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	v1
This version publication date	06 November 2016
First version publication date	06 November 2016

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	Interim
Date of interim/final analysis	09 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2015
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 2 years and 10 months).

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	177
Not completed	50
Physician decision	8
Consent withdrawn by subject	15
Adverse Event	19
Protocol Violation	1
Unspecified	6
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	227	227	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.7		
standard deviation	± 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 2 years and 10 months).

Primary: Change From Baseline in Clinical Disease Activity Index (CDAI) at Week 24

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) at Week 24[1]

End point description:

The CDAI is the 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 centimeter (cm) visual analogue scale (VAS). Higher scores represent greater affection 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. Full Analysis Set (FAS) included all recruited participants who received at least one dose of SC tocilizumab. Here, number of subjects analysed indicates participants who were evaluable for this outcome.

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 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 the 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 affection 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. FAS; Here, number of subjects analysed indicates participants who were evaluable for this outcome.

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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences.

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 the 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 affection 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. FAS; Here, number of subjects analysed indicates participants who were evaluable for this outcome.

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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	190			
Units: units on a scale				
arithmetic mean (standard deviation)	-20.2 (± 12.55)			

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 the 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 affection 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. FAS; Here, number of subjects analysed indicates participants who were evaluable for this outcome.

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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences.

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 the 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 affection 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. FAS; Here, number of subjects analysed indicates participants who were evaluable for this outcome.

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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences.

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 the 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 affection 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. FAS; Here, number of subjects analysed indicates participants who were evaluable for this outcome.

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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences.

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 the 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 affection 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. FAS; Here, number of subjects analysed indicates participants who were evaluable for this outcome.

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 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: Percentage of Participants Achieving Clinical Remission According to CDAI at Week 52

End point title	Percentage of Participants Achieving Clinical Remission According to CDAI at Week 52

End point description:

The CDAI is the 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 affection due to disease activity. CDAI total score = 0-76. CDAI score </=2.8 indicates disease remission.

End point type	Secondary

End point timeframe:

Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: percentage of participants				
number (not applicable)				

Notes:

[8] - Outcome Measure Data Not Reported

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 affection 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.

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	0[9]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[9] - Outcome Measure Data Not Reported

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 five outcome parameters: TJC and SJC based on a 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 affection 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.

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	0[10]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[10] - Outcome Measure Data Not Reported

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, 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.

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	0[11]			
Units: percentage of participants				
number (not applicable)				

Notes:

[11] - Outcome Measure Data Not Reported

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 DAS-28-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.

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	0[12]			
Units: percentage of participants				
number (not applicable)				

Notes:

[12] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

TJC was defined as the total number of painful joints based on a 28-joint assessment.

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	0[13]			
Units: joints				
arithmetic mean (standard deviation)	()			

Notes:

[13] - Outcome Measure Data Not Reported

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 a 28-joint assessment.

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	0[14]			
Units: joints				
arithmetic mean (standard deviation)	()			

Notes:

[14] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Reasons for DMARDs Dose Reductions and/or Discontinuation

End point title	Percentage of Participants With Reasons for DMARDs Dose Reductions and/or Discontinuation

End point description:

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	0[15]			
Units: percentage of participants				
number (not applicable)				

Notes:

[15] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Reasons for Non-DMARDs Dose Reductions and/or Discontinuation

End point title	Percentage of Participants With Reasons for Non-DMARDs Dose Reductions and/or Discontinuation

End point description:

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	0[16]			
Units: percentage of participants				
number (not applicable)				

Notes:

[16] - Outcome Measure Data Not Reported

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: "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.

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	0[17]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[17] - Outcome Measure Data Not Reported

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.

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	0[18]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[18] - Outcome Measure Data Not Reported

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:

Participant's assessed pain using a 0-100 mm VAS. Intensity of pain range (over past week): 0 mm = no pain to 100 mm = worst possible pain.

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	0[19]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[19] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

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

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

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	0[20]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[20] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Short Form-Health and Labor Questionnaire (SF-HLQ) Score at Weeks 24 and 52

End point title	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 consists 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 was reported.

End point type	Secondary

End point timeframe:

Weeks 24 and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[21]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[21] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

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

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

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).

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	0[22]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[22] - Outcome Measure Data Not Reported

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.

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	0[23]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[23] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were Treatment Compliant, as Assessed Using Participant Diary Cards and Return Records

End point title	Percentage of Participants Who Were Treatment Compliant, as Assessed Using Participant Diary Cards and Return Records

End point description:

End point type	Secondary

End point timeframe:

Weeks 24 and 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[24]			
Units: percentage of participants				
number (not applicable)				

Notes:

[24] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-drug Antibodies (ADA) to Tocilizumab

End point title	Percentage of Participants With Anti-drug Antibodies (ADA) to Tocilizumab

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 38, 52, and at 8 weeks after last dose (up to Week 60)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[25]			
Units: percentage of participants				
number (not applicable)				

Notes:

[25] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Tocilizumab Concentration

End point title	Mean Tocilizumab Concentration

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 38, 52, and at 8 weeks after last dose (up to Week 60)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[26]			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	()			

Notes:

[26] - Outcome Measure Data Not Reported

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:

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 38, 52, and at 8 weeks after last dose (up to Week 60)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[27]			
Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[27] - Outcome Measure Data Not Reported

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to approximately 2 years

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) are adverse events occurring between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pre-treatment state. FAS included all recruited participants who received at least one dose of SC tocilizumab.

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 2 years and 10 months).

Serious adverse events	Tocilizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 227 (5.29%)		
number of deaths (all causes)	1		
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		
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			

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	24 / 227 (10.57%)		
Investigations			
Transaminases increased			
subjects affected / exposed	15 / 227 (6.61%)		
occurrences (all)	18		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 227 (7.05%)		
occurrences (all)	18		
Infections and infestations			
Influenza			
subjects affected / exposed	24 / 227 (10.57%)		
occurrences (all)	30		

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The reported results include the results of primary analysis only.

Notes: