Clinical trial results:
Multicenter, Randomized, Parallel Group Study To Compare The Incidence Of Tocilizumab Related Infusion Reactions in Patients With Moderate To Severe Active RA, When Infusion is Given Over 31 Minutes Compared To 1 Hour

Summary

EudraCT number	2011-002363-15
Trial protocol	IS DK
Global end of trial date	02 September 2013

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	ML27901

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01468077
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 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, 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	25 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 July 2013
Global end of trial reached?	Yes
Global end of trial date	02 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall aim of this multicenter, randomized, parallel group study was to evaluate the incidence of tocilizumab related infusion reactions in participants with moderate to severe active Rheumatoid Arthritis (RA), when infusion was administered over 31 minutes (Fast Administration) compared to being administered over 1 hour (Normal Administration).

The primary objective:
- To compare incidence of tocilizumab infusion reactions between 60 minutes and 31 minutes dose administrations.

The secondary objectives were:
- To evaluate adverse events (AE) resulting from the two infusion times.
- To evaluate the Disease Activity Score Based on 28-Joint Count (DAS28) less than (<)2.6 after 24 weeks of infusion.
- To evaluate American College of Rheumatology Percent Improvement (ACR20, ACR50, ACR70 and ACR90) responses after 24 weeks of infusion.

Protection of trial subjects:

The investigators were required to ensure this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study conduct fully adhered to the principles outlined in "Guideline for Good Clinical Practice" International Conference on Harmonisation (ICH) Tripartite Guideline [January 1997] or with local law if it afforded greater protection to the participant. The investigators were also required to ensure compliance with the EU (European Union) Clinical Study Directive [2001/20/EC]. All investigators were trained according to Roche standard operational procedures (SOPs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2011
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	Denmark: 41
Country: Number of subjects enrolled	Iceland: 6
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)	32
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Between 14 November 2011 to 02 September 2013, a total of 52 participants were screened and 47 were randomized into either the Fast or Normal Administration treatment groups. Five participants failed screening, due to Aspartate Aminotransferase (AST) levels above inclusion criteria (2), previous serious antibody reactions (2), and infection (1).

Period 1

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

Blinding implementation details:

There are no blinding details as this was an open-label study. Participants were randomized in groups of four with two participants for each arm, and all investigators picked numbered envelopes in sequential order.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tocilizumab, Normal Administration

Arm description:

Participants received tocilizumab 8 milligrams per kilogram (mg/kg) intravenously (IV) over 60 minutes once every 4 weeks for a total of 6 infusions during a 24-week treatment period.

Arm type	Active comparator
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:

Participants received an infusion of 8 mg/kg tocilizumab every 4 weeks during the 24-week treatment period. The infusion was given a total of 6 times, at Week 0 (Day 1) and at Week 4, 8, 12, 16 and 20.

Arm title	Tocilizumab, Fast Administration

Arm description:

Participants received tocilizumab 8 mg/kg IV once every 4 weeks for a total of 6 infusions during a 24-week treatment period. The first infusion (Baseline) was given over 60 minutes, and over 31 minutes the following 5 infusions.

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:

Participants received an infusion of 8 mg/kg tocilizumab every 4 weeks during the 24-week treatment period. The infusion was given a total of 6 times, at Week 0 (Day 1) and at Week 4, 8, 12, 16 and 20.

Number of subjects in period 1	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration
Started	22	25
Completed	18	22
Not completed	4	3
Adverse Event	2	2
Physician Decision	1	-
Lack of efficacy	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab, Normal Administration
Reporting group description:	
Participants received tocilizumab 8 milligrams per kilogram (mg/kg) intravenously (IV) over 60 minutes once every 4 weeks for a total of 6 infusions during a 24-week treatment period.	
Reporting group title	Tocilizumab, Fast Administration
Reporting group description:	
Participants received tocilizumab 8 mg/kg IV once every 4 weeks for a total of 6 infusions during a 24-week treatment period. The first infusion (Baseline) was given over 60 minutes, and over 31 minutes the following 5 infusions.	

Reporting group values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration	Total
Number of subjects	22	25	47
Age categorical Units: Subjects			
Age continuous			
Age of the ITT population at Baseline			
Units: years			
arithmetic mean	57.5	59.8	
standard deviation	± 11.8	± 13.1	-
Gender categorical			
Baseline gender characteristics of ITT population			
Units: Subjects			
Female	17	20	37
Male	5	5	10

End points

End points reporting groups

Reporting group title	Tocilizumab, Normal Administration
Reporting group description:	
Participants received tocilizumab 8 milligrams per kilogram (mg/kg) intravenously (IV) over 60 minutes once every 4 weeks for a total of 6 infusions during a 24-week treatment period.	
Reporting group title	Tocilizumab, Fast Administration
Reporting group description:	
Participants received tocilizumab 8 mg/kg IV once every 4 weeks for a total of 6 infusions during a 24-week treatment period. The first infusion (Baseline) was given over 60 minutes, and over 31 minutes the following 5 infusions.	

Primary: Percentage of Participants With Any Infusion Reaction

End point title	Percentage of Participants With Any Infusion Reaction
End point description:	
An infusion reaction was defined as any AE that occurred during the infusion or during the 24 hours following the infusion and possibly or probably related to tocilizumab.	
End point type	Primary
End point timeframe:	
Baseline (Day 1), and Weeks 4, 8, 12, 16, and 20	

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[1]	25[2]		
Units: Percentage of Participants				
number (not applicable)	13.6	12		

Notes:

[1] - Safety Analysis Set (SAS) Population: Randomized participants infused at least once with tocilizumab

[2] - SAS Population

Statistical analyses

Statistical analysis title	Participants With Any Infusion Reactions
Statistical analysis description:	
The Confidence Interval calculated by Exact method based on binomial distribution	
Comparison groups	Tocilizumab, Normal Administration v Tocilizumab, Fast Administration
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0.0164

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2685
upper limit	0.2988

Secondary: Percentage of Participants Discontinuing Tocilizumab in Response to an AE or a Serious Adverse Event (SAE)

End point title	Percentage of Participants Discontinuing Tocilizumab in Response to an AE or a Serious Adverse Event (SAE)

End point description:

All occurrences of participants who received at least 1 infusion of tocilizumab and then stopped tocilizumab infusions due to an AE or SAE were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[3]	25[4]		
Units: Percentage of Participants				
number (not applicable)	9	8		

Notes:

[3] - SAS Population

[4] - SAS Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Discontinuing Tocilizumab for Other Reasons

End point title	Percentage of Participants Discontinuing Tocilizumab for Other Reasons

End point description:

Participants that stopped the administration of tocilizumab and discontinued the study prematurely due to reasons other than an AE or SAE were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Weeks, 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[5]	25[6]		
Units: Percentage of Participants				
number (not applicable)	9	4		

Notes:

[5] - SAS Population

[6] - SAS Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Increased Liver Enzyme Values of Greater Than (>)1.5 Times, or >3 Times, or >5 Times Over the Upper Limit of Normal (ULN) by Visit Among Participants Who Completed All Visits

End point title	Percentage of Participants With Increased Liver Enzyme Values of Greater Than (>)1.5 Times, or >3 Times, or >5 Times Over the Upper Limit of Normal (ULN) by Visit Among Participants Who Completed All Visits

End point description:

Increased liver enzyme values defined as Alanine Aminotransferase (ALT) and AST values of >1.5 times, or >3 times, or >5 times over the ULN. Almost none of the participants had increased measurements of AST, thus only values of ALT were presented. None of the participants presented with increased values of ALT above 3 or 5 ULN at any of the visits.

ITT Completers is defined as a subset of the participants in the ITT population who completed all study visits.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[7]	21[8]		
Units: Percentage of Participants				
number (not applicable)				
ALT>1.5 ULN Week 4	12	5		
ALT>1.5 ULN Week 8	6	10		
ALT>1.5 ULN Week 12	6	5		
ALT>1.5 ULN Week 16	6	10		
ALT>1.5 ULN Week 20	12	5		
ALT>1.5 ULN Week 24	24	5		

Notes:

[7] - ITT Completers with liver enzyme datasets for each analyzed visit

[8] - ITT Completers with liver enzyme datasets for each analyzed visit

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Increased Lipid Values by Visit Among Participants Who Completed All Visits

End point title	Percentage of Participants With Increased Lipid Values by Visit Among Participants Who Completed All Visits

End point description:

Increased levels of high density lipoproteins (HDL) equal to or greater than (≥)1.5 millimoles per liter (mmol/L), and low density lipoproteins (LDL) ≥4.1 mmol/L, and total cholesterol ≥5.1 mmol/L, are defined according to the Adult Treatment Panel III (ATP-III) guidelines.

End point type	Secondary

End point timeframe:

Screening and Weeks 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[9]	22[10]		
Units: Percentage of Participants				
number (not applicable)				
High HDL (≥1.5 mmol/L), Screening	44	46		
High HDL (≥1.5 mmol/L), Week 4	44	55		
High HDL (≥1.5 mmol/L), Week 8	50	36		
High HDL (≥1.5 mmol/L), Week 12	39	50		
High HDL (≥1.5 mmol/L), Week 16	44	41		
High HDL (≥1.5 mmol/L), Week 20	39	36		
High HDL (≥1.5 mmol/L), Week 24	44	46		
High LDL (≥4.1 mmol/L), Screening	0	14		
High LDL (≥4.1 mmol/L), Week 4	11	27		
High LDL (≥4.1 mmol/L), Week 8	6	32		
High LDL (≥4.1 mmol/L), Week 12	6	36		
High LDL (≥4.1 mmol/L), Week 16	6	23		
High LDL (≥4.1 mmol/L), Week 20	11	32		
High LDL (≥4.1 mmol/L), Week 24	6	18		
High total cholesterol (≥5.1 mmol/L), Screening	33	59		
High total cholesterol (≥5.1 mmol/L), Week 4	56	73		
High total cholesterol (≥5.1 mmol/L), Week 8	61	73		
High total cholesterol (≥5.1 mmol/L), Week 12	56	68		
High total cholesterol (≥5.1 mmol/L), Week 16	61	64		
High total cholesterol (≥5.1 mmol/L), Week 20	61	59		
High total cholesterol (≥5.1 mmol/L), Week 24	56	64		

Notes:

[9] - ITT Completers

[10] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Reduction of at Least 1.2 Points in DAS28 by Visit Among Participants Who Completed All Visits

End point title	Percentage of Participants With a Reduction of at Least 1.2 Points in DAS28 by Visit Among Participants Who Completed All Visits

End point description:

Improvement in RA disease activity was measured by the DAS28 score, which is an index combining measurements of swollen and tender joints, acute phase response High sensitivity C-Reactive Protein (hsCRP), and global assessment of disease activity by the participant. A clinically meaningful improvement was defined as a reduction of at least 1.2 units in DAS28 during the study period. A low disease activity was defined as DAS28 <3.2, and remission was defined as DAS28 <2.6.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[11]	22[12]		
Units: Percentage of Participants				
number (not applicable)				
Week 4	67	55		
Week 8	89	73		
Week 12	89	82		
Week 16	94	77		
Week 20	94	82		
Week 24	89	86		

Notes:

[11] - ITT Completers

[12] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a DAS28 Score Below 3.2 (Low Disease Activity) by Visit Among Participants Who Completed all Visits

End point title	Percentage of Participants Achieving a DAS28 Score Below 3.2 (Low Disease Activity) by Visit Among Participants Who Completed all Visits

End point description:

Improvement in RA disease activity was measured by the DAS28 score, which is an index combining measurements of swollen and tender joints, acute phase response hsCRP, and global assessment of disease activity by the participant. A clinically meaningful improvement was defined as a reduction of at least 1.2 units in DAS28 during the study period. A low disease activity was defined as DAS28 <3.2, and remission was defined as DAS28 <2.6.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[13]	22[14]		
Units: Percentage of Participants				
number (not applicable)				
Week 4	44	27		
Week 8	67	55		
Week 12	78	82		
Week 16	94	68		
Week 20	89	73		
Week 24	83	77		

Notes:

[13] - ITT Completers

[14] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a DAS28 Score Below 2.6 (Remission) by Visit Among Participants Who Completed All Visits

End point title	Percentage of Participants Achieving a DAS28 Score Below 2.6 (Remission) by Visit Among Participants Who Completed All Visits

End point description:

Improvement in RA disease activity was measured by the DAS28 score, which is an index combining measurements of swollen and tender joints, acute phase response hsCRP, and global assessment of disease activity by the participant. A clinically meaningful improvement was defined as a reduction of at least 1.2 units in DAS28 during the study period. A low disease activity was defined as DAS28 <3.2, and remission was defined as DAS28 <2.6.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[15]	22[16]		
Units: Percentage of Participants				
number (not applicable)				
Week 4	22	9		
Week 8	28	36		
Week 12	50	73		
Week 16	78	46		
Week 20	72	59		
Week 24	61	55		

Notes:

[15] - ITT Completers

[16] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 Score by Visit Among Participants Who Completed All Visits

End point title	DAS28 Score by Visit Among Participants Who Completed All Visits

End point description:

Improvement in RA disease activity was measured by the DAS28 score, which is an index combining measurements of swollen and tender joints, acute phase response hsCRP, and global assessment of disease activity by the participant. A clinically meaningful improvement was defined as a reduction of at least 1.2 units in DAS28 during the study period. A low disease activity was defined as DAS28 <3.2, and remission was defined as DAS28 <2.6.

End point type	Secondary

End point timeframe:

Baseline, Weeks, 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[17]	22[18]		
Units: Scores On A Scale				
arithmetic mean (standard deviation)				
Baseline (n=18, 21)	5 (± 1.1)	5 (± 0.9)		
Week 4 (n=18, 21)	3.3 (± 0.8)	3.6 (± 1)		
Week 8 (n=18, 22)	2.9 (± 0.8)	3.1 (± 1.2)		
Week 12 (n=18, 22)	2.6 (± 0.9)	2.4 (± 1)		
Week 16 (n=18, 21)	2.3 (± 0.4)	2.6 (± 1)		
Week 20 (n=18, 22)	2.3 (± 0.6)	2.6 (± 0.9)		
Week 24 (n=18, 22)	2.3 (± 0.6)	2.5 (± 1)		

Notes:

[17] - ITT Completers; n=the number of participants analyzed for the given parameter at the specific visit

[18] - ITT Completers; n=the number of participants analyzed for the given parameter at the specific visit

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving American College of Rheumatology 20 Percent (%) Improvement (ACR20 Response) by Visit Among Participants Who Completed all Visits

End point title	Percentage of Participants Achieving American College of Rheumatology 20 Percent (%) Improvement (ACR20 Response) by Visit Among Participants Who Completed all Visits

End point description:

ACR20 response is defined as an improvement of ≥20% in swollen joint count (SJC; 66 joints) and tender joint count (TJC; 68 joints) as well as ≥20% improvement in at least 3 of the following 5 remaining ACR assessments: Patient Global Assessment of Pain; Patient Global Assessment of Disease Activity; Physician Global Assessment of Disease Activity; Health Assessment Questionnaire-Disability Index (HAQ-DI); and acute phase reactive factors (Erythrocyte Sedimentation Rate [ESR] or C-Reactive Protein [CRP]).

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[19]	22[20]		
Units: Percentage of Participants				
number (not applicable)				
Week 4	50	41		
Week 8	67	59		
Week 12	72	68		
Week 16	83	77		
Week 20	83	73		
Week 24	89	91		

Notes:

[19] - ITT Completers

[20] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR 50% Improvement (ACR50 Response) by Visit Among Participants Who Completed all Visits

End point title	Percentage of Participants Achieving ACR 50% Improvement

	(ACR50 Response) by Visit Among Participants Who Completed all Visits

End point description:

ACR50 response is defined as an improvement of ≥50% in SJC (66 joints) and TJC (68 joints) as well as ≥50% improvement in at least 3 of the following 5 remaining ACR assessments: Patient Global Assessment of Pain; Patient Global Assessment of Disease Activity; Physician Global Assessment of Disease Activity; HAQ-DI; and acute phase reactive factors (ESR or CRP).

End point type	Secondary

End point timeframe:

Weeks, 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[21]	22[22]		
Units: Percentage of Participants				
number (not applicable)				
Week 4	28	18		
Week 8	28	36		
Week 12	50	50		
Week 16	44	46		
Week 20	67	55		
Week 24	72	73		

Notes:

[21] - ITT Completers

[22] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR 70% Improvement (ACR70 Response) by Visit Among Participants Who Completed All Visits

End point title	Percentage of Participants Achieving ACR 70% Improvement (ACR70 Response) by Visit Among Participants Who Completed All Visits

End point description:

ACR70 response is defined as an improvement of ≥70% in SJC (66 joints) and TJC (68 joints) as well as ≥70% improvement in at least 3 of the following 5 remaining ACR assessments: Patient Global Assessment of Pain; Patient Global Assessment of Disease Activity; Physician Global Assessment of Disease Activity; HAQ-DI; and acute phase reactive factors (ESR or CRP).

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 20 and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[23]	22[24]		
Units: Percentage of Participants				
number (not applicable)				
Week 4	11	5		
Week 8	17	23		
Week 12	22	36		
Week 16	11	27		
Week 20	22	18		
Week 24	22	36		

Notes:

[23] - ITT Completers

[24] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR 90% Improvement (ACR90 Response) by Visit Among Participants Who Completed all Visits

End point title	Percentage of Participants Achieving ACR 90% Improvement (ACR90 Response) by Visit Among Participants Who Completed all Visits

End point description:

ACR90 response is defined as an improvement of ≥90% in SJC (66 joints) and TJC (68 joints) as well as ≥90% improvement in at least 3 of the following 5 remaining ACR assessments: Patient Global Assessment of Pain; Patient Global Assessment of Disease Activity; Physician Global Assessment of Disease Activity; HAQ-DI; and acute phase reactive factors (ESR or CRP).

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 20 and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[25]	22[26]		
Units: Percentage of Participants				
number (not applicable)				
Week 4	0	0		
Week 8	0	9		
Week 12	0	14		
Week 16	0	0		
Week 20	6	5		
Week 24	6	9		

Notes:

[25] - ITT Completers

[26] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Secondary: High Sensitivity C-Reactive Protein (hsCRP) Levels by Visit Among Participants Who Completed all Visits

End point title	High Sensitivity C-Reactive Protein (hsCRP) Levels by Visit Among Participants Who Completed all Visits

End point description:

hsCRP is a marker for inflammation and is measured in milligrams per liter (mg/L). High levels of this protein indicate inflammation in diseases such as RA.

End point type	Secondary

End point timeframe:

Screening, Baseline, Weeks 4, 8, 12, 16, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[27]	22[28]		
Units: mg/L				
arithmetic mean (standard deviation)				
Screening	22.8 (± 19.8)	25.9 (± 36)		
Baseline	23.5 (± 22.7)	27 (± 32.1)		
Week 4	4.7 (± 6.6)	3.1 (± 3.4)		
Week 8	3.3 (± 3.3)	4.5 (± 3.8)		
Week 12	3.2 (± 3.4)	2.6 (± 3.3)		
Week 16	2.8 (± 3.1)	3.1 (± 3.3)		
Week 20	2.9 (± 3)	3 (± 3.2)		
Week 24	3.2 (± 3.5)	3.4 (± 3.6)		

Notes:

[27] - ITT Population

[28] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Modified Health Assessment Questionnaire (M-HAQ) Score by Visit Among Participants Who Completed all Visits

End point title	Modified Health Assessment Questionnaire (M-HAQ) Score by Visit Among Participants Who Completed all Visits

End point description:

M-HAQ is a self-reported, valid assessment of functional disability in RA. Assessment based on ability of participants to perform daily activities in 8 categories: dressing, arising, eating, walking, reaching, gripping, hygiene, and carrying out daily activities. Scores range 0 to 3; without any difficulty=0, with some difficulty=1, with much difficulty=2, unable to do=3.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[29]	22[30]		
Units: Scores On A Scale				
arithmetic mean (standard deviation)				
Baseline	1.29 (± 0.71)	1.5 (± 0.74)		
Week 4	0.97 (± 0.64)	1.1 (± 0.64)		
Week 8	0.79 (± 0.67)	0.95 (± 0.68)		
Week 12	0.8 (± 0.7)	0.98 (± 0.62)		
Week 16	0.82 (± 0.69)	0.94 (± 0.69)		
Week 20	0.75 (± 0.61)	1.05 (± 0.77)		
Week 24	0.68 (± 0.63)	1.07 (± 0.82)		

Notes:

[29] - ITT Population

[30] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Improvement of at Least 0.22 Units in M-HAQ Compared to Baseline Per Visit Among Participants Who Completed all Visits

End point title	Percentage of Participants With Improvement of at Least 0.22 Units in M-HAQ Compared to Baseline Per Visit Among Participants Who Completed all Visits

End point description:

M-HAQ is a self-reported, valid assessment of functional disability in RA. Assessment based on ability of participants to perform daily activities in 8 categories: dressing, arising, eating, walking, reaching, gripping, hygiene, and carrying out daily activities. Scores range 0 to 3; without any difficulty=0, with some difficulty=1, with much difficulty=2, unable to do=3.

End point type	Secondary

End point timeframe:

Weeks 4, 8. 12, 20, and 24

End point values	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[31]	22[32]		
Units: Percentage of Participants				
number (not applicable)				
Week 4	44.4	45.5		
Week 8	72.2	59.1		
Week 12	72.2	54.5		
Week 16	77.8	63.6		
Week 20	66.7	59.1		

Week 24	72.2	50		

Notes:

[31] - ITT Completers

[32] - ITT Completers

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening through Week 24 or early withdrawal. For early withdrawal two follow-up visits occurred; at 4 weeks and at 12 weeks after the last infusion. A telephone call was sufficient for the last visit if laboratory procedures were not needed.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Tocilizumab, Normal Administration

Reporting group description:

Participants received tocilizumab 8 milligrams per kilogram (mg/kg) intravenously (IV) over 60 minutes once every 4 weeks for a total of 6 infusions during a 24-week treatment period.

Reporting group title	Tocilizumab, Fast Administration

Reporting group description:

Participants received tocilizumab 8 mg/kg IV once every 4 weeks for a total of 6 infusions during a 24-week treatment period. The first infusion (Baseline) was given over 60 minutes, and over 31 minutes the following 5 times.

Serious adverse events	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma cutis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective tenosynovitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tocilizumab, Normal Administration	Tocilizumab, Fast Administration	
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 22 (90.91%)	17 / 25 (68.00%)	
Vascular disorders Flushing subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0	
Hypertension subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	3 / 25 (12.00%) 3	
Pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 25 (8.00%) 2	
Chest pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0	
Feeling cold subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2	0 / 25 (0.00%) 0	
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0	
Reproductive system and breast disorders Menorrhagia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 25 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 22 (9.09%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 22 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Dysphonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 22 (4.55%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Migraine			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 22 (4.55%)	4 / 25 (16.00%)	
occurrences (all)	2	5	
Anaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	

Eye disorders			
Dry eye			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Eye allergy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Dry mouth			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 22 (4.55%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 22 (4.55%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Contusion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Dermatitis acneiform			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Erythema			

subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 25 (4.00%)	
occurrences (all)	2	2	
Rheumatoid arthritis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 25 (4.00%)	
occurrences (all)	1	3	
Joint swelling			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 22 (13.64%)	5 / 25 (20.00%)	
occurrences (all)	4	6	
Rhinitis			
subjects affected / exposed	3 / 22 (13.64%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Skin infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Wound infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Abscess			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Abscess limb			

subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Infective tenosynovitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Otitis media			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 25 (12.00%)	
occurrences (all)	2	3	

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