Clinical trial results:
Multicenter, Open Label, Phase IIIb Study to Evaluate the Safety and Tolerability of Subcutaneous Tocilizumab as Monotherapy and/or in Combination with Methotrexate or Other Non-Biologic Disease-Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis

Summary

EudraCT number	2013-000359-42
Trial protocol	GR
Global end of trial date	10 July 2016

Results information

Result version number	v1 (current)
This version publication date	20 July 2017
First version publication date	20 July 2017

Trial information

Trial identification

Sponsor protocol code	ML28695

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01941095
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the efficacy and safety of subcutaneous (SC) tocilizumab, administered as monotherapy and/or in combination with methotrexate or other non-biologic disease-modifying antirheumatic drugs (DMARDs) for 52 weeks duration.

Protection of trial subjects:

The study was conducted in full conformance with the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever affords the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 97
Worldwide total number of subjects	97
EEA total number of subjects	97

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)	68
From 65 to 84 years	29

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 100 participants were enrolled, out of which 97 participants received treatment. Analyses were performed in 97 participants.

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:

Participants received tocilizumab 162 milligrams (mg) SC injection once a week (QW) either as monotherapy or in combination with methotrexate or other non-biologic DMARDs during the treatment period of 52 weeks. The choice of monotherapy or combination treatment was according to the physician's judgment up to Week 24. Depending upon the participant's response to study regimen at Week 24, participant might either continue/discontinue/switch to tocilizumab monotherapy or may lead to intensification of methotrexate/non-biologic DMARDs with tocilizumab at a fixed dose of 162 mg SC QW till Week 52.

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

Dosage and administration details:

Participants received tocilizumab at a fixed dose of 162 mg SC QW either as monotherapy or in combination with non-biologic
DMARDs.

Number of subjects in period 1	Tocilizumab
Started	97
Completed	41
Not completed	56
Anaphylaxis or serious hypersensitivity	2
Consent withdrawn by subject	17
Physician decision	3
Insufficient therapeutic response	13
Adverse event	11
Lost to follow-up	10

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab

Reporting group description:

Participants received tocilizumab 162 milligrams (mg) SC injection once a week (QW) either as monotherapy or in combination with methotrexate or other non-biologic DMARDs during the treatment period of 52 weeks. The choice of monotherapy or combination treatment was according to the physician's judgment up to Week 24. Depending upon the participant's response to study regimen at Week 24, participant might either continue/discontinue/switch to tocilizumab monotherapy or may lead to intensification of methotrexate/non-biologic DMARDs with tocilizumab at a fixed dose of 162 mg SC QW till Week 52.

Reporting group values	Tocilizumab	Total	
Number of subjects	97	97	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 56.27 ± 12.77	 -	
Gender Categorical Units: Subjects			
Female	86	86	
Male	11	11	

End points

End points reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Participants received tocilizumab 162 milligrams (mg) SC injection once a week (QW) either as monotherapy or in combination with methotrexate or other non-biologic DMARDs during the treatment period of 52 weeks. The choice of monotherapy or combination treatment was according to the physician's judgment up to Week 24. Depending upon the participant's response to study regimen at Week 24, participant might either continue/discontinue/switch to tocilizumab monotherapy or may lead to intensification of methotrexate/non-biologic DMARDs with tocilizumab at a fixed dose of 162 mg SC QW till Week 52.

Primary: Percentage of Participants Who Achieved Disease Activity Score Based on 28 Joint Count and Erythrocyte Sedimentation Rate (DAS28-ESR) Remission at Week 24

End point title	Percentage of Participants Who Achieved Disease Activity Score Based on 28 Joint Count and Erythrocyte Sedimentation Rate (DAS28-ESR) Remission at Week 24[1]

End point description:

DAS28-ESR score is a measure of participant's disease activity calculated using tender joint count in 28 joints (TJC28), swollen joint count in 28 joints (SJC28), patient global assessment of disease activity (PGA) (general health [GH]) using visual analog scale (VAS): 0 millimeter (mm)=no disease activity to 100 mm=maximum disease activity, displayed on the 100 mm horizontal VAS, and acute phase response (ESR in millimeters per hour [mm/hr]). The score is calculated using the following formula: DAS28-ESR = [0.56 multiplied by (*) square root (√) of TJC28] plus (+) [0.28*√SJC28]+[0.70*the natural logarithm (ln) ESR]+[0.014*GH]. DAS28-ESR score varies from 0 to 10, where higher scores represent greater disease activity. DAS28-ESR score of less than (<) 2.6 represents DAS28-ESR remission. Full analysis set included all recruited participants who received at least one dose of SC tocilizumab. Number of subjects analyzed = participants evaluable for this endpoint.

End point type	Primary

End point timeframe:

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: No inferential statistics was planned for this endpoint

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: percentage of participants				
number (not applicable)	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Maintained DAS28-ESR Remission From Week 24 up to Week 52 Among Participants on Tocilizumab Monotherapy Since Week 24

End point title	Percentage of Participants Who Maintained DAS28-ESR Remission From Week 24 up to Week 52 Among Participants on Tocilizumab Monotherapy Since Week 24

End point description:

DAS28-ESR score is a measure of participant's disease activity calculated using TJC28, SJC28, PGA using VAS 0 mm=no disease activity to 100 mm=maximum disease activity, displayed on the 100 mm horizontal VAS, and acute phase response (ESR in mm/hr) for a total possible score of 0 to 10. The score is calculated using the following formula: DAS28-ESR = [0.56 * √TJC28 + [0.28*√SJC28]+[0.70*ln ESR]+[0.014*GH]. DAS28-ESR score varies from 0 to 10, where higher scores represent greater disease activity. DAS28-ESR score <2.6 represents DAS28-ESR remission. Per protocol analysis. Number of subjects analyzed = participants evaluable for this endpoint. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: percentage of participants				
number (not applicable)				
Week 24 (n=80)	38.7			
Week 28 (n=79)	34.2			
Week 32 (n=74)	36.5			
Week 36 (n=74)	36.5			
Week 40 (n=74)	36.5			
Week 44 (n=71)	35.2			
Week 48 (n=70)	35.7			
Week 52 (n=67)	38.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved DAS28-ESR Remission/Low Disease Activity (LDA) From Week 28 up to Week 52 Among Participants With Intensification of Methotrexate/Other Non-Biologic DMARDs in Combination with Tocilizumab Since Week 24

End point title	Percentage of Participants Who Achieved DAS28-ESR Remission/Low Disease Activity (LDA) From Week 28 up to Week 52 Among Participants With Intensification of Methotrexate/Other Non-Biologic DMARDs in Combination with Tocilizumab Since Week 24

End point description:

DAS28-ESR score is a measure of participant's disease activity calculated using TJC28, SJC28, PGA using VAS 0 mm=no disease activity to 100 mm=maximum disease activity, displayed on the 100 mm horizontal VAS, and acute phase response (ESR in mm/hr) for a total possible score of 0 to 10. The score is calculated using the following formula: DAS28-ESR = [0.56 * √TJC28 + [0.28*√SJC28]+[0.70*ln ESR]+[0.014*GH]. DAS28-ESR score varies from 0 to 10, where higher scores represent greater disease activity. DAS28-ESR score <2.6 represents DAS28-ESR remission. DAS28-ESR score greater than or equal to (>/=) 2.6 and <3.2 represents LDA. Full analysis set. Number of subjects analyzed = participants evaluable for this endpoint. Here, n = number of participants analyzed for this

specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: percentage of participants				
number (not applicable)				
Week 28 (n=79): Remission	5.1			
Week 32 (n=74): Remission	8.1			
Week 36 (n=74): Remission	4.1			
Week 40 (n=74): Remission	9.5			
Week 44 (n=72): Remission	6.9			
Week 48 (n=71): Remission	8.5			
Week 52 (n=67): Remission	6			
Week 28 (n=79): LDA	7.6			
Week 32 (n=74): LDA	1.4			
Week 36 (n=74): LDA	6.8			
Week 40 (n=74): LDA	6.8			
Week 44 (n=72): LDA	6.9			
Week 48 (n=71): LDA	4.2			
Week 52 (n=67): LDA	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in DAS28-ESR up to Week 52

End point title	Change From Baseline in DAS28-ESR up to Week 52

End point description:

DAS28-ESR score is a measure of participant's disease activity calculated using TJC28, SJC28, PGA using VAS 0 mm=no disease activity to 100 mm=maximum disease activity, displayed on the 100 mm horizontal VAS, and acute phase response (ESR in mm/hr) for a total possible score of 0 to 10. The score is calculated using the following formula: DAS28-ESR = [0.56 * √TJC28 + [0.28*√SJC28]+[0.70*ln ESR]+[0.014*GH]. DAS28-ESR score varies from 0 to 10, where higher scores represent greater disease activity. A negative change from baseline indicates an improvement. Full analysis set. Number of subjects analyzed = participants evaluable for this endpoint. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Week 2 (n=96)	-0.99 (-1.33 to -0.64)			
Change at Week 4 (n=95)	-1.7 (-2.06 to -1.36)			
Change at Week 8 (n=93)	-2.2 (-2.54 to -1.84)			
Change at Week 12 (n=87)	-2.56 (-2.91 to -2.2)			
Change at Week 16 (n=85)	-2.59 (-2.91 to -2.27)			
Change at Week 20 (n=82)	-2.93 (-3.24 to -2.62)			
Change at Week 24 (n=80)	-3.14 (-3.45 to -2.83)			
Change at Week 28 (n=79)	-3.22 (-3.53 to -2.9)			
Change at Week 32 (n=74)	-3.34 (-3.66 to -3.01)			
Change at Week 36 (n=74)	-3.32 (-3.64 to -3)			
Change at Week 40 (n=74)	-3.4 (-3.73 to -3.07)			
Change at Week 44 (n=71)	-3.45 (-3.78 to -3.11)			
Change at Week 48 (n=70)	-3.42 (-3.76 to -3.08)			
Change at Week 52 (n=67)	-3.4 (-3.73 to -3.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With American College of Rheumatology 20 (ACR20) Response

End point title	Number of Participants With American College of Rheumatology 20 (ACR20) Response

End point description:

ACR20 response was defined as >/=20% improvement from baseline in both TJC28 and SJC28 as well as in 3 out of 5 additional parameters: Separate patient and physician's global assessment of disease activity on VAS (0 mm=no disease activity to 100 mm=maximum disease activity), patient's assessment of pain on VAS (0 mm=no pain to 100 mm=unbearable pain), Health Assessment Questionnaire - Disability Index (HAQ-DI) (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do), and acute phase response (ESR in mm/hr, for a total possible score of 0 to 10). Full analysis set. Number of subjects analyzed=participants evaluable for this endpoint. Here, n=number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: participants				
Week 2 (n=96)	19			
Week 4 (n=95)	19			
Week 8 (n=93)	23			
Week 12 (n=87)	9			
Week 16 (n=85)	13			
Week 20 (n=82)	16			
Week 24 (n=80)	9			
Week 28 (n=79)	13			
Week 32 (n=74)	10			
Week 36 (n=74)	11			
Week 40 (n=74)	10			
Week 44 (n=72)	12			
Week 48 (n=71)	13			
Week 52 (n=67)	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Good, Moderate, or No Response According to European League Against Rheumatism (EULAR) Response Criteria

End point title	Percentage of Participants With Good, Moderate, or No Response According to European League Against Rheumatism (EULAR) Response Criteria

End point description:

Response to treatment was determined using EULAR criteria based upon DAS28 absolute scores at the assessment visit and the DAS28 reduction from the baseline visit. Participants with a score lesser than or equal to (</=) 3.2 and reduction of greater than (>) 1.2 points were assessed as having a 'good' response. Participants with a score >3.2 with reduction of >1.2 points, or a score </=5.1 with reduction of >0.6 to </=1.2 points, were assessed as having a 'moderate' response. Participants with a score >5.1 with reduction of >0.6 to </=1.2 points, or any score with reduction </=0.6 points, were assessed as having 'no response'. Full analysis set. Number of subjects analyzed = participants evaluable for this endpoint. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: percentage of participants				
number (not applicable)				
Week 2 (n=96): Good response	9.4			
Week 2 (n=96): Moderate response	44.8			
Week 2 (n=96): No response	45.8			
Week 4 (n=95): Good response	9.5			
Week 4 (n=95): Moderate response	38.9			
Week 4 (n=95): No response	51.6			
Week 8 (n=93): Good response	10.8			
Week 8 (n=93): Moderate response	23.6			
Week 8 (n=93): No response	65.6			
Week 12 (n=87): Good response	9.2			
Week 12 (n=87): Moderate response	20.7			
Week 12 (n=87): No response	70.1			
Week 16 (n=85): Good response	5.9			
Week 16 (n=85): Moderate response	15.3			
Week 16 (n=85): No response	78.8			
Week 20 (n=82): Good response	6.1			
Week 20 (n=82): Moderate response	26.8			
Week 20 (n=82): No response	67.1			
Week 24 (n=80): Good response	6.2			
Week 24 (n=80): Moderate response	21.2			
Week 24 (n=80): No response	72.6			
Week 28 (n=79): Good response	6.3			
Week 28 (n=79): Moderate response	11.4			
Week 28 (n=79): No response	82.3			
Week 32 (n=74): Good response	0			
Week 32 (n=74): Moderate response	18.9			
Week 32 (n=74): No response	81.1			
Week 36 (n=74): Good response	1.3			
Week 36 (n=74): Moderate response	14.9			
Week 36 (n=74): No response	83.8			
Week 40 (n=74): Good response	5.4			
Week 40 (n=74): Moderate response	17.6			
Week 40 (n=74): No response	77			
Week 44 (n=72): Good response	2.8			
Week 44 (n=72): Moderate response	13.9			
Week 44 (n=72): No response	83.3			
Week 48 (n=71): Good response	5.7			
Week 48 (n=71): Moderate response	11.4			
Week 48 (n=71): No response	82.9			
Week 52 (n=67): Good response	94			
Week 52 (n=67): Moderate response	6			
Week 52 (n=67): No response	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simplified Disease Activity Index (SDAI) Score up to Week 52

End point title	Change From Baseline in Simplified Disease Activity Index (SDAI) Score up to Week 52

End point description:

SDAI is an index for measuring disease activity. SDAI is the numerical sum of five outcome parameters: TJC28 and SJC28, PGA and physician global assessment of disease activity assessed on VAS (0 centimeter [cm]-10 cm); 0 cm= no disease activity and 10 cm= worst disease activity, and CRP (in milligrams per deciliter [mg/dL]). SDAI total score ranges from 0 to 86, with higher scores indicating increased (or severe) disease activity. SDAI score </=3.3 indicates clinical remission, >3.4 to 11 = low disease activity, >11 to 26 = moderate disease activity, and >26 = high (or severe) disease activity. Full analysis set. Number of subjects analyzed = participants evaluable for this endpoint. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Week 2 (n=96)	-3.41 (-7.17 to 0.12)			
Change at Week 4 (n=95)	-6.54 (-10.26 to -2.97)			
Change at Week 8 (n=93)	-8.72 (-12.89 to -5.18)			
Change at Week 12 (n=87)	-11.07 (-14.74 to -8.04)			
Change at Week 16 (n=85)	-13.47 (-17 to -10.6)			
Change at Week 20 (n=82)	-13.88 (-17.42 to -10.94)			
Change at Week 24 (n=80)	-14.08 (-17.72 to -11.25)			
Change at Week 28 (n=79)	-15.37 (-18.87 to -12.41)			
Change at Week 32 (n=74)	-16.09 (-19.63 to -13.07)			
Change at Week 36 (n=74)	-15.61 (-19.14 to -12.58)			
Change at Week 40 (n=74)	-14.86 (-18.66 to -11.84)			
Change at Week 44 (n=71)	-16.31 (-20.06 to -13.24)			
Change at Week 48 (n=70)	-16.47 (-20.13 to -13.45)			
Change at Week 52 (n=67)	-17.35 (-21.01 to -14.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in TJC28 up to Week 52

End point title	Change From Baseline in TJC28 up to Week 52

End point description:

28 joints were assessed for tenderness and joints were classified as tender/not tender giving a total possible tender joint count score of 0 to 28. A negative change from baseline indicated improvement. Full analysis set. Number of subjects analyzed = participants evaluable for this endpoint. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: tender joints				
arithmetic mean (confidence interval 95%)				
Change at Week 2 (n=96)	-1.3 (-3.18 to -0.56)			
Change at Week 4 (n=95)	-3.26 (-5.09 to -1.42)			
Change at Week 8 (n=93)	-4.97 (-6.69 to -3.25)			
Change at Week 12 (n=87)	-5.82 (-7.55 to -4.09)			
Change at Week 16 (n=85)	-6.39 (-8.08 to -4.7)			
Change at Week 20 (n=82)	-7.03 (-8.67 to -5.38)			
Change at Week 24 (n=80)	-7.72 (-9.34 to -6.09)			
Change at Week 28 (n=79)	-7.91 (-9.51 to -6.31)			
Change at Week 32 (n=74)	-8.38 (-10 to -6.77)			
Change at Week 36 (n=74)	-8.28 (-9.86 to -6.66)			
Change at Week 40 (n=74)	-8.22 (-9.84 to -6.59)			
Change at Week 44 (n=71)	-8.63 (-10.25 to -7.01)			
Change at Week 48 (n=70)	-8.26 (-9.97 to -6.54)			

Change at Week 52 (n=67)	-8.75 (-10.41 to -7.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SJC28 up to Week 52

End point title	Change From Baseline in SJC28 up to Week 52

End point description:

28 joints were assessed for swelling and joints were classified as swollen/not swollen giving a total possible swollen joint count score of 0 to 28. A negative change from baseline indicated improvement. Full analysis set. Number of subjects analyzed = participants evaluable for this endpoint. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: swollen joints				
arithmetic mean (confidence interval 95%)				
Change at Week 2 (n=96)	-1.82 (-3.51 to -0.13)			
Change at Week 4 (n=95)	-3.08 (-4.7 to -1.46)			
Change at Week 8 (n=93)	-4.71 (-6.2 to -3.21)			
Change at Week 12 (n=87)	-5.24 (-6.68 to -3.79)			
Change at Week 16 (n=85)	-5.79 (-7.27 to -4.31)			
Change at Week 20 (n=82)	-6.06 (-7.55 to -4.57)			
Change at Week 24 (n=80)	-6.6 (-8.03 to -5.18)			
Change at Week 28 (n=79)	-6.65 (-8.09 to -5.21)			
Change at Week 32 (n=74)	-6.73 (-8.19 to -5.27)			
Change at Week 36 (n=74)	-6.76 (-8.22 to -5.28)			
Change at Week 40 (n=74)	-6.91 (-8.37 to -5.44)			
Change at Week 44 (n=71)	-6.82 (-8.31 to -5.33)			
Change at Week 48 (n=70)	-6.63 (-8.15 to -5.1)			

Change at Week 52 (n=67)	-6.98 (-8.52 to -5.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Corticosteroid Dose Reduction or Discontinuation

End point title	Percentage of Participants With Corticosteroid Dose Reduction or Discontinuation

End point description:

Full analysis set. Number of subjects analyzed = participants who used corticosteroids during the study.

End point type	Secondary

End point timeframe:

From Baseline up to Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: percentage of participants				
number (not applicable)	48.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants by Reasons (Categories) for Corticosteroid Dose Reduction or Discontinuation

End point title	Number of Participants by Reasons (Categories) for Corticosteroid Dose Reduction or Discontinuation

End point description:

Reasons for corticosteroid dose reduction included: Safety Reasons (including elevated liver function test results, respiratory infections, infections and infestations, gastrointestinal disorders etc.); Other Reasons (disease remission, improvement etc.); and Unknown Reasons (including no reason). Number of participants by reasons (Safety, Other, Unknown) for corticosteroid dose reduction or discontinuation were reported. Full analysis set. Number of subjects analyzed = participants with corticosteroid dose reduction/discontinuation.

End point type	Secondary

End point timeframe:

From Baseline up to Week 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: participants				
Safety	6			
Other	10			
Unknown	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Tocilizumab Antibodies (ATA)

End point title	Number of Participants With Anti-Tocilizumab Antibodies (ATA)

End point description:

All samples were tested using a screening assay and, if positive, by a confirmation assay to determine specificity and a neutralizing assay to test for the ability to inhibit the activity of tocilizumab. Number of participants with a positive assay result for screening assay (ATA - Screen), confirmatory assay (ATA - Confirmatory), and neutralizing assay (ATA - Neutralizing) was reported separately. Full analysis set. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 12, 24, 36, 52, and 8 weeks after Week 52 dose (Week 60)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: participants				
Week 1 (n=97): ATA - Screen	7			
Week 1 (n=97): ATA - Confirmatory	4			
Week 1 (n=97): ATA - Neutralizing	0			
Week 12 (n=87): ATA - Screen	3			
Week 12 (n=87): ATA - Confirmatory	0			
Week 12 (n=87): ATA - Neutralizing	0			
Week 24 (n=78): ATA - Screen	3			
Week 24 (n=78): ATA - Confirmatory	1			
Week 24 (n=78): ATA - Neutralizing	1			
Week 36 (n=73): ATA - Screen	2			
Week 36 (n=73): ATA - Confirmatory	0			
Week 36 (n=73): ATA - Neutralizing	0			
Week 52 (n=67): ATA - Screen	2			
Week 52 (n=67): ATA - Confirmatory	0			
Week 52 (n=67): ATA - Neutralizing	0			
Week 60 (n=41): ATA - Screen	1			
Week 60 (n=41): ATA - Confirmatory	1			
Week 60 (n=41): ATA - Neutralizing	0			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Full analysis set. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 12, 24, 36, 52, and 8 weeks after Week 52 dose (Week 60)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Week 1 (n=97)	39450 (± 10740)			
Week 12 (n=87)	553.43 (± 120.36)			
Week 24 (n=78)	572.03 (± 136.68)			
Week 36 (n=73)	570.78 (± 139.16)			
Week 52 (n=67)	537.73 (± 152.55)			
Week 60 (n=41)	42850 (± 13800)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tocilizumab Serum Levels

End point title	Tocilizumab Serum Levels

End point description:

Full analysis set. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 12, 24, 36, 52, and 8 weeks after Week 52 dose (Week 60)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: microgrms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Week 1 (n=97)	0.38 (± 0.17)			
Week 12 (n=87)	41.98 (± 25.04)			
Week 24 (n=78)	44.67 (± 28.83)			
Week 36 (n=73)	47.9 (± 28.29)			
Week 52 (n=67)	45.37 (± 28.13)			
Week 60 (n=41)	6.46 (± 4.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: PGA, Using VAS Score

End point title	PGA, Using VAS Score

End point description:

PGA was assessed on a 0 to 100 mm horizontal VAS. The extreme left end of the line = 0 mm, and was described as "no disease activity" (symptom-free and no arthritis symptoms) and the extreme right end = 100 mm, and was described as "maximum disease activity" (maximum arthritis disease activity). Higher values correspond to worst state of participant (high disease activity). Full analysis set. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: mm				
arithmetic mean (standard deviation)				
Week 1 (n=97)	28.26 (± 20.25)			
Week 2 (n=96)	27.57 (± 20.08)			
Week 4 (n=95)	28.36 (± 19.37)			
Week 8 (n=93)	32.28 (± 22.09)			
Week 12 (n=87)	28.73 (± 23.01)			

Week 16 (n=85)	24.4 (± 19.02)			
Week 20 (n=82)	28.15 (± 20.22)			
Week 24 (n=80)	32.63 (± 23.44)			
Week 28 (n=79)	26.02 (± 18.79)			
Week 32 (n=74)	27.08 (± 20.98)			
Week 36 (n=74)	30.79 (± 22.37)			
Week 40 (n=74)	30.5 (± 21.93)			
Week 44 (n=71)	25.79 (± 16.33)			
Week 48 (n=70)	23.86 (± 19.11)			
Week 52 (n=67)	23.08 (± 17.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Assessment of Pain, Using VAS Score

End point title	Patient Assessment of Pain, Using VAS Score

End point description:

The participant's level of pain was assessed on a 0 to 100 mm horizontal VAS. The extreme left end of the line = 0 mm, and was described as "no pain" and the extreme right end = 100 mm, and was described as "unbearable pain". Higher values correspond to worst state of participant (higher level of pain). Full analysis set. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: mm				
arithmetic mean (standard deviation)				
Week 1 (n=97)	46.4 (± 27.43)			
Week 2 (n=96)	52.04 (± 24.46)			
Week 4 (n=95)	49.87 (± 23.35)			
Week 8 (n=93)	42.72 (± 23.2)			
Week 12 (n=87)	37.21 (± 21.29)			
Week 16 (n=85)	34.24 (± 22.49)			
Week 20 (n=82)	31 (± 19.42)			

Week 24 (n=80)	29.57 (± 19.66)			
Week 28 (n=79)	29.63 (± 19.07)			
Week 32 (n=74)	25.5 (± 17.95)			
Week 36 (n=74)	26.78 (± 22.13)			
Week 40 (n=74)	27.5 (± 21.93)			
Week 44 (n=71)	26.88 (± 19.96)			
Week 48 (n=70)	23.61 (± 18.63)			
Week 52 (n=67)	23.98 (± 20.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: HAQ-DI Score

End point title	HAQ-DI Score

End point description:

The Stanford HAQ-DI is a patient-reported questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Responses in each component set were scored from 0 (without any difficulty) to 3 (unable to do). The highest score recorded for any question in a category determines the score for the category, unless aids, devices, or help from another person was required. The HAQ-DI score was calculated as the sum of the category scores divided by the number of categories scored, giving a possible range of scores from 0 to 3. Scores of 0 to 1 are generally considered to represent "mild to moderate difficulty", 1 to 2 as "moderate to severe disability", and 2 to 3 as "severe to very severe disability". Full analysis set. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=97)	1.31 (± 0.66)			
Week 2 (n=96)	1.22 (± 0.64)			
Week 4 (n=95)	1.09 (± 0.66)			
Week 8 (n=93)	0.91 (± 0.66)			
Week 12 (n=87)	0.82 (± 0.58)			
Week 16 (n=85)	0.72 (± 0.59)			
Week 20 (n=82)	0.68 (± 0.56)			
Week 24 (n=80)	0.66 (± 0.55)			
Week 28 (n=79)	0.66 (± 0.57)			

Week 32 (n=74)	0.59 (± 0.58)			
Week 36 (n=74)	0.63 (± 0.58)			
Week 40 (n=74)	0.6 (± 0.59)			
Week 44 (n=71)	0.59 (± 0.61)			
Week 48 (n=70)	0.56 (± 0.59)			
Week 52 (n=67)	0.54 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Received All Planned Study Medication (Compliance)

End point title	Percentage of Participants Who Received All Planned Study Medication (Compliance)

End point description:

Compliance (in terms of percentage of participants who received all planned study medication) was assessed on the basis of participant diary cards and return records. Full analysis set. Here, n = number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: percentage of participants				
number (not applicable)				
Week 1 (n=97)	66			
Week 2 (n=96)	97.9			
Week 4 (n=95)	100			
Week 8 (n=93)	100			
Week 12 (n=87)	98.9			
Week 16 (n=85)	97.6			
Week 20 (n=82)	98.8			
Week 24 (n=80)	100			
Week 28 (n=79)	100			
Week 32 (n=74)	100			
Week 36 (n=74)	100			
Week 40 (n=74)	100			
Week 44 (n=71)	100			
Week 48 (n=70)	100			
Week 52 (n=67)	100			

Statistical analyses

No statistical analyses for this end point

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

End point title	Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Total Score

End point description:

FACIT-Fatigue (FACIT-F) total score is sum of FACIT-General (FACIT-G) subscale score and FACIT-F subscale score. FACIT-G consists of 27 questions grouped in 4 domains of general health-related quality of life: physical, social/family, emotional, and functional well-being; each item ranges from 0 (not at all) to 4(very much). FACIT-G score ranges between 0-108. FACIT-F subscale is 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). For all items, except for 2 negatively stated ones, code was reversed and new score was calculated as 4 minus participant's response. Sum of all responses resulted in FACIT-F subscale score for total possible score of 0(worse score) to 52(better score). FACIT-F total score (FACIT-G plus FACIT-F subscale scores) ranges from 0 (better score) to 160 (worse score). Full analysis set. Here, n=number of participants analyzed for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=97)	89.68 (± 24.32)			
Week 2 (n=96)	91.83 (± 22.91)			
Week 4 (n=95)	100.38 (± 24.36)			
Week 8 (n=93)	103.16 (± 26.28)			
Week 12 (n=87)	106.39 (± 24.74)			
Week 16 (n=85)	110.17 (± 24.96)			
Week 20 (n=82)	112.6 (± 25.5)			
Week 24 (n=80)	114.21 (± 25.23)			
Week 28 (n=79)	114.85 (± 26.95)			
Week 32 (n=74)	117.01 (± 26)			
Week 36 (n=74)	116.5 (± 26.17)			
Week 40 (n=74)	116.59 (± 26.2)			
Week 44 (n=71)	119.67 (± 26.64)			
Week 48 (n=70)	119.83 (± 26.51)			
Week 52 (n=67)	121.82 (± 25.34)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to end of study (Week 60)

Adverse event reporting additional description:

Safety population included all participants who received at least one dose of SC tocilizumab. Adverse events were reported separately for the participants who received tocilizumab monotherapy and tocilizumab in combination with methotrexate or other non-biologic DMARDs.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Tocilizumab + Methotrexate or Other Non-Biologic DMARDs

Reporting group description:

Participants received tocilizumab 162 mg SC injection QW in combination with methotrexate or other non-biologic DMARDs during the treatment period of 52 weeks.

Reporting group title	Tocilizumab Monotherapy

Reporting group description:

Participants received tocilizumab 162 mg SC injection QW as monotherapy during the treatment period of 52 weeks.

Serious adverse events	Tocilizumab + Methotrexate or Other Non-Biologic DMARDs	Tocilizumab Monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 66 (7.58%)	2 / 31 (6.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 66 (1.52%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 66 (1.52%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 66 (3.03%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 66 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tocilizumab + Methotrexate or Other Non-Biologic DMARDs	Tocilizumab Monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 66 (57.58%)	19 / 31 (61.29%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 66 (19.70%)	9 / 31 (29.03%)	
occurrences (all)	24	17	
Aspartate aminotransferase increased			

subjects affected / exposed	9 / 66 (13.64%)	8 / 31 (25.81%)	
occurrences (all)	14	15	
Blood glucose increased			
subjects affected / exposed	3 / 66 (4.55%)	2 / 31 (6.45%)	
occurrences (all)	4	7	
Blood triglycerides increased			
subjects affected / exposed	3 / 66 (4.55%)	3 / 31 (9.68%)	
occurrences (all)	6	4	
Blood urea increased			
subjects affected / exposed	3 / 66 (4.55%)	1 / 31 (3.23%)	
occurrences (all)	4	1	
Blood uric acid increased			
subjects affected / exposed	1 / 66 (1.52%)	3 / 31 (9.68%)	
occurrences (all)	3	5	
White blood cell count decreased			
subjects affected / exposed	1 / 66 (1.52%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Hepatic enzyme increased			
subjects affected / exposed	5 / 66 (7.58%)	1 / 31 (3.23%)	
occurrences (all)	6	3	
Neutrophil count decreased			
subjects affected / exposed	2 / 66 (3.03%)	3 / 31 (9.68%)	
occurrences (all)	3	4	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 66 (3.03%)	3 / 31 (9.68%)	
occurrences (all)	2	4	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 66 (3.03%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 66 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Sciatica			

subjects affected / exposed	1 / 66 (1.52%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	2 / 66 (3.03%)	2 / 31 (6.45%)	
occurrences (all)	3	3	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	8 / 66 (12.12%)	4 / 31 (12.90%)	
occurrences (all)	12	13	
Lymphopenia			
subjects affected / exposed	4 / 66 (6.06%)	1 / 31 (3.23%)	
occurrences (all)	6	1	
Neutropenia			
subjects affected / exposed	5 / 66 (7.58%)	6 / 31 (19.35%)	
occurrences (all)	8	16	
Thrombocytopenia			
subjects affected / exposed	4 / 66 (6.06%)	2 / 31 (6.45%)	
occurrences (all)	4	3	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	5 / 66 (7.58%)	1 / 31 (3.23%)	
occurrences (all)	10	2	
Oedema peripheral			
subjects affected / exposed	2 / 66 (3.03%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Injection site pruritus			
subjects affected / exposed	1 / 66 (1.52%)	2 / 31 (6.45%)	
occurrences (all)	1	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 66 (3.03%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Nausea			
subjects affected / exposed	0 / 66 (0.00%)	4 / 31 (12.90%)	
occurrences (all)	0	5	
Abdominal pain			

subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	2 / 31 (6.45%) 2	
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 6	1 / 31 (3.23%) 1	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5	5 / 31 (16.13%) 5	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 6	3 / 31 (9.68%) 3	
Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 66 (12.12%) 9	4 / 31 (12.90%) 5	
Lower respiratory tract infection subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4	2 / 31 (6.45%) 2	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 6	2 / 31 (6.45%) 3	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4	0 / 31 (0.00%) 0	
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5	0 / 31 (0.00%) 0	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 2	3 / 31 (9.68%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2014	Protocol ML28695 had been amended in order to provide participants the investigational medicinal product (IMP) until it becomes commercially available and reimbursed in Greek market. Additional changes to the protocol were as follows: • Participants who completed 60 weeks in the study before tocilizumab SC became commercially available and reimbursed, would enter an extension phase until the IMP became commercially available and reimbursed in the Greek market. • Efficacy and Safety outcome measures would continue to be collected/ monitored according to the revised schedule of assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported