8)			
Change at Week 8 (n=64)	-14.4 (\pm 9.2)			
Change at Week 12 (n=63)	-17.2 (\pm 10.8)			
Change at Week 16 (n=67)	-18.5 (\pm 11.1)			
Change at Week 20 (n=57)	-19.7 (\pm 11.2)			
Change at Week 24 (n=56)	-19.9 (\pm 11.8)			
Change at early withdrawal visit (n=18)	-8 (\pm 10.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) at Weeks 2, 4, 8, 16, 20, 24, and Early Withdrawal

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) at Weeks 2, 4, 8, 16, 20, 24, and Early Withdrawal
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End point description:

The CDAI is the numerical sum of four outcome parameters: TJC and SJC based on a 28-joint assessment, patient and physician's global assessment of disease activity assessed on 0-10 cm VAS (0 cm= no disease activity and 10 cm= worst disease activity). CDAI total score = 0-76. CDAI \leq 2.8 indicates clinical remission, >2.8 to 10 = low disease activity, >10 to 22 = moderate disease activity, and >22 = high (or severe) disease activity. FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=150)	24.32 (\pm 11.84)			
Change at Week 2 (n=148)	-4.7 (\pm 7.3)			
Change at Week 4 (n=144)	-9.4 (\pm 7.2)			
Change at Week 8 (n=135)	-13.4 (\pm 8.7)			
Change at Week 12 (n=132)	-15.4 (\pm 9.2)			
Change at Week 16 (n=129)	-16.7 (\pm 10.1)			
Change at Week 20 (n=122)	-17.8 (\pm 10.2)			
Change at Week 24 (n=121)	-18.3 (\pm 11.1)			
Change at early withdrawal visit (n=27)	-6.4 (\pm 10.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total TJC at Weeks 2, 4, 8, 12, 16, 20, 24, and Early Withdrawal

End point title	Change From Baseline in Total TJC at Weeks 2, 4, 8, 12, 16, 20, 24, and Early Withdrawal
End point description:	Number of tender joints was determined by examining 28 joints for TJC28 and 68 joints for TJC68, and identified the joints that were painful under pressure or to passive motion. The number of tender joints was recorded on the joint assessment form at each visit, no tenderness = 0, tenderness = 1; total was calculated by adding all the joints for a maximum score of 28 for a TJC28 and 68 for a TJC68. A reduction in number of tender joints compared to baseline indicates improvement. FAS population. Here, "n" = participants who were evaluable at specified timepoint.
End point type	Secondary
End point timeframe:	Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: tender joints				
arithmetic mean (standard deviation)				
TJC28: Baseline (n=150)	7.7 (± 6.5)			
TJC28: Change at Week 2 (n=148)	-1.38 (± 3.71)			
TJC28: Change at Week 4 (n=144)	-2.94 (± 3.89)			
TJC28: Change at Week 8 (n=136)	-4.33 (± 4.82)			
TJC28: Change at Week 12 (n=133)	-4.68 (± 5.05)			
TJC28: Change at Week 16 (n=130)	-5.36 (± 5.55)			
TJC28: Change at Week 20 (n=123)	-5.79 (± 5.24)			
TJC28: Change at Week 24 (n=121)	-5.96 (± 5.67)			
TJC28: Change at early withdrawal visit (n=27)	-1.07 (± 4.59)			
TJC68: Baseline (n=150)	13.2 (± 10)			
TJC68: Change at Week 2 (n=148)	-2.4 (± 5.84)			
TJC68: Change at Week 4 (n=144)	-5.15 (± 6.25)			
TJC68: Change at Week 8 (n=136)	-7.19 (± 7.57)			
TJC68: Change at Week 12 (n=133)	-7.98 (± 8.46)			
TJC68: Change at Week 16 (n=130)	-9.45 (± 9.07)			
TJC68: Change at Week 20 (n=123)	-9.86 (± 9.04)			
TJC68: Change at Week 24 (n=121)	-10.02 (± 8.94)			
TJC68: Change at early withdrawal visit (n=27)	-1.93 (± 8.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total SJC at Weeks 2, 4, 8, 12, 16, 20, 24, and Early Withdrawal

End point title	Change From Baseline in Total SJC at Weeks 2, 4, 8, 12, 16, 20, 24, and Early Withdrawal
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End point description:

Number of swollen joints was determined by examination of 28 joints for SJC28 and 66 joints for SJC66 and identifying when swelling was present. The number of swollen joints was recorded on the joint assessment form at each visit, no swelling = 0, swelling =1; total was calculated by adding all the joints for a maximum score of 28 for a SJC28 and 66 for a SJC66. A reduction in number of swollen joints compared to baseline indicates improvement. FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and at Early Withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: swollen joints				
arithmetic mean (standard deviation)				
SJC28: Baseline (n=150)	6.2 (± 5.4)			
SJC28: Change at Week 2 (n=148)	-1.18 (± 3.04)			
SJC28: Change at Week 4 (n=144)	-2.44 (± 3.33)			
SJC28: Change at Week 8 (n=136)	-3.62 (± 3.86)			
SJC28: Change at Week 12 (n=133)	-4.24 (± 4.17)			
SJC28: Change at Week 16 (n=130)	-4.61 (± 4.14)			
SJC28: Change at Week 20 (n=123)	-4.92 (± 4.24)			
SJC28: Change at Week 24 (n=121)	-5.23 (± 4.63)			
SJC28: Change at early withdrawal visit (n=27)	-1.33 (± 4.18)			
SJC66: Baseline (n=150)	9.1 (± 7.3)			
SJC66: Change at Week 2 (n=148)	-1.84 (± 4.16)			
SJC66: Change at Week 4 (n=144)	-3.94 (± 4.35)			
SJC66: Change at Week 8 (n=136)	-5.61 (± 4.74)			
SJC66: Change at Week 12 (n=133)	-6.5 (± 5.79)			
SJC66: Change at Week 16 (n=130)	-6.78 (± 5.95)			
SJC66: Change at Week 20 (n=123)	-7.52 (± 6.44)			
SJC66: Change at Week 24 (n=121)	-7.8 (± 6.86)			
SJC66: Change at early withdrawal visit (n=27)	-2.33 (± 4.89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Dose Reductions or Discontinuation Categorized by Reasons

End point title	Percentage of Participants With Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Dose Reductions or Discontinuation Categorized by Reasons
End point description: Results are reported for percentage of participants who had NSAIDs dose reductions or discontinuation by reasons for dose reductions or discontinuation (unknown reasons, safety reasons, other reasons, lack of efficacy, and discomfort). FAS population	
End point type	Secondary
End point timeframe: From Week 16 and before Week 20; From Week 20 and before Week 24	

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Unknown reasons (Week 16 to Week 20)	0			
Safety reasons (Week 16 to Week 20)	0.7			
Other reasons (Week 16 to Week 20)	0.7			
Lack of efficacy (Week 16 to Week 20)	0			
Discomfort (Week 16 to Week 20)	0			
Unknown reasons (Week 20 to Week 24)	0			
Safety reasons (Week 20 to Week 24)	0			
Other reasons (Week 20 to Week 24)	0			
Lack of efficacy (Week 20 to Week 24)	0			
Discomfort (Week 20 to Week 24)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Corticosteroid Dose Reductions or Discontinuation Categorized by Reasons

End point title	Percentage of Participants With Corticosteroid Dose Reductions or Discontinuation Categorized by Reasons
End point description: Results are reported for percentage of participants who had corticosteroid dose reductions or discontinuation by reasons for dose reductions or discontinuation (unknown reasons, safety reasons, other reasons, lack of efficacy, and discomfort). FAS population	
End point type	Secondary

End point timeframe:

From Week 16 and before Week 20; From Week 20 and before Week 24

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Unknown reasons (Week 16 to Week 20)	0			
Safety reasons (Week 16 to Week 20)	1.3			
Other reasons (Week 16 to Week 20)	0.7			
Lack of efficacy (Week 16 to Week 20)	0			
Discomfort (Week 16 to Week 20)	0			
Unknown reasons (Week 20 to Week 24)	0			
Safety reasons (Week 20 to Week 24)	0			
Other reasons (Week 20 to Week 24)	1.3			
Lack of efficacy (Week 20 to Week 24)	0.7			
Discomfort (Week 20 to Week 24)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Discontinuation or First Dose Reduction of Corticosteroids or NSAIDs

End point title	Time to Discontinuation or First Dose Reduction of Corticosteroids or NSAIDs
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End point description:

Time to discontinuation or first dose reduction of corticosteroids or NSAIDs (weeks) = (Date of the first dose reduction or end date of corticosteroids or NSAIDs treatment - date of first drug intake of this study) + 1. FAS population. Time to discontinuation or first dose reduction was based on first occurring event (corticosteroid discontinuation or corticosteroid first dose reduction or NSAIDs discontinuation or NSAIDs first dose reduction, whichever occurred first).

End point type	Secondary
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End point timeframe:

Baseline up to Week 32

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: weeks				
median (confidence interval 95%)	25.3 (25 to 28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Levels of Tocilizumab

End point title	Serum Levels of Tocilizumab
End point description:	FAS population. Here, "n" = participants who were evaluable at specified timepoint.
End point type	Secondary
End point timeframe:	Baseline, Weeks 12 and 24, Early Withdrawal (up to Week 24), Follow-up Visit (8 weeks after last dose of tocilizumab, up to 32 weeks)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Baseline (n=4)	0.5 (± 0.3)			
Week 12 (n=123)	42.3 (± 25.2)			
Week 24 (n=112)	46.5 (± 29.2)			
Early withdrawal (n=17)	16.8 (± 19.3)			
Follow-up visit (n=3)	60.9 (± 29.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Levels of Soluble Interleukin-6 Receptors (sIL-6Rs)

End point title	Serum Levels of Soluble Interleukin-6 Receptors (sIL-6Rs)
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End point description:

FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type Secondary

End point timeframe:

Baseline, Weeks 12 and 24, Early Withdrawal (up to Week 24), Follow-up Visit (8 weeks after last dose of tocilizumab, up to 32 weeks)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=139)	38.3 (± 10.4)			
Week 12 (n=126)	516.6 (± 137.7)			
Week 24 (n=115)	536.5 (± 161.6)			
Early withdrawal (n=21)	380.4 (± 215.2)			
Follow-up visit (n=26)	117.5 (± 194.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment of Disease Activity VAS Scores

End point title Patient Global Assessment of Disease Activity VAS Scores

End point description:

Patient global assessment of disease activity was measured on a 0 to 100 mm horizontal VAS where 0 mm=no disease activity and 100 mm=maximum disease activity. FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type Secondary

End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and Early withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=150)	54.8 (± 22.3)			
Week 2 (n=148)	43.6 (± 23)			
Week 4 (n=144)	35.5 (± 23)			
Week 8 (n=136)	27.2 (± 21.8)			
Week 12 (n=133)	22.2 (± 20.3)			
Week 16 (n=129)	21.3 (± 21)			
Week 20 (n=123)	19.2 (± 18.6)			
Week 24 (n=121)	18.8 (± 19.5)			
Early withdrawal (n=27)	40.4 (± 30.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Pain VAS Scores

End point title	Patient Pain VAS Scores
End point description:	This assessment represents the participant's assessment of his/her current level of pain on a 100 mm horizontal VAS where 0 mm = no pain to 100 mm = unbearable pain. FAS population. Here, "n" = participants who were evaluable at specified timepoint.
End point type	Secondary
End point timeframe:	Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and Early withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=150)	52.5 (± 22.1)			
Week 2 (n=148)	44.4 (± 21.9)			
Week 4 (n=144)	35.8 (± 22.3)			
Week 8 (n=136)	27.6 (± 21.3)			
Week 12 (n=133)	21.7 (± 19)			
Week 16 (n=129)	20.9 (± 20.2)			

Week 20 (n=123)	19.5 (± 18)			
Week 24 (n=121)	19.6 (± 18.8)			
Early withdrawal (n=27)	42.8 (± 30.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Assessment Questionnaire-Disability Index (HAQ-DI) Score

End point title	Health Assessment Questionnaire-Disability Index (HAQ-DI) Score
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End point description:

The HAQ-DI questionnaire measures functional status (disability) and health-related quality of life. It measures the participant's ability to perform everyday tasks. The index consists of 20 questions regarding the function of the upper and lower extremities. These questions are summarized in 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common activities over past week. Each question is evaluated according to the degree of severity on a 4-point scale. Total score for HAQ-DI was the average of all questions and ranges from 0 = without any difficulty to 3 = unable to do. FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and early withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=147)	1.2329 (± 0.5708)			
Week 2 (n=147)	1.0978 (± 0.5906)			
Week 4 (n=143)	0.9673 (± 0.5734)			
Week 8 (n=134)	0.8249 (± 0.5587)			
Week 12 (n=131)	0.746 (± 0.533)			
Week 16 (n=129)	0.6996 (± 0.5682)			
Week 20 (n=122)	0.662 (± 0.5333)			
Week 24 (n=119)	0.6681 (± 0.5745)			
Early withdrawal (n=27)	1.2315 (± 0.6853)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Compliant to Tocilizumab Treatment as Measured by Diary Cards and Return Records

End point title	Percentage of Participants Compliant to Tocilizumab Treatment as Measured by Diary Cards and Return Records
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End point description:

A diary card was provided to participants to record home injections. Participants were asked to return all empty drug supply boxes, unused pre-filled syringe, and diary cards to the clinic at each visit as a measure of drug accountability and participant compliance. A participant was considered compliant if the participant correctly administered all scheduled doses of SC tocilizumab during the assessment period. FAS population. Here, "n" = participants who were evaluable at specified timepoint.

End point type	Secondary
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End point timeframe:

Weeks 2, 4, 8, 12, 16, 20, 24, and early withdrawal (up to Week 24)

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Week 2 (n=148)	90.5			
Week 4 (n=144)	95.8			
Week 8 (n=136)	91.9			
Week 12 (n=133)	97.7			
Week 16 (n=130)	93.8			
Week 20 (n=123)	95.1			
Week 24 (n=121)	92.6			
Early withdrawal (n=27)	88.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Score

End point title	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Score
End point description: The FACIT-F score was calculated according to a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. FACIT-F is a 13-item questionnaire. Participants scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the participant's response to the questions (with the exception of 2 negatively stated), the greater the participants fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the participant's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). FAS population. Here, "n" = participants who were evaluable at specified timepoint.	
End point type	Secondary
End point timeframe: Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, and early withdrawal (up to Week 24)	

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=133)	29.84 (± 9.43)			
Week 2 (n=134)	33.07 (± 9.34)			
Week 4 (n=133)	35.1 (± 10.37)			
Week 8 (n=126)	37.34 (± 9.25)			
Week 12 (n=126)	37.89 (± 8.52)			
Week 16 (n=122)	37.93 (± 9.11)			
Week 20 (n=118)	39.65 (± 8.87)			
Week 24 (n=114)	39.93 (± 8.65)			
Early withdrawal (n=27)	33.48 (± 12.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Tocilizumab Antibodies

End point title	Percentage of Participants With Anti-Tocilizumab Antibodies
End point description: FAS population. Here, "n" = participants who were evaluable at specified timepoint.	
End point type	Secondary
End point timeframe: Baseline, Weeks 12 and 24, early withdrawal (up to Week 24), follow-up visit (8 weeks after last dose of tocilizumab, up to 32 weeks)	

End point values	Tocilizumab Alone or in Combination with Methotrexate or DMARD			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Baseline (n=147)	6.1			
Week 12 (n=5)	40			
Week 24 (n=121)	7.4			
Early withdrawal (n=22)	9.1			
Follow-up visit (n=26)	11.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 32

Adverse event reporting additional description:

FAS population

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Tocilizumab Alone or in Combination with Methotrexate or DMARD
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Reporting group description:

Participants received a weekly SC injection of tocilizumab 162 mg as monotherapy or in combination with methotrexate or other non-biologic DMARDs for 24 weeks.

	Tocilizumab Alone or in Combination with Methotrexate or DMARD		
Serious adverse events			
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 150 (9.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Scapula fracture			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tibia fracture			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prophylaxis			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Psoriasis			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint range of motion decreased			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tocilizumab Alone or in Combination with Methotrexate or DMARD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 150 (51.33%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 150 (7.33%)		
occurrences (all)	12		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed occurrences (all)	18 / 150 (12.00%) 19		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	8 / 150 (5.33%) 8		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	18 / 150 (12.00%) 20 9 / 150 (6.00%) 10		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	8 / 150 (5.33%) 9		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	8 / 150 (5.33%) 9		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	35 / 150 (23.33%) 42		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported