Clinical trial results:
A MULTICENTER, OPEN-LABEL, SINGLE ARM, LONG-TERM EXTENSION STUDY OF WA19926 TO DESCRIBE SAFETY DURING TREATMENT WITH TOCILIZUMAB IN PATIENTS WITH EARLY, MODERATE TO SEVERE RHEUMATOID ARTHRITIS

Summary

EudraCT number	2011-006125-14
Trial protocol	HU
Global end of trial date	18 December 2014

Results information

Result version number	v1
This version publication date	08 July 2016
First version publication date	08 July 2016

Trial information

Trial identification

Sponsor protocol code	ML28146

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01649804
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	18 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2014
Global end of trial reached?	Yes
Global end of trial date	18 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study was to evaluate the long term safety of tocilizumab therapy in all enrolled participants.

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	27 July 2012
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	Hungary: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	11
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total number of 12 participants were enrolled in Hungary.

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 (RoActemra/Actemra) 8 milligram/kilogram (mg/kg) intravenously every 4 weeks for 104 weeks. Dose could be reduced due to safety reasons at any time during the study.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra/Actemra
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tocilizumab (RoActemra/Actemra) 8 milligram/kilogram (mg/kg) intravenously every 4 weeks for 104 weeks. Dose could be reduced due to safety reasons at any time during the study.

Number of subjects in period 1	Tocilizumab
Started	12
Completed	4
Not completed	8
Administrative/Other	8

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab
Reporting group description:	
Tocilizumab (RoActemra/Actemra) 8 milligram/kilogram (mg/kg) intravenously every 4 weeks for 104 weeks. Dose could be reduced due to safety reasons at any time during the study.	

Reporting group values	Tocilizumab	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	51.25		
standard deviation	± 8.67	-	
Gender, Male/Female Units: participants			
Female	8	8	
Male	4	4	

End points

End points reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Tocilizumab (RoActemra/Actemra) 8 milligram/kilogram (mg/kg) intravenously every 4 weeks for 104 weeks. Dose could be reduced due to safety reasons at any time during the study.

Primary: Percentage of Participants with Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs of Special Interest (AESIs)

End point title	Percentage of Participants with Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs of Special Interest (AESIs)[1]

End point description:

An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. A SAE was any experience that: resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or was medically significant. Adverse Events of Special Interest for this study were: Serious and/or medically significant infections; myocardial infarction/Acute coronary syndrome; Gastrointestinal perforation; Malignancies; Anaphylaxis/hypersensitivity reactions; Demyelinating disorders; Stroke and Serious and/or medically significant bleeding and hepatic events. Analysis population included all the enrolled participants in the study.

End point type	Primary

End point timeframe:

End of Study (Week 104 or early withdrawal)

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: Statistical analysis was not performed as planned.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)				
AEs	75			
SAEs	0			
AESI	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Remission, Low, Medium, and High Disease Activity, as Measured by Disease Activity Index 28 Erythrocyte Sedimentation Rate (DAS28-ESR)

End point title	Number of Participants With Remission, Low, Medium, and High Disease Activity, as Measured by Disease Activity Index 28 Erythrocyte Sedimentation Rate (DAS28-ESR)

End point description:	
The DAS28 (ESR) score is a measure of the participant's disease activity. It is calculated using the tender joint count (28 joints), swollen joint count (28 joints), erythrocyte sedimentation rate (ESR) and general health status. The DAS28-ESR scale ranges from 0 to 10, where higher scores represent higher disease activity. Analysis population included all the enrolled participants in the study.	
End point type	Secondary
End point timeframe:	
Screening and End of Study (Week 104 or early withdrawal)	

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: participants				
number (not applicable)				
Remission (Baseline)	5			
Low Disease Activity (Baseline)	1			
Moderate Disease Activity (Baseline)	4			
High Disease Activity (Baseline)	2			
Remission (End of Study)	10			
Low Disease Activity (End of Study)	1			
Moderate Disease Activity (End of Study)	0			
High Disease Activity (End of Study)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Remission, Low, Medium, and High Disease Activity, as Measured by Simplified Disease Activity Index (SDAI)

End point title	Number of Participants With Remission, Low, Medium, and High Disease Activity, as Measured by Simplified Disease Activity Index (SDAI)
End point description:	
The SDAI was defined as the numerical sum of 5 outcome parameters: tender and swollen joint count (based on a 28-joint assessment), participant and physician global assessment of disease activity on a 100 millimeter (mm) Visual analogue scale (VAS) (VAS; 0 = no disease activity and 100 = worst disease activity) and level of C-reactive protein (CRP) (milligram per deciliter [mg/dl], normal < 1 mg/dl). SDAI total score = 0-86 where a higher score reflects worsening disease. 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. Analysis population included all the enrolled participants in the study.	
End point type	Secondary
End point timeframe:	
Screening and End of Study (Week 104 or early withdrawal)	

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: participants				
number (not applicable)				
Remission (Baseline)	0			
Low Disease Activity (Baseline)	6			
Moderate Disease Activity (Baseline)	3			
High Disease Activity (Baseline)	3			
Remission (End of Study)	3			
Low Disease Activity (End of Study)	7			
Moderate Disease Activity (End of Study)	1			
High Disease Activity (End of Study)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Decreased, Unchanged, and Increased Tender Joint Count (TJC)

End point title	Number of Participants With Decreased, Unchanged, and Increased Tender Joint Count (TJC)

End point description:

Tender joint count was performed by a skilled assessor, evaluating 68 joints for tenderness. Analysis population included all the evaluable participants for this outcome measure. "n" included all the participants analyzed on that particular time point.

End point type	Secondary

End point timeframe:

Week 12 and Week 104

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
number (not applicable)				
Decreased (Week 12; n=11)	5			
Unchanged (Week 12; n=11)	4			
Increased (Week 12;n=11)	2			
Decreased (Week 104;n=4)	2			
Unchanged (Week 104;n=4)	2			
Increased (Week 104;n=4)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Decreased, Unchanged, and Increased Swollen Joint Count (SJC)

End point title	Number of Participants With Decreased, Unchanged, and Increased Swollen Joint Count (SJC)

End point description:

Swollen joint count was performed by a skilled assessor, evaluating 66 joints for swelling. Analysis population included all the evaluable participants for this outcome measure. "n" included all the participants analyzed on that particular time point.

End point type	Secondary

End point timeframe:

Week 12 and Week 104

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
number (not applicable)				
Decreased (Week 12; n=11)	3			
Unchanged (Week 12; n=11)	7			
Increased (Week 12;n=11)	1			
Decreased (Week 104;n=4)	2			
Unchanged (Week 104;n=4)	2			
Increased (Week 104;n=4)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Rheumatoid Arthritis (RA) Flare

End point title	Time to Rheumatoid Arthritis (RA) Flare

End point description:

RA flare was defined as any worsening of the participant’s disease activity that in the opinion of the Investigator required treatment intensification beyond supportive therapy which included restarting of the study drug treatment. Time to RA flare was defined as the period of drug-free remission until documentation of RA flare. Data were not analyzed as there were no participants who had achieved clinical remission during the study.

End point type	Secondary

End point timeframe:

End of Study (Week 104 or early withdrawal)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Weeks				
median (full range (min-max))	(to)			

Notes:

[2] - No participant had achieved clinical remission during the study hence data was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clinical Remission

End point title	Percentage of Participants with Clinical Remission

End point description:

Clinical remission was based on DAS28 (ESR) and SDAI. DAS28 (ESR) score is calculated using TJC (28 joints), SJC (28 joints), ESR and general health status. DAS28-ESR scale ranges from 0-10, where higher scores represent higher disease activity. DAS28 <=3.2 implied low disease activity, DAS >3.2 to 5.1 implied moderate disease activity and DAS >5.1 implied high disease activity, and DAS28 <2.6 = clinical remission. SDAI was defined as numerical sum of 5 outcome parameters: tender and swollen joint count (based on 28-joint assessment),participant and physician global assessment of disease activity on 100 mm VAS (VAS; 0 =no disease activity and 100= worst disease activity) and level of C-reactive protein (CRP) (mg/dl, normal < 1 mg/dl). SDAI total score = 0-86 where a higher score reflects worsening disease. 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.

End point type	Secondary

End point timeframe:

End of Study (Week 104 or early withdrawal)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Decreased, Unchanged, and Increased Participants Global Assessment of Disease Activity

End point title	Number of Participants With Decreased, Unchanged, and Increased Participants Global Assessment of Disease Activity

End point description:

The participant global assessment of disease activity was measured using a 100 mm VAS ranging from 0=very good to 100=very bad. Analysis population included all the evaluable participants for this outcome measure. "n" included all the participants analyzed on that particular time point.

End point type	Secondary

End point timeframe:

Week 12 and Week 104

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
number (not applicable)				
Decreased (Week 12; n=11)	6			
Unchanged (Week 12; n=11)	0			
Increased (Week 12;n=11)	5			
Decreased (Week 104;n=4)	2			
Unchanged (Week 104;n=4)	0			
Increased (Week 104;n=4)	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Decreased, Unchanged, and Increased Participant Global assessment of Pain

End point title	Number of Participants With Decreased, Unchanged, and Increased Participant Global assessment of Pain

End point description:

A participant's overall assessment of pain on a VAS was assessed with a question concerning the amount of pain due to arthritis. Pain was assessed on a 100 mm VAS scale with a left-hand marker "no pain" (0 mm) or right-hand marker "extreme pain" (100 mm). Analysis population included all the evaluable participants for this outcome measure. "n" included all the participants analyzed on that particular time point.

End point type	Secondary

End point timeframe:

Week 12 and Week 104

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
number (not applicable)				
Decreased (Week 12; n=11)	7			
Unchanged (Week 12; n=11)	4			
Increased (Week 12;n=11)	0			
Decreased (Week 104;n=4)	2			
Unchanged (Week 104;n=4)	0			
Increased (Week 104;n=4)	2			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The Health Assessment Questionnaire Disability Index (HAQ-DI) is a participant-completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 4 (unable to do). HAQ-DI=sum of worst scores in each domain divided by the number of domains answered.Analysis population included all the enrolled participants in the study.

End point type	Secondary

End point timeframe:

End of Study (Week 104 or early withdrawal)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: units on a scale				
arithmetic mean (standard deviation)	1.18 (± 0.953)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
End of Study (Week 104 or early withdrawal)	
Adverse event reporting additional description:	
An AE was any untoward medical occurrence in a study participant administered a pharmaceutical product, and which did not necessarily have a causal relationship with the treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Tocilizumab
Reporting group description:	
Tocilizumab (RoActemra/Actemra) 8 mg/kg intravenously every 4 weeks for 104 weeks. Dose could be reduced due to safety reasons at any time during the study.	

Serious adverse events	Tocilizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tocilizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)		
Investigations			
White blood cell count decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			

Sciatica			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Ranula			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Dermatitis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Otitis externa			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cystitis			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	5		
Influenza			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported