Clinical trial results:
Prospective, multicentre, placebo controlled, double-blind study to compare the efficacy of maintenance treatment with Tocilizumab with or without glucocorticoid discontinuation in rheumatoid arthritis patients

Summary

EudraCT number	2014-004673-16
Trial protocol	DE FR IT
Global end of trial date	09 February 2018

Results information

Result version number	v1 (current)
This version publication date	23 February 2019
First version publication date	23 February 2019

Trial information

Trial identification

Sponsor protocol code	MA29585

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hoffmann- LaRoche
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	23 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2018
Global end of trial reached?	Yes
Global end of trial date	09 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the change in disease activity as assessed by Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28 ESR) from randomization to Week 24 post-randomization, in subjects with stable low disease activity (LDA, DAS28 ESR score ≤ 3.2) who have been randomized to either continue or taper prednisone in a double-blinded fashion.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol. All the investigators were trained according to the applicable Sponsor standard operating procedures, and strictly adhered to the stated provisions. This was documented by investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and to follow International Conference on Harmonization (ICH) GCP guidelines. Approval from Institutional Review Boards (IRBs) and Ethics Committee (EC) was obtained before study start and was documented in a letter to investigator specifying the date the committee met, and granted approval. Approval from relevant competent authority was also obtained prior to starting the study. Protocol amendments were prepared by the Sponsor, and were submitted to IRB/EC and to Regulatory Authorities in accordance with the local regulatory requirements. Audits were performed by the Sponsor Quality Assurance group in compliance with GCP. An independent Data Monitoring Committee (iDMC) shared responsibility for evaluating the safety of the subjects participating in the trial at regular intervals throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2016
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	France: 13
Country: Number of subjects enrolled	Germany: 129
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Russian Federation: 52
Country: Number of subjects enrolled	Serbia: 44
Country: Number of subjects enrolled	Tunisia: 6
Worldwide total number of subjects	259
EEA total number of subjects	157

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)	198
From 65 to 84 years	60
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall, 314 patients were enrolled into the study. 246 subjects were Track TCZ-naive subjects and 68 subjects were Track TCZ-experienced subjects. A total of 9 TCZ-naive subjects failed to complete 4 weeks' treatment with SPOL prednisone 5 mg/day and were withdrawn from the study prior to randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Tocilizumab+prednisone (tapering dose)

Arm description:

Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously or 8 mg/kg intravenously every 4 weeks; and prednisone at a dose of 5 milligram per day (mg/day) with 1 mg decrements every 4 weeks or matching placebo orally for 24 weeks.

Arm type	Active comparator
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously or 8 mg/kg intravenously every 4 weeks

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone at a dose of 5 milligram per day (mg/day) with 1 mg decrements every 4 weeks or matching placebo orally for 24 weeks.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone at a dose of 5 milligram per day (mg/day) or matching placebo orally for 24 weeks.

Investigational medicinal product name	Placebo matched to prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Prednisone at a dose of 5 milligram per day (mg/day) with 1 mg decrements every 4 weeks or matching placebo orally for 24 weeks.

Arm title	Tocilizumab+prednisone (constant dose)

Arm description:

Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously or 8 mg/kg intravenously every 4 weeks; and prednisone at a dose of 5 milligram per day (mg/day) or matching placebo orally for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously or 8 mg/kg intravenously every 4 weeks

Investigational medicinal product name	Placebo matched to prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone at a dose of 5 milligram per day (mg/day) with 1 mg decrements every 4 weeks or matching placebo orally for 24 weeks.

Number of subjects in period 1	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)
Started	131	128
Completed	116	113
Not completed	15	15
Consent withdrawn by subject	2	2
Physician decision	1	2
Adverse event, non-fatal	5	5
Non-compliance	1	2
Study terminated by sponsor	1	-
Lack of efficacy	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab+prednisone (tapering dose)
Reporting group description:	
Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously or 8 mg/kg intravenously every 4 weeks; and prednisone at a dose of 5 milligram per day (mg/day) with 1 mg decrements every 4 weeks or matching placebo orally for 24 weeks.	
Reporting group title	Tocilizumab+prednisone (constant dose)
Reporting group description:	
Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously or 8 mg/kg intravenously every 4 weeks; and prednisone at a dose of 5 milligram per day (mg/day) or matching placebo orally for 24 weeks.	

Reporting group values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)	Total
Number of subjects	131	128	259
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: Years			
arithmetic mean	54.8	54.0	
standard deviation	± 14.0	± 12.8	-
Sex: Female, Male Units: Subjects			
Female	103	97	200
Male	28	31	59
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	3	3
Black or African American	0	0	0
White	129	123	252
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	120	114	234

Unknown or Not Reported	10	14	24

End points

End points reporting groups

Reporting group title	Tocilizumab+prednisone (tapering dose)
Reporting group description:	
Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously or 8 mg/kg intravenously every 4 weeks; and prednisone at a dose of 5 milligram per day (mg/day) with 1 mg decrements every 4 weeks or matching placebo orally for 24 weeks.	
Reporting group title	Tocilizumab+prednisone (constant dose)
Reporting group description:	
Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously or 8 mg/kg intravenously every 4 weeks; and prednisone at a dose of 5 milligram per day (mg/day) or matching placebo orally for 24 weeks.	

Primary: Change from baseline in Disease Activity Score in 28 joints - Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 24 post-randomization

End point title	Change from baseline in Disease Activity Score in 28 joints - Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 24 post-randomization
End point description:	
Comparing the impact on disease activity of continued versus tapered prednisone in Rheumatoid Arthritis participants with stable low disease activity (LDA) (DAS28-ESR score ≤ 3.2). The DAS28 is a combined index for measuring disease activity in RA. The index includes swollen and tender joint counts, ESR, and general health status.	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Units on a Scale				
least squares mean (confidence interval 95%)	0.538 (0.346 to 0.729)	-0.075 (-0.271 to 0.121)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Tocilizumab+prednisone (constant dose) v Tocilizumab+prednisone (tapering dose)

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Least Square Means
Point estimate	0.613
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.346
upper limit	0.879

Secondary: Treatment Success

End point title	Treatment Success

End point description:

Comparing the proportion of participants who continued versus tapered prednisone with LDA (DAS28-ESR score ≤ 3.2) at Week 24 who did not suffer a flare due to RA and who showed no confirmed adrenal insufficiency requiring replacement therapy.

End point type	Secondary

End point timeframe:

Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Percentage of Participants				
number (confidence interval 95%)	64.9 (56.1 to 73.0)	77.3 (69.1 to 84.3)		

Statistical analyses

Statistical analysis title	Odds Ratio
Comparison groups	Tocilizumab+prednisone (constant dose) v Tocilizumab+prednisone (tapering dose)
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.018
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.285
upper limit	0.889

Statistical analysis title	Relative Risk
Comparison groups	Tocilizumab+prednisone (constant dose) v Tocilizumab+prednisone (tapering dose)
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.021
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	0.833
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.714
upper limit	0.972

Secondary: Change from baseline in clinical disease activity index (CDAI) at Week 24

End point title	Change from baseline in clinical disease activity index (CDAI) at Week 24
End point description:	
Comparison between participants who continued versus tapered prednisone in Clinical Disease Activity Index (CDAI) score.	
End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Units on a Scale				
least squares mean (confidence interval 95%)	2.663 (1.454 to 3.872)	0.321 (-0.914 to 1.556)		

Statistical analyses

Statistical analysis title	Least Square Means
Comparison groups	Tocilizumab+prednisone (tapering dose) v Tocilizumab+prednisone (constant dose)
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Least Square Means
Point estimate	2.342
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	4.023

Secondary: Percentage of participants with >=1 flare

End point title	Percentage of participants with >=1 flare
End point description:	
Percentage of participants with >=1 flare	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Percentage of Participants				
number (not applicable)	26.0	10.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with >=1 administration of flare rescue medication

End point title	Percentage of participants with >=1 administration of flare rescue medication
End point description:	
The proportion of participants with at least one administration of RA flare rescue medication.	
End point type	Secondary

End point timeframe: Randomization to 24 weeks

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Percentage of Participants				
number (not applicable)	20.6	6.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first administration of flare rescue medication

End point title	Time to first administration of flare rescue medication
End point description: Time of onset of first administration of RA flare rescue medication since randomization date	
End point type	Secondary
End point timeframe: Randomization to 24 weeks	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Weeks				
arithmetic mean (standard deviation)	13.59 (± 6.77)	8.76 (± 5.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of administrations of flare rescue medication

End point title	Number of administrations of flare rescue medication
End point description: Proportion of participants who received courses of RA flare rescue medication by number of courses received.	
End point type	Secondary

End point timeframe:

Randomization to 24 weeks

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Percentage of Participants				
number (not applicable)				
0 courses	79.4	93.8		
1 course	15.3	3.9		
2 courses	4.6	1.6		
3 courses	0	0.8		
>3 courses	0.8	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative prednisone exposure (dose)

End point title	Cumulative prednisone exposure (dose)

End point description:

In Post-randomization prednisone arm, Cumulative dose = (number of capsules taken during week 1 to 4 * 1 mg) + (3/4 * number of capsules taken during week 5 to 8 * 1 mg) + (1/2 * number of capsules taken during week 9 to 12 * 1 mg) + (1/4 * number of capsules taken during week 13 to 16 * 1 mg). In continued arm, cumulative dose = (1/4 * number of capsule taken * 5 mg). Cumulative prednisone dose is defined as cumulative blinded prednisone + cumulative flare rescue prednisone.

End point type	Secondary

End point timeframe:

Randomization to 24 weeks

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: mg				
arithmetic mean (standard deviation)				
Cumulative blinded prednisone dose	267.099 (± 40.048)	769.459 (± 175.882)		
Cumulative flare rescue prednisone dose	98.519 (± 51.921)	121.875 (± 54.898)		
Cumulative prednisone dose	287.405 (± 63.184)	777.136 (± 172.881)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who maintain LDA (DAS28 ESR score <=3.2) or remission (DAS28 ESR score <2.6) and the percentage of participants who maintain the baseline disease activity level

End point title	Percentage of participants who maintain LDA (DAS28 ESR score <=3.2) or remission (DAS28 ESR score <2.6) and the percentage of participants who maintain the baseline disease activity level

End point description:

The proportion of participants who maintained LDA and the proportion of participants who maintained the baseline disease activity level at Week 24. LDA was defined as DAS28 ESR score <= 3.2. Remission was defined as DAS28 ESR score <= 2.6. Participants who maintained the baseline activity was defined as DAS28-ESR at Week 24 <= DAS28-ESR at baseline.

End point type	Secondary

End point timeframe:

Randomization to Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Percentage of Participants				
number (not applicable)				
LDA at baseline	97.7	96.9		
LDA at Week 24	73.4	83.1		
Baseline DAS28-ESR ≤ 2.6	78.6	76.6		
Remission at Week 24	61.2	81.6		
Maintained baseline activity at Week 24	36.6	54.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who permanently discontinue study treatment due to insufficient flare control

End point title	Percentage of participants who permanently discontinue study treatment due to insufficient flare control

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Percentage of Participants				
number (not applicable)	0	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in simplified disease activity index (SDAI) at Week 24

End point title	Change from baseline in simplified disease activity index (SDAI) at Week 24

End point description:

The SDAI is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28-joint assessment), patient and physician global assessment of disease activity [visual analogue scale (VAS) 0-10 cm] and level of C-reactive protein (mg/dl, normal <1 mg/dl).

End point type	Secondary

End point timeframe:

Randomization to Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: SDAI Score				
least squares mean (confidence interval 95%)	2.511 (1.296 to 3.727)	0.248 (-0.994 to 1.489)		

Statistical analyses

Statistical analysis title	Least Square Means
Comparison groups	Tocilizumab+prednisone (tapering dose) v Tocilizumab+prednisone (constant dose)
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.009
Method	ANCOVA
Parameter estimate	Least Square Means
Point estimate	2.264
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.574
upper limit	3.953

Secondary: Time to first RA flare

End point title	Time to first RA flare
End point description:	
The mean time of onset for the first RA flare since randomization.	
End point type	Secondary
End point timeframe:	
Randomization to 24 weeks	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Weeks				
arithmetic mean (standard deviation)	15.64 (± 7.13)	12.11 (± 7.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of RA flares

End point title	Number of RA flares
End point description:	
Number of visits with RA flares reported.	
End point type	Secondary
End point timeframe:	
Randomization to 24 weeks	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Percentage of Visits				
number (not applicable)				
1 Visit	16.0	7.0		
2 Visits	6.9	3.9		
3 Visits	2.3	0		
>3 Visits	0.8	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Swollen 66 Joint Counts

End point title	Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Swollen 66 Joint Counts
End point description:	
Count of swollen joints based upon 66 assessed joints.	
End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Number of swollen joints				
arithmetic mean (standard deviation)	0.129 (± 6.687)	-0.107 (± 1.618)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in American College of Rheumatology (ACR) core

set components at Week 24: Tender 68 Joint Counts

End point title	Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Tender 68 Joint Counts

End point description:

Count of tender joints based on 68 assessed joints.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Number of tender joints				
arithmetic mean (standard deviation)	0.793 (± 7.764)	-0.330 (± 2.729)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Patient's Assessment of Pain

End point title	Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Patient's Assessment of Pain

End point description:

Scored on a Visual Analogue Scale (VAS) from 0 to 100 mm.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: mm				
arithmetic mean (standard deviation)	4.648 (± 24.315)	-8.010 (± 25.980)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Patient's global assessment of disease activity

End point title	Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Patient's global assessment of disease activity
End point description: Scored on a Visual Analogue Scale (VAS) from 0 to 10 cm.	
End point type	Secondary
End point timeframe: Baseline to Week 24	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: cm				
arithmetic mean (standard deviation)	0.280 (± 2.000)	-0.153 (± 1.506)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Physician's Global Assessment of Disease Activity

End point title	Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Physician's Global Assessment of Disease Activity
End point description: Scored on a Visual Analogue Scale (VAS) from 0 to 10 cm.	
End point type	Secondary
End point timeframe: Baseline to Week 24	

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: cm				
arithmetic mean (standard deviation)	0.345 (± 1.463)	-0.248 (± 1.167)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Health Assessment Questionnaire–Disability Index (HAQ-DI)

End point title	Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Health Assessment Questionnaire–Disability Index (HAQ-DI)

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Questionnaire score				
arithmetic mean (standard deviation)	0.167 (± 0.486)	-0.087 (± 0.527)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: High Sensitivity C-Reactive Protein (hsCRP)

End point title	Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: High Sensitivity C-Reactive Protein (hsCRP)

End point description:

End point type	Secondary

End point timeframe:
Baseline to Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: mg/dL				
arithmetic mean (standard deviation)	-0.135 (± 1.470)	-0.040 (± 0.277)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Erythrocyte Sedimentation Rate (ESR)

End point title	Changes from baseline in American College of Rheumatology (ACR) core set components at Week 24: Erythrocyte Sedimentation Rate (ESR)

End point description:

End point type	Secondary

End point timeframe:
Baseline to Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: mm/hr				
arithmetic mean (standard deviation)	1.517 (± 7.892)	-0.679 (± 5.433)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in Rheumatoid Arthritis Impact of Disease (RAID) Final score

End point title	Changes from baseline in Rheumatoid Arthritis Impact of Disease (RAID) Final score

End point description:

The RAID is a participant-completed questionnaire specific for RA consisting of a 1-10 rating for pain, functional disability, fatigue, sleep, physical well-being, emotional well-being and coping. Scores are weighted to produce a final numerical result.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Questionnaire Score				
arithmetic mean (standard deviation)	0.469 (± 2.109)	-0.220 (± 1.940)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) score

End point title	Changes from baseline in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) score

End point description:

The WPAI:SHP is a 6-item questionnaire evaluating the effect of the underlying disease or condition on the participant’s ability to work and perform regular activities

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Tocilizumab+prednisone (tapering dose)	Tocilizumab+prednisone (constant dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	128		
Units: Percent				
arithmetic mean (standard deviation)				
Percent work time missed due to problem	4.535 (± 23.283)	0.572 (± 31.455)		
Percent impairment while working due to problem	-0.851 (± 24.920)	-5.584 (± 23.343)		

Percent overall work impairment due to problem	6.219 (± 29.223)	-6.191 (± 30.531)		
Percent activity impairment due to problem	3.398 (± 23.786)	-4.190 (± 21.608)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization to Week 28

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Tocilizumab+prednisone (constant dose)

Reporting group description:

Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously; and prednisone at a dose of 5 milligram per day (mg/day) or matching placebo orally for 24 weeks.

Reporting group title	Tocilizumab+prednisone (tapering dose)

Reporting group description:

Participants will receive tocilizumab at a dose of 162 milligram (mg) once a week subcutaneously; and prednisone at a dose of 5 milligram per day (mg/day) with 1 mg decrements every 4 weeks or matching placebo orally for 24 weeks.

Serious adverse events	Tocilizumab+prednisone (constant dose)	Tocilizumab+prednisone (tapering dose)	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 128 (3.13%)	7 / 131 (5.34%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
BLOOD GLUCOSE FLUCTUATION			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

SCIATICA			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
PSYCHOTIC DISORDER			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
SPINAL COLUMN STENOSIS			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

PNEUMONIA			
subjects affected / exposed	1 / 128 (0.78%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS GANGRENOUS			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 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+prednisone (constant dose)	Tocilizumab+prednisone (tapering dose)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 128 (16.41%)	46 / 131 (35.11%)	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 128 (2.34%)	9 / 131 (6.87%)	
occurrences (all)	3	10	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 128 (1.56%)	9 / 131 (6.87%)	
occurrences (all)	2	10	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	5 / 128 (3.91%)	7 / 131 (5.34%)	
occurrences (all)	5	7	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 128 (1.56%)	8 / 131 (6.11%)	
occurrences (all)	2	12	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	9 / 128 (7.03%)	13 / 131 (9.92%)	
occurrences (all)	12	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2015	Open-label prednisone tablets were to be offered during the 4 weeks preceding randomization for patients in both tracks and provided for the treatment of any flare following randomization (during the 24-week Tapering Phase); To facilitate the conduct and analysis of NSAIDs use, NSAID average use was captured as mean daily intake by considering the number of days on which NSAIDs had been taken during a period of interest (at screening, Week 12, and Week 24);Increasing the dose of NSAIDs during a flare was discouraged to minimize any confounding effect of NSAID use; In order to minimize screen failures due to temporary ailments or abnormalities, patients could be re-screened or re-tested, depending on the inclusion/exclusion criteria they failed, if authorized by the Sponsor; Timing of assessments of immunogenicity was clarified so that immunogenicity sampling was event-driven and therefore only patients who experienced anaphylaxis or other hypersensitivity reaction were evaluated at the time of the event and 8 weeks after, as part of standard immunogenicity sampling protocol.
22 June 2016	Amendment based on requests from the iDMC, investigator feedback, updated internal guidance and definitions, newly identified errata and updates to the IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported