Clinical trial results:
A National, Open-Label, Single-Arm, Phase IIIb Study to Evaluate the Efficacy of Weekly Tocilizumab Subcutaneous, Administered as Monotherapy or in Combination With Methotrexate and/or Other DMARDs in Rheumatoid Arthritis (RA) Patients

Summary

EudraCT number	2013-001569-17
Trial protocol	IT
Global end of trial date	05 July 2016

Results information

Result version number	v2 (current)
This version publication date	28 June 2017
First version publication date	06 November 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	ML28699

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01941940
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	05 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of subcutaneous (SC) tocilizumab administered in monotherapy or in combination with methotrexate (MTX) and/or other non-biological disease modifying antirheumatic drugs (DMARDs) using Clinical Disease Activity Index (CDAI) over time up to Week 24, including onset of action at Week 2.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP). Approval from the Independent Ethics Committee/Institutional Review Board (IEC/IRB) was obtained before study start and was documented in a letter to the Investigator specifying the date on which the committee met and granted the approval. The Sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2013
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	Italy: 227
Worldwide total number of subjects	227
EEA total number of subjects	227

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)	177
From 65 to 84 years	49

85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of a total of 288 participants screened, 60 participants were excluded due to screening failure and 1 participant did not receive study treatment based on investigator's decision. Thus, total 227 participants were included in 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

Arm description:

Tocilizumab at a fixed dose of 162 milligrams (mg) was administered as SC injection alone or along with methotrexate and/or other non-biological DMARDs irrespective of body weight, once every week for a total of 52 weeks. After 52-weeks of treatment, at the discretion of the treating physician, participants could continue the study treatment with SC tocilizumab until it became commercially available in Italy (maximum up to 638 days).

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

Dosage and administration details:

Tocilizumab at a fixed dose of 162 mg as SC injection was administered once every week.

Number of subjects in period 1	Tocilizumab
Started	227
Completed	194
Not completed	33
Physician decision	2
Consent withdrawn by subject	15
Adverse Event	11
Death	1
Unknown	1
Unspecified	1
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab

Reporting group description:

Tocilizumab at a fixed dose of 162 milligrams (mg) was administered as SC injection alone or along with methotrexate and/or other non-biological DMARDs irrespective of body weight, once every week for a total of 52 weeks. After 52-weeks of treatment, at the discretion of the treating physician, participants could continue the study treatment with SC tocilizumab until it became commercially available in Italy (maximum up to 638 days).

Reporting group values	Tocilizumab	Total	
Number of subjects	227	227	
Age Categorical Units: Subjects			
Age Continuous			
Full Analysis Set (FAS) included all recruited participants who received at least one dose of SC tocilizumab.			
Units: years arithmetic mean standard deviation	 54.7 ± 12.12	 -	
Gender Categorical Units: Subjects			
Female	197	197	
Male	30	30	

End points

End points reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Tocilizumab at a fixed dose of 162 milligrams (mg) was administered as SC injection alone or along with methotrexate and/or other non-biological DMARDs irrespective of body weight, once every week for a total of 52 weeks. After 52-weeks of treatment, at the discretion of the treating physician, participants could continue the study treatment with SC tocilizumab until it became commercially available in Italy (maximum up to 638 days).

Primary: Change From Baseline in CDAI at Week 24

End point title	Change From Baseline in CDAI at Week 24[1]

End point description:

The CDAI is a numerical sum of 4 outcome parameters: tender joint count (TJC) and swollen joint count (SJC) based on a 28-joint assessment, patient's global assessment of disease activity (PtGDA) and physician global assessment of disease activity (PGDA) assessed on 0-10 centimeters (cm) visual analogue scale (VAS). Higher scores represent greater affectation due to disease activity. CDAI total score = 0-76. CDAI score less than or equal to (</=) 2.8 indicates disease remission, greater than (>) 2.8 to 10 indicates low disease activity, >10 to 22 indicates moderate disease activity, and >22 indicates high disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to EudraCT database limitations it is not possible to add statistical analysis in a single arm study.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	183			
Units: units on a scale				
arithmetic mean (standard deviation)	-21.6 (± 13.25)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in CDAI at Week 20

End point title	Change From Baseline in CDAI at Week 20[2]

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. Higher scores represent greater affectation due to disease activity. CDAI total score = 0-76. CDAI score </=2.8 indicates disease remission, >2.8 to 10 indicates low disease activity, >10 to 22 indicates moderate disease activity, and >22 indicates high disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 20

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were only planned for this analysis.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	185			
Units: units on a scale				
arithmetic mean (standard deviation)	-21.3 (± 12.87)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in CDAI at Week 16

End point title	Change From Baseline in CDAI at Week 16[3]

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. Higher scores represent greater affectation due to disease activity. CDAI total score = 0-76. CDAI score </=2.8 indicates disease remission, >2.8 to 10 indicates low disease activity, >10 to 22 indicates moderate disease activity, and >22 indicates high disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 16

Notes:

[3] - 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: Descriptive statistics were only planned for this analysis.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	191			
Units: units on a scale				
arithmetic mean (standard deviation)	-20.2 (± 12.53)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in CDAI at Week 12

End point title	Change From Baseline in CDAI at Week 12[4]

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. Higher scores represent greater affectation due to disease activity. CDAI total score = 0-76. CDAI score </=2.8 indicates disease remission, >2.8 to 10 indicates low disease activity, >10 to 22 indicates moderate disease activity, and >22 indicates high disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 12

Notes:

[4] - 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: Descriptive statistics were only planned for this analysis.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	198			
Units: units on a scale				
arithmetic mean (standard deviation)	-19.1 (± 12.46)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in CDAI at Week 8

End point title	Change From Baseline in CDAI at Week 8[5]

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. Higher scores represent greater affectation due to disease activity. CDAI total score = 0-76. CDAI score </=2.8 indicates disease remission, >2.8 to 10 indicates low disease activity, >10 to 22 indicates moderate disease activity, and >22 indicates high disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 8

Notes:

[5] - 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: Descriptive statistics were only planned for this analysis.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	203			
Units: units on a scale				
arithmetic mean (standard deviation)	-17.7 (± 12.07)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in CDAI at Week 4

End point title	Change From Baseline in CDAI at Week 4[6]

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. Higher scores represent greater affectation due to disease activity. CDAI total score = 0-76. CDAI score </=2.8 indicates disease remission, >2.8 to 10 indicates low disease activity, >10 to 22 indicates moderate disease activity, and >22 indicates high disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 4

Notes:

[6] - 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: Descriptive statistics were only planned for this analysis.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	212			
Units: units on a scale				
arithmetic mean (standard deviation)	-14 (± 11.57)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in CDAI at Week 2

End point title	Change From Baseline in CDAI at Week 2[7]

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. Higher scores represent greater affectation due to disease activity. CDAI total score = 0-76. CDAI score </=2.8 indicates disease remission, >2.8 to 10 indicates low disease activity, >10 to 22 indicates moderate disease activity, and >22 indicates high disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 2

Notes:

[7] - 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: Due to EudraCT database limitations it is not possible to add statistical analysis in a single arm study.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: units on a scale				
arithmetic mean (standard deviation)	-9.1 (± 9.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving Clinical Remission According to CDAI up to Week 52

End point title	Number of Participants Achieving Clinical Remission According to CDAI up to Week 52

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. Higher scores represent greater affectation due to disease activity. CDAI total score = 0-76. CDAI score </=2.8 during any two consecutive visits, not including the baseline visit indicates disease remission. Analysis was performed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to Week 52 (Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 38, and 52)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: participants	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Disease Activity Score Based on 28-Joints Count and Erythrocyte Sedimentation Rate (DAS28-ESR) at Weeks 2, 24, and 52

End point title	Change from Baseline in Disease Activity Score Based on 28-Joints Count and Erythrocyte Sedimentation Rate (DAS28-ESR) at Weeks 2, 24, and 52

End point description:

DAS28-ESR is calculated from the TJC and SJC based on a 28-joint assessment, the erythrocyte sedimentation rate (ESR) in millimeters per hour (mm/hour) and PtGDA assessed on 0-10 cm VAS. Higher scores indicate greater affectation due to disease activity. DAS28-ESR total score= 0-9.4. DAS28-ESR </=3.2 indicates low disease activity, DAS28-ESR >3.2 to 5.1 indicates moderate to high disease activity, and DAS28-ESR </=3.2 indicates remission. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	216			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=216)	5.81 (± 1.08)			
Change at Week 2 (n=208)	-1.5 (± 1.04)			
Change at Week 24 (n=174)	-3.2 (± 1.47)			
Change at Week 52 (n=31)	-3.6 (± 1.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simplified Disease Activity Index (SDAI) at Weeks 2, 24, and 52

End point title	Change From Baseline in Simplified Disease Activity Index (SDAI) at Weeks 2, 24, and 52

End point description:

SDAI is a numerical sum of 5 outcome parameters: TJC and SJC based on 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS and C-reactive protein (CRP) in milligrams per deciliter (mg/dL). Higher scores indicate greater affectation due to disease activity. SDAI total score = 0-86. SDAI </=3.3 indicates disease remission, >3.4 to 11 indicates low disease activity, >11 to 26 indicates moderate disease activity, and >26 indicates high disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	215			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=215)	48.7 (± 45.79)			
Change at Week 2 (n=203)	-26.5 (± 44.04)			
Change at Week 24 (n=176)	-38.9 (± 48.75)			
Change at Week 52 (n=29)	-39.3 (± 26.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an American College of Rheumatology 20% (ACR20), 50% (ACR50), and 70% (ACR70) Response

End point title	Percentage of Participants With an American College of Rheumatology 20% (ACR20), 50% (ACR50), and 70% (ACR70) Response

End point description:

The ACR 20, 50, and 70 responses: greater than or equal to (>/=) 20 percent (%), 50%, and 70% improvement in TJC and SJC (28 assessed joints), and 20%, 50%, 70% improvement in 3 of the following 5 criteria, respectively: 1) PGDA, 2) PtGDA, 3) participant's assessment of pain, 4) participant's assessment of functional disability via a health assessment questionnaire, and 5) CRP or ESR at each visit. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: percentage of participants				
number (not applicable)				
Week 2: ACR 20 (n=222)	18.5			
Week 2: ACR 50 (n=222)	6.3			
Week 2: ACR 70 (n=222)	11.7			
Week 24: ACR 20 (n=192)	8.3			
Week 24: ACR 50 (n=192)	4.7			
Week 24: ACR 70 (n=192)	65.6			
Week 52: ACR 20 (n=70)	0			
Week 52: ACR 50 (n=70)	0			
Week 52: ACR 70 (n=70)	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With European League Against Rheumatism (EULAR) Response Based on DAS28

End point title	Percentage of Participants With European League Against Rheumatism (EULAR) Response Based on DAS28

End point description:

The DAS28-based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline >1.2 with DAS28 </=3.2; moderate responders: change from baseline >1.2 with DAS28 >3.2 to </=5.1 or change from baseline >0.6 to </=1.2 with DAS28 </=5.1; non-responders: change from baseline </=0.6 or change from baseline >0.6 and </=1.2 with DAS28 >5.1. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: percentage of participants				
number (not applicable)				
Week 2: No Response (n=222)	32.4			
Week 2: Moderate Response (n=222)	50.5			
Week 2: Good Response (n=222)	17.1			
Week 24: No Response (n=192)	13.5			
Week 24: Moderate Response (n=192)	25			
Week 24: Good Response (n=192)	61.5			
Week 52: No Response (n=70)	55.7			
Week 52: Moderate Response (n=70)	8.6			
Week 52: Good Response (n=70)	35.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total TJC at Weeks 2, 24, and 52

End point title	Change From Baseline in Total TJC at Weeks 2, 24, and 52

End point description:

TJC was defined as the total number of painful joints based on 68-joint assessment (TJC-68) and 28-joint assessment (TJC-28). Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	224			
Units: tender joints				
arithmetic mean (standard deviation)				
TJC-68, Baseline (n=223)	16.91 (± 10.86)			
TJC-68, Change at Week 2 (n=218)	-5.4 (± 8.38)			
TJC-68, Change at Week 24 (n=188)	-12.9 (± 11.18)			
TJC-68, Change at Week 52 (n=69)	-16.5 (± 10.35)			
TJC-28, Baseline (n=224)	11.32 (± 6.241)			
TJC-28, Change at Week 2 (n=219)	-3.7 (± 5.4)			
TJC-28, Change at Week 24 (n=189)	-8.6 (± 6.62)			
TJC-28, Change at Week 52 (n=70)	-11 (± 6.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total SJC at Weeks 2, 24, and 52

End point title	Change From Baseline in Total SJC at Weeks 2, 24, and 52

End point description:

SJC was defined as the total number of swollen joints based on 66-joint assessment (SJC-66) and 28-joint assessment (SJC-28). Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	224			
Units: swollen joints				
arithmetic mean (standard deviation)				
SJC-66, Baseline (n=223)	9.53 (± 6.713)			
SJC-66, Change at Week 2 (n=218)	-3.7 (± 4.94)			
SJC-66, Change at Week 24 (n=188)	-8.3 (± 6.73)			
SJC-66, Change at Week 52 (n=69)	-9.1 (± 6.66)			
SJC-28, Baseline (n=224)	7.9 (± 5.203)			
SJC-28, Change at Week 2 (n=219)	-2.9 (± 3.91)			
SJC-28, Change at Week 24 (n=189)	-6.7 (± 5.17)			
SJC-28, Change at Week 52 (n=70)	-7.6 (± 4.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameters: DAS28-ESR and CDAI, Assessed Using Correlation Coefficient

End point title	Association Between Disease Activity Parameters: DAS28-ESR and CDAI, Assessed Using Correlation Coefficient

End point description:

DAS28-ESR is calculated from the TJC and SJC based on a 28-joint assessment, the ESR in mm/hour and PtGDA. DAS28-ESR total score= 0-9.4. Higher scores indicate greater affectation due to disease activity. The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. CDAI total score = 0-76. Higher scores represent greater affectation due to disease activity. Correlation coefficient for relationship between DAS28-ESR and CDAI at different time points is reported. Correlation coefficient value range= -1 to 1. Higher positive value indicates greater positive relationship and higher negative value indicates greater negative relationship. Analysis was performed on FAS; Here, 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	213[8]			
Units: correlation coefficient				
number (not applicable)				
Week 2 (n=213)	0.86514			
Week 24 (n=182)	0.86944			
Week 52 (n=32)	0.87301			

Notes:

[8] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameters: DAS28-ESR and SDAI, Assessed Using Correlation Coefficient

End point title	Association Between Disease Activity Parameters: DAS28-ESR and SDAI, Assessed Using Correlation Coefficient

End point description:

DAS28-ESR is calculated from the TJC and SJC based on a 28-joint assessment, the ESR in mm/hour and PtGDA. DAS28-ESR total score= 0-9.4. Higher scores indicate greater affectation due to disease activity. SDAI is a numerical sum of 5 outcome parameters: TJC and SJC based on a 28-joint

assessment, PtGDA and PGDA assessed on 0-10 cm VAS and CRP in mg/dL. SDAI total score= 0-86. Higher scores indicate greater affectation due to disease activity. Correlation coefficient for relationship between DAS28-ESR and SDAI at different time points is reported. Correlation coefficient value range= -1 to 1. Higher positive value indicates greater positive relationship and higher negative value indicates greater negative relationship. Analysis was performed on FAS; Here, 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	213[9]			
Units: correlation coefficient				
number (not applicable)				
Week 2 (n=213)	0.88118			
Week 24 (n=182)	0.8706			
Week 52 (n=31)	0.81995			

Notes:

[9] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameters: CDAI and SDAI, Assessed Using Correlation Coefficient

End point title	Association Between Disease Activity Parameters: CDAI and SDAI, Assessed Using Correlation Coefficient

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. CDAI total score = 0-76. Higher scores represent greater affectation due to disease activity. SDAI is a numerical sum of 5 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS and CRP in mg/dL. SDAI total score= 0-86. Higher scores indicate greater affectation due to disease activity. Correlation coefficient for relationship between CDAI and SDAI at different time points is reported. Correlation coefficient value range= -1 to 1. Higher positive value indicates greater positive relationship and higher negative value indicates greater negative relationship. Analysis was performed on FAS; Here, 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	213[10]			
Units: correlation coefficient				
number (not applicable)				
Week 2 (n=213)	0.98602			
Week 24 (n=185)	0.97515			
Week 52 (n=31)	0.97389			

Notes:

[10] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameter (DAS28-ESR) and Treatment Response Parameters (ACR20, ACR50, and ACR70), Assessed Using Regression Coefficient

End point title	Association Between Disease Activity Parameter (DAS28-ESR) and Treatment Response Parameters (ACR20, ACR50, and ACR70), Assessed Using Regression Coefficient

End point description:

DAS28-ESR is calculated from the TJC and SJC based on a 28-joint assessment, the ESR in mm/hour and PtGDA. DAS28-ESR total score= 0-9.4. The ACR 20, 50, and 70 responses: >/=20%, 50%, and 70% improvement in TJC and SJC, and 20%, 50%, 70% improvement in 3 of the following 5 criteria, respectively: 1) PGDA, 2) PtGDA, 3) participant's assessment of pain, 4) participant's assessment of functional disability via a health assessment questionnaire, and 5) CRP at each visit. Regression coefficients for relationship between DAS28-ESR and ACR responses (ACR20, ACR50, and ACR70) at different time points are reported. Regression coefficient value range= not defined (any negative or positive value is possible). Higher positive value indicates greater extent of positive relationship and higher negative value indicates greater extent of negative relationship. Analysis was performed on FAS; Here, 'n' = number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	213[11]			
Units: regression coefficient				
number (not applicable)				
Week 2: DAS28-ESR and ACR20 (n=213)	-1.02676			
Week 2: DAS28-ESR and ACR50 (n=213)	-1.31737			
Week 2: DAS28-ESR and ACR70 (n=213)	-1.504			
Week 24: DAS28-ESR and ACR20 (n=182)	-1.71191			
Week 24: DAS28-ESR and ACR50 (n=182)	-1.54281			
Week 24: DAS28-ESR and ACR70 (n=182)	-1.43977			

Week 52: DAS28-ESR and ACR20 (n=32)	-2.05036			
Week 52: DAS28-ESR and ACR50 (n=32)	-2.05036			
Week 52: DAS28-ESR and ACR70 (n=32)	-2.05036			

Notes:

[11] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameter (DAS28-ESR) and Treatment Response Parameter (EULAR), Assessed Using Regression Coefficient

End point title	Association Between Disease Activity Parameter (DAS28-ESR) and Treatment Response Parameter (EULAR), Assessed Using Regression Coefficient

End point description:

DAS28-ESR is calculated from the TJC and SJC based on a 28-joint assessment, the ESR in mm/hour and PtGDA. DAS28-ESR total score= 0-9.4. EULAR response criteria (based on DAS28 score): Good responders (change from baseline >1.2 with DAS28 </=3.2); Moderate responders (change from baseline >1.2 with DAS28 >3.2 to </=5.1 or change from baseline >0.6 to </=1.2 with DAS28 </=5.1); Non-responders (change from baseline </=0.6 or change from baseline >0.6 and </=1.2 with DAS28 >5.1). Regression coefficient for relationship between DAS28-ESR and EULAR Good response at different time points is reported. Regression coefficient value range= not defined (any negative or positive value is possible). Higher positive value indicates greater extent of positive relationship and higher negative value indicates greater extent of negative relationship. Analysis was performed on FAS; Here, 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	213[12]			
Units: regression coefficient				
number (not applicable)				
Week 2: DAS28-ESR and EULAR (n=213)	-1.62883			
Week 24: DAS28-ESR and EULAR (n=182)	-1.36226			
Week 52: DAS28-ESR and EULAR (n=32)	-1.47781			

Notes:

[12] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameter (CDAI) and Treatment Response Parameters (ACR20, ACR50, and ACR70), Assessed Using Regression

Coefficient

End point title	Association Between Disease Activity Parameter (CDAI) and Treatment Response Parameters (ACR20, ACR50, and ACR70), Assessed Using Regression Coefficient

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. CDAI total score = 0-76. The ACR 20, 50, and 70 responses: >/=20%, 50%, and 70% improvement in TJC and SJC, and 20%, 50%, 70% improvement in 3 of the following 5 criteria, respectively: 1) PGDA, 2) PtGDA, 3) participant's assessment of pain, 4) participant's assessment of functional disability via a health assessment questionnaire, and 5) CRP at each visit. Regression coefficients for relationship between CDAI and ACR responses (ACR20, ACR50, and ACR70) at different time points are reported. Regression coefficient value range= not defined (any negative or positive value is possible). Higher positive value indicates greater extent of positive relationship and higher negative value indicates greater extent of negative relationship. Analysis was performed on FAS; Here, 'n' = number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	220[13]			
Units: regression coefficient				
number (not applicable)				
Week 2: CDAI and ACR20 (n=220)	-9.65473			
Week 2: CDAI and ACR50 (n=220)	-10.67389			
Week 2: CDAI and ACR70 (n=220)	-13.3881			
Week 24: CDAI and ACR20 (n=186)	-13.18433			
Week 24: CDAI and ACR50 (n=186)	-11.95933			
Week 24: CDAI and ACR70 (n=186)	-11.18299			
Week 52: CDAI and ACR20 (n=32)	-18.94643			
Week 52: CDAI and ACR50 (n=32)	-18.94643			
Week 52: CDAI and ACR70 (n=32)	-18.94643			

Notes:

[13] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameter (CDAI) and Treatment Response Parameter (EULAR), Assessed Using Regression Coefficient

End point title	Association Between Disease Activity Parameter (CDAI) and Treatment Response Parameter (EULAR), Assessed Using Regression Coefficient

End point description:

The CDAI is a numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS. CDAI total score = 0-76. EULAR response criteria (based on DAS28 score): Good responders (change from baseline >1.2 with DAS28 </=3.2); Moderate responders (change from baseline >1.2 with DAS28 >3.2 to </=5.1 or change from baseline >0.6 to </=1.2 with DAS28 </=5.1); Non-responders (change from baseline </=0.6 or change from baseline >0.6 and </=1.2 with DAS28 >5.1). Regression coefficient for relationship between CDAI and EULAR Good response at different time points is reported. Regression coefficient value range= not defined (any

negative or positive value is possible). Higher positive value indicates greater extent of positive relationship and higher negative value indicates greater extent of negative relationship. Analysis was performed on FAS; Here, 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	220[14]			
Units: regression coefficient				
number (not applicable)				
Week 2: CDAI and EULAR (n=220)	-10.97686			
Week 24: CDAI and EULAR (n=186)	-7.03184			
Week 52: CDAI and EULAR (n=32)	-9.46563			

Notes:

[14] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameter (SDAI) and Treatment Response Parameters (ACR20, ACR50, and ACR70), Assessed Using Regression Coefficient

End point title	Association Between Disease Activity Parameter (SDAI) and Treatment Response Parameters (ACR20, ACR50, and ACR70), Assessed Using Regression Coefficient

End point description:

SDAI is a numerical sum of 5 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS and CRP in mg/dL. SDAI total score= 0-86. The ACR 20, 50, and 70 responses: >/=20%, 50%, and 70% improvement in TJC and SJC, and 20%, 50%, 70% improvement in 3 of the following 5 criteria, respectively: 1) PGDA, 2) PtGDA, 3) participant's assessment of pain, 4) participant's assessment of functional disability via a health assessment questionnaire, and 5) CRP at each visit. Regression coefficients for relationship between SDAI and ACR responses (ACR20, ACR50, and ACR70) at different time points are reported. Regression coefficient value range= not defined (any negative or positive value is possible). Higher positive value indicates greater extent of positive relationship and higher negative value indicates greater extent of negative relationship. Analysis was performed on FAS; Here, 'n' = number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	213[15]			
Units: regression coefficient				
number (not applicable)				
Week 2: SDAI and ACR20 (n=213)	-9.44923			
Week 2: SDAI and ACR50 (n=213)	-10.7423			
Week 2: SDAI and ACR70 (n=213)	-13.31421			
Week 24: SDAI and ACR20 (n=185)	-14.1979			
Week 24: SDAI and ACR50 (n=185)	-12.65454			
Week 24: SDAI and ACR70 (n=185)	-11.78067			
Week 52: SDAI and ACR20 (n=31)	-22.83519			
Week 52: SDAI and ACR50 (n=31)	-22.83519			
Week 52: SDAI and ACR70 (n=31)	-22.83519			

Notes:

[15] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Association Between Disease Activity Parameter (SDAI) and Treatment Response Parameter (EULAR), Assessed Using Regression Coefficient

End point title	Association Between Disease Activity Parameter (SDAI) and Treatment Response Parameter (EULAR), Assessed Using Regression Coefficient

End point description:

The SDAI is a numerical sum of 5 outcome parameters: TJC and SJC based on a 28-joint assessment, PtGDA and PGDA assessed on 0-10 cm VAS and CRP in mg/dL. SDAI total score= 0-86. EULAR response criteria (based on DAS28 score): Good responders (change from baseline >1.2 with DAS28 </=3.2); Moderate responders (change from baseline >1.2 with DAS28 >3.2 to </=5.1 or change from baseline >0.6 to </=1.2 with DAS28 </=5.1); Non-responders (change from baseline </=0.6 or change from baseline >0.6 and </=1.2 with DAS28 >5.1). Regression coefficient for relationship between SDAI and EULAR Good response at different time points is reported. Regression coefficient value range= not defined (any negative or positive value is possible). Higher positive value indicates greater extent of positive relationship and higher negative value indicates greater extent of negative relationship. Analysis was performed on FAS; Here, 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	213[16]			
Units: regression coefficient				
number (not applicable)				
Week 2: SDAI and EULAR (n=213)	-11.73463			
Week 24: SDAI and EULAR (n=185)	-7.32435			
Week 52: SDAI and EULAR (n=31)	-9.64146			

Notes:

[16] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of DMARDs Dose Reductions and/or Discontinuation Events by Reasons

End point title	Percentage of DMARDs Dose Reductions and/or Discontinuation Events by Reasons

End point description:

Percentage of DMARDs dose reduction and/or discontinuation events is reported by different reasons. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants with DMARDs dose reductions and/or discontinuation.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	79[17]			
Units: percentage of events				
number (not applicable)				
Safety	27.7			
Discomfort	9.5			
Lack of Efficacy	29.7			
Other Than Above	31.1			
Unknown	2			

Notes:

[17] - Total number of DMARDs dose reduction and/or discontinuation events = 148

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Non-DMARDs Dose Reductions and/or Discontinuation Events by Reasons

End point title	Percentage of Non-DMARDs Dose Reductions and/or Discontinuation Events by Reasons

End point description:

Percentage of non-DMARDs dose reduction and/or discontinuation events is reported by different reasons. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants with non-DMARDs dose reductions and/or discontinuation.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	154[18]			
Units: percentage of events				
number (not applicable)				
Safety	9.5			
Discomfort	1.3			
Lack of Efficacy	8.8			
Other Than Above	73.7			
Unknown	6.8			

Notes:

[18] - Total number of non-DMARDs dose reduction and/or discontinuation events = 547

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PtGDA VAS Score at Weeks 2, 24, and 52

End point title	Change From Baseline in PtGDA VAS Score at Weeks 2, 24, and 52

End point description:

Participants answered the following question: "Considering all the ways your arthritis affects you, how are you feeling today." Participants responded by using a 0 - 100 millimeter (mm) VAS, where 0 mm = very well and 100 mm = very poorly. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	226			
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=226)	61.31 (± 23.526)			
Change at Week 2 (n=220)	-10.6 (± 20.99)			
Change at Week 24 (n=186)	-28.4 (± 27.4)			
Change at Week 52 (n=32)	-38.4 (± 27.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PGDA VAS Score at Weeks 2, 24, and 52

End point title	Change From Baseline in PGDA VAS Score at Weeks 2, 24, and 52

End point description:

The physician assessed participant's current disease activity on a 0-100 mm VAS, where 0 mm = no disease activity and 100 mm = maximum disease activity. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	226			
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=226)	57.36 (± 19.228)			
Change at Week 2 (n=220)	-15.3 (± 17.49)			
Change at Week 24 (n=186)	-38 (± 25.13)			
Change at Week 52 (n=32)	-43.9 (± 17.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Participant Pain VAS Score at Weeks 2, 24, and 52

End point title	Participant Pain VAS Score at Weeks 2, 24, and 52

End point description:

Participants assessed their pain using a 0-100 mm VAS. Intensity of pain range (over past week): 0 mm = no pain to 100 mm = worst possible pain. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	226			
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n=226)	58.21 (± 23.622)			
Change at Week 2 (n=220)	-11.4 (± 22.38)			
Change at Week 24 (n=186)	-26.5 (± 27.31)			
Change at Week 52 (n=32)	-36 (± 26.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Weeks 2, 24, and 52

End point title	Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Weeks 2, 24, and 52

End point description:

HAQ-DI is a participant-reported assessment of ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week. Each item scored on 4-point scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	223			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=223)	1.04 (± 0.687)			
Change at Week 2 (n=215)	-0.2 (± 0.44)			
Change at Week 24 (n=183)	-0.4 (± 0.63)			
Change at Week 52 (n=31)	-0.5 (± 0.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Missed Working Days Assessed Using Short Form-Health and Labor Questionnaire (SF-HLQ) Score at Weeks 24 and 52

End point title	Missed Working Days Assessed Using Short Form-Health and Labor Questionnaire (SF-HLQ) Score at Weeks 24 and 52

End point description:

The SF-HLQ assessed productivity losses related to health problems in individuals with paid or unpaid work and consisted of three modules (absenteeism from paid work, production losses without absenteeism from paid work and hindrance in the performance of paid and unpaid work). Any missed working days or number of worked days with reduced efficiency during the last month were reported. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 24 and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: days				
arithmetic mean (standard deviation)				
Week 24 (n=69)	6.4 (± 45.09)			
Week 52 (n=7)	0.3 (± 0.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Total Score at Weeks 2, 24, and 52

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Total Score at Weeks 2, 24, and 52

End point description:

FACIT total score is sum of Functional Assessment of Cancer Therapy-General (FACT-G) score and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; additional concerns) score. FACT-G is a core questionnaire that evaluates quality of life (QoL) in cancer population. FACT-G consists of 27 questions grouped in 4 domains of general health-related QoL: physical well-being, social/family well-being, emotional well-being, and functional well-being; each item ranges from 0 (not at all) to 4 (very much). FACT-G score ranges between 0-108. FACIT-F is a 13-item questionnaire that evaluates self-reported fatigue and its impact upon daily activities. Each item ranges from 0 (Not at all) to 4 (Very much). The sum of all responses result in the FACIT total score with a total possible range of 0 (better score) to 160 (worse score). Negative change from baseline represents a better QoL. Analysis was performed on FAS; Here, 'n'=number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 24, and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	207[19]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=207)	72.41 (± 16.806)			
Change at Week 2 (n=196)	-5.8 (± 14.1)			
Change at Week 24 (n=165)	-11.1 (± 18.6)			
Change at Week 52 (n=60)	-43.8 (± 34.87)			

Notes:

[19] - 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pittsburgh Sleep Quality Index (PSQI) at Weeks 24 and 52

End point title	Change From Baseline in Pittsburgh Sleep Quality Index (PSQI) at Weeks 24 and 52

End point description:

PSQI is a questionnaire with 18 questions to assess sleep quality. The 18 questions are distributed to 7 elements (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction). A participant indicates how frequently each item was experienced on a scale from 0 to 3. The global score is the sum score of all 7 elements and ranges from 0-21 with higher values indicating worse sleep quality. A score of >/=5 indicates poor sleepers. Per-protocol analysis set (PPAS) included all participants in FAS without any major protocol violation and who completed 24 weeks of treatment period. 'Number of Subjects Analysed' = participants evaluable for this outcome; 'n' = participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=103)	11 (± 2.719)			
Change at Week 24 (n=73)	-0.7 (± 2.39)			
Change at Week 52 (n=16)	-0.9 (± 2.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Compliance, as Assessed Using Participant Diary Cards and Return Records

End point title	Treatment Compliance, as Assessed Using Participant Diary Cards and Return Records

End point description:

Treatment Compliance was calculated as (total actual doses taken for the period) / (total planned or prescribed dose for the period) x 100. Analysis was performed on FAS; Here, 'Number of Subjects Analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Weeks 24 and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: percentage of planned dose				
arithmetic mean (standard deviation)				
Week 24 (n=221)	94.9 (± 10.2)			
Week 52 (n=222)	94.7 (± 10.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) of Special Interest

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) of Special Interest

End point description:

An AE is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. TEAEs are AEs occurring between the first dose of study drug and up to 28 days after the last dose that were absent before treatment or that worsened relative to pre-treatment state. Following AEs were considered as AEs of special interest: anaphylactic reaction, hypersensitivity, stress cardiomyopathy, Gilbert’s syndrome, gastrointestinal perforation, injection site erythema, injection site hypersensitivity, injection site irritation, injection site pruritus, arthritis bacterial, cellulitis, klebsiella infection, oral candidiasis, pneumonia, skin infection, vulvovaginal candidiasis, alanine aminotransferase increased, hepatic enzyme increased, brain neoplasm malignant, and urticaria. Analysis was performed on FAS.

End point type	Secondary

End point timeframe:

Baseline up to 95 weeks

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: percentage of participants				
number (not applicable)	7.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-therapeutic Antibodies (ATA) to Tocilizumab

End point title	Percentage of Participants With Anti-therapeutic Antibodies (ATA) to Tocilizumab

End point description:

Percentage of participants with positive results for ATA against tocilizumab at different time points is reported. Analysis was performed on FAS; Here, 'n' signifies the number of participants evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 38, 52, at 8 weeks after last dose (up to Week 60), at early withdrawal (up to Week 52), at Follow-up Visits 1 (Week 64), 2 (Week 76), and 3 (Week 88)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: percentage of participants				
number (not applicable)				
Baseline (n=227)	2.6			
Week 12 (n=6)	100			
Week 24 (n=179)	1.7			
Week 38 (n=6)	33.3			
Week 52 (n=161)	1.2			
8 Weeks After Last Dose (up to Week 60) (n=41)	2.4			
Early Withdrawal (up to Week 52) (n=31)	6.5			
Follow-up Visit 1 (Week 64) (n=16)	100			
Follow-up Visit 2 (Week 76) (n=11)	100			
Follow-up Visit 3 (Week 88) (n=3)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Tocilizumab Concentration

End point title	Mean Tocilizumab Concentration

End point description:

Analysis was performed on FAS; Here 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 38, 52, at early withdrawal (up to Week 52), at Follow-up Visit 2 (Week 76)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Baseline (n=2)	35.6 (± 48.89)			
Week 12 (n=186)	46.4 (± 23.01)			
Week 24 (n=177)	52.6 (± 28.21)			
Week 38 (n=169)	55.2 (± 30.55)			
Week 52 (n=165)	54 (± 29)			
Early Withdrawal (up to Week 52) (n=19)	24.8 (± 22.9)			
Follow-up Visit 2 (Week 76) (n=17)	49.2 (± 34.05)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Analysis was performed on FAS; Here 'n' signifies the number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 38, 52, at early withdrawal (up to Week 52), at Follow-up Visit 2 (Week 76)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	227			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=213)	43.6 (± 49.3)			

Week 12 (n=189)	543.9 (± 144.34)			
Week 24 (n=181)	536.3 (± 144.32)			
Week 38 (n=171)	557.8 (± 144.23)			
Week 52 (n=168)	539.4 (± 147.04)			
Early Withdrawal (up to Week 52) (n=32)	329.1 (± 257.3)			
Follow-up Visit 2 (Week 76) (n=18)	523.4 (± 161.14)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to approximately 95 weeks

Adverse event reporting additional description:

FAS; TEAEs are adverse events occurring between the first dose of study drug and up to 28 days after the last dose that were absent before treatment or that worsened relative to pre-treatment state.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Tocilizumab at a fixed dose of 162 mg was administered as SC injection alone or along with methotrexate and/or other non-biological DMARDs irrespective of body weight, once every week for a total of 52 weeks. After 52-weeks of treatment, at the discretion of the treating physician, participants could continue the study treatment with SC tocilizumab until it became commercially available in Italy (maximum up to 638 days).

Serious adverse events	Tocilizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 227 (7.49%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Carcinoembryonic antigen increased			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Wrist fracture			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aneurysm			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Bladder neoplasm surgery			
subjects affected / exposed	1 / 227 (0.44%)		
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 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal perforation			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Pleurisy			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella infection			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device breakage			

subjects affected / exposed	1 / 227 (0.44%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 227 (15.86%)		
Investigations			
Transaminases increased			
subjects affected / exposed	15 / 227 (6.61%)		
occurrences (all)	19		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 227 (7.05%)		
occurrences (all)	18		
Infections and infestations			
Bronchitis			
subjects affected / exposed	15 / 227 (6.61%)		
occurrences (all)	18		
Influenza			
subjects affected / exposed	23 / 227 (10.13%)		
occurrences (all)	29		
Urinary tract infection			
subjects affected / exposed	12 / 227 (5.29%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2014	In the original protocol, on-site visits in the period from Week 24 to Week 52 were scheduled every 14 weeks (Week 24, Week 38, and Week 52). After Week 52, if participants continued the study treatment until tocilizumab became commercially available in Italy, on site assessments were expected every 3 months. During the above-mentioned study period, monthly telephone calls contacts were added to the schedule of assessments in order to collect details on any AE and changes in concomitant medications between an on-site visit and the next one.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported