EU Clinical Trials Register

Clinical trial results:
A multicenter, open-label, long-term extension study of WA22762 and NA25220 to evaluate safety and efficacy of subcutaneous tocilizumab in patients with moderate to severe rheumatoid arthritis

Summary

EudraCT number	2012-002632-87
Trial protocol	ES
Global end of trial date	19 May 2015

Results information

Result version number	v1 (current)
This version publication date	03 August 2016
First version publication date	03 August 2016

Trial information

Trial identification

Sponsor protocol code	ML28488

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01772316
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, 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	19 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of subcutaneous (SC) tocilizumab therapy with regard to adverse events (AEs) and clinical laboratory assessments, including immunogenicity in subjects who have completed the 2010-018375-22 or 2010-019912-18 core studies and who may continue to benefit from tocilizumab treatment administered subcutaneously.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

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)	30
From 65 to 84 years	17

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 47 subjects were enrolled in the trial and received treatment. All subjects enrolled were included in the safety analysis. Of the 47 subjects , 13 subjects were not included in the statistical analysis for outcome measures because they did not meet eligibility criteria.

Period 1

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

Arms

Arm title	Tocilizumab Subcutaneous (SC)

Arm description:

Subjects received Tocilizumab 162 milligram (mg) given as 0.9 milliliter (mL) of a 180 milligram per milliliter (mg/mL) solution administered once a week (for subjects entering from 2012-002632-87) or once every two weeks (for subjects entering from 2010-019912-18) by SC injection and as a single fixed dose irrespective of body weight.

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:

Subjects received tocilizumab 162 mg SC weekly or every two weeks, 96 weeks

Number of subjects in period 1	Tocilizumab Subcutaneous (SC)
Started	47
Completed	40
Not completed	7
Withdrawn by sponsor decision	5
Inform consent withdrawn	1
Serious adverse event	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	47	47	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	59.3		
standard deviation	± 10.3	-	
Gender categorical Units: Subjects			
Female	40	40	
Male	7	7	

End points

End points reporting groups

Reporting group title	Tocilizumab Subcutaneous (SC)

Reporting group description:

Subjects received Tocilizumab 162 milligram (mg) given as 0.9 milliliter (mL) of a 180 milligram per milliliter (mg/mL) solution administered once a week (for subjects entering from 2012-002632-87) or once every two weeks (for subjects entering from 2010-019912-18) by SC injection and as a single fixed dose irrespective of body weight.

Primary: Percentage of Subjects With an Adverse Event (AE)

End point title	Percentage of Subjects With an Adverse Event (AE)[1]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation subject that was administered study drug, regardless of causal attribution. Safety analysis set included all subjects who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Randomisation of first subject to clinical cutoff date (19MAY2015) (approximately 29 months)

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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: percentage of subjects				
number (not applicable)	83			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Withdrawn From the Study Due to Lack of Therapeutic Response

End point title	Percentage of Subjects Withdrawn From the Study Due to Lack of Therapeutic Response[2]

End point description:

Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration.

End point type	Primary

End point timeframe:

Randomisation of first subject to clinical cutoff date (19MAY2015) (approximately 29 months)

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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Disease Activity Score 28 - Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 48

End point title	Change From Baseline in Disease Activity Score 28 - Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 48[3]

End point description:

The DAS28 is a combined index for measuring disease activity in rheumatoid arthritis. The index included SJC, TJC, acute phase response (ESR or high sensitivity C-reactive protein [hsCRP]) and general health status. For this study, ESR was used to calculate DAS28 score. The index was calculated using the following formula: DAS28 = $(0.56 \times \sqrt{[TJC28]}) + (0.28 \times \sqrt{[SJC28]}) + (0.7 \times \ln[ESR]) + (0.014 \times GH)$. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. Change in DAS28ESR=DAS28-ESR at Week 48 - DAS28-ESR at Baseline. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration. Here, n signifies the number of subjects evaluable at specified time points.

End point type	Primary

End point timeframe:

Baseline, Week 48

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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 30)	2.9 (± 1.4)			
Change at Week 48 (n= 30)	-0.832 (± 0.292)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in DAS28-ESR at Week 96

End point title	Change From Baseline in DAS28-ESR at Week 96[4]

End point description:

The DAS28 is a combined index for measuring disease activity in rheumatoid arthritis. The index included SJC, TJC, acute phase response (ESR or high sensitivity C-reactive protein [hsCRP]) and general health status. For this study, ESR was used to calculate DAS28 score. The index was calculated using the following formula: DAS28 = (0.56 × √[TJC28]) + (0.28 × √[SJC28]) + (0.7 × ln[ESR]) + (0.014 × GH). The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. Change in DAS28-ESR = DAS28-ESR at Week 96 - DAS28-ESR at Baseline. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration.

End point type	Primary

End point timeframe:

Baseline, Week 96

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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.804 (± 0.23)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Simplified Disease Activity Index (SDAI) at Week 48

End point title	Change From Baseline in Simplified Disease Activity Index (SDAI) at Week 48[5]

End point description:

The SDAI was the numerical sum of five outcome parameter: SJC and TJC, Patient Global Assessment of Disease Activity (PGA) and Investigator Global Assessment of Disease Activity (IGA), and level of hsCRP. The index was calculated using the following formula SDAI = TJC28 + SJC28 + PGA + IGA + CRP. Change in SDAI = SDAI at Week 48 - SDAI at Baseline. SDAI total score = 0-86. SDAI <=3.3 indicates clinical remission, >3.4 to 11 = low disease activity, >11 to 26 = moderate disease activity, and >26 = high (or severe) disease activity. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration. Here, n signifies the number of subjects evaluable at specified time points.

End point type	Primary

End point timeframe:

Baseline, Week 48

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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 30)	12.2 (± 10.7)			
Change at Week 48 (n= 30)	-7.572 (± 2.115)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in SDAI at Week 96

End point title	Change From Baseline in SDAI at Week 96[6]

End point description:

The SDAI was the numerical sum of five outcome parameter: SJC and TJC, PGA and IGA, and level of hsCRP. The index was calculated using the following formula SDAI = TJC28 + SJC28 + PGA + IGA + CRP. Change in SDAI = SDAI at Week 96 - SDAI at Baseline. SDAI total score = 0-86. SDAI <=3.3 indicates clinical remission, >3.4 to 11 = low disease activity, >11 to 26 = moderate disease activity, and >26 = high (or severe) disease activity. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration.

End point type	Primary

End point timeframe:

Baseline, Week 96

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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)	-6.599 (± 2.21)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Total Tender Joint Count (TJC) at Week 48

End point title	Change From Baseline in Total Tender Joint Count (TJC) at Week 48[7]

End point description:

An assessment of 66 joints for swelling and 68 joints for tenderness was made. Joints were assessed and classified as tender/not tender and swollen/not swollen by pressure and joint manipulation on

physical examination. A smaller number indicated improvement. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration. Here, 'n' represents the number of subjects with a measure at specified time point.

End point type	Primary

End point timeframe:

Baseline, Week 48

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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 33)	2.5 (± 4.1)			
Change at Week 48 (n= 33)	1.3 (± 2)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Total TJC at Week 96

End point title	Change From Baseline in Total TJC at Week 96[8]

End point description:

An assessment of 66 joints for swelling and 68 joints for tenderness was made. Joints were assessed and classified as tender/not tender and swollen/not swollen by pressure and joint manipulation on physical examination. A smaller number indicated improvement. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration.

End point type	Primary

End point timeframe:

Baseline, Week 96

Notes:

[8] - 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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	33[9]			
Units: units on a scale				
arithmetic mean (standard deviation)	1.5 (± 3.6)			

Notes:

[9] - Number of subjects analysed signifies those subjects who were evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Swollen Joint Count (SJC) at Week 48

End point title	Change From Baseline in Swollen Joint Count (SJC) at Week

End point description:

An assessment of 66 joints for swelling and 68 joints for tenderness was made. Joints were assessed and classified as tender/not tender and swollen/not swollen by pressure and joint manipulation on physical examination. A negative number indicated improvement. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration.

End point type	Primary

End point timeframe:

Baseline, Week 48

Notes:

[10] - 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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	1.8 (± 3.4)			
Change at Week 48	-1.531 (± 0.587)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in SJC at Week 96

End point title	Change From Baseline in SJC at Week 96[11]

End point description:

An assessment of 66 joints for swelling and 68 joints for tenderness was made. Joints were assessed and classified as tender/not tender and swollen/not swollen by pressure and joint manipulation on physical examination. Change in SJC = SJC at Week 96 - SJC at Baseline. A negative number indicated improvement.Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration.

End point type	Primary

End point timeframe:

Randomisation of first subject to clinical cutoff date (19MAY2015) (approximately 29 months)

Notes:

[11] - 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: The descriptive data was planned to be reported for the endpoint.

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)	-1.188 (± 0.543)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Remission (DAS28 Less Than [<]2.6 or SDAI Less Than or equal to [<=] 3.3) at Weeks 48 and 96

End point title	Percentage of Subjects With Remission (DAS28 Less Than [<]2.6 or SDAI Less Than or equal to [<=] 3.3) at Weeks 48 and 96

End point description:

Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration.

End point type	Secondary

End point timeframe:

Week 48, Week 96

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of subjects				
number (not applicable)				
DAS <2.6 at Week 48	71.9			
DAS <2.6 at Week 96	62.5			
SDAI <=3.3 at Week 48	28.6			
SDAI <=3.3 at Week 96	29.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease-Modifying Antirheumatic Drugs (DMARDs)/Corticosteroid Dose Reductions and/or Discontinuation

End point title	Percentage of Subjects With Disease-Modifying Antirheumatic Drugs (DMARDs)/Corticosteroid Dose Reductions and/or Discontinuation

End point description:

Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration.

End point type	Secondary

End point timeframe:

Randomisation of first subject to clinical cutoff date (19MAY2015) (approximately 29 months)

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of subjects				
number (not applicable)	38.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Visual Analog Score (VAS) at Specified Time Points

End point title	Patient Global Visual Analog Score (VAS) at Specified Time Points

End point description:

This assessment represents the patient's overall assessment of their current disease activity on a 100 millimeter (mm) horizontal VAS. The extreme left end of the line should be described as "no disease activity" (symptom free and no arthritis symptoms) and the extreme right end as "maximum disease activity" (maximum arthritis disease activity). Scores ranged from 0 to 100 with a higher score indicating more disease activity. A negative change score indicated less disease activity. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration. Here, 'n' represents the number of subjects with a measure at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 48, Week 96

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=34)	30.8 (± 21.8)			
Week 48 (n=33)	30 (± 22.6)			
Week 96 (n=33)	26 (± 21.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Pain VAS Score at Specified Time Points

End point title	Patient Pain VAS Score at Specified Time Points

End point description:

This assessment represents the patient's assessment of his/her current level of pain on a 100 mm horizontal VAS. The extreme left end of the line should be described as "no pain" and the extreme right end as "unbearable pain". Scores ranged from 0 to 100 with a higher score indicating more pain. A negative change score indicated less pain. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration. Here, 'n' represents the number of subjects with a measure at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 48, Week 96

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=34)	32.4 (± 21.8)			
Week 48 (n=33)	29.8 (± 21.3)			
Week 96 (n=33)	27 (± 22.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Specified Time Points

End point title	Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Specified Time Points

End point description:

The HAQ-DI is a questionnaire specific for rheumatoid arthritis and consists of 20 questions referring to 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. A negative change score indicates improvement. Per-protocol population included all subjects who had at least one dose of study medication and at least one safety evaluation after dose administration. Here, 'n' represents the number of subjects with a measure at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 48, Week 96

End point values	Tocilizumab Subcutaneous (SC)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=34)	0.8 (± 0.6)			
Week 48 (n=33)	0.7 (± 0.5)			
Week 96 (n=33)	0.8 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomisation of first subject to clinical cutoff date (19MAY2015) (approximately 29 months)

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence in a clinical investigation subject that was administered study drug, regardless of causal attribution.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Subjects received Tocilizumab 162 mg given as 0.9 mL of a 180 mg/mL solution administered once a week (for subjects entering from 2012-002632-87) or once every two weeks (for subjects entering from 2010-019912-18) by SC injection and as a single fixed dose irrespective of body weight. All subjects receiving study drug were included in the safety analysis set.

Serious adverse events	Tocilizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 47 (6.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 47 (2.13%)		
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	39 / 47 (82.98%)		
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 47 (14.89%)		
occurrences (all)	8		
Pain in extremity			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Respiratory tract infection			
subjects affected / exposed	13 / 47 (27.66%)		
occurrences (all)	23		
Urinary tract infection			

subjects affected / exposed	5 / 47 (10.64%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?   No

Interruptions (globally)

Were there any global interruptions to the trial?   No

Limitations and caveats

 None reported