EU Clinical Trials Register

Clinical trial results:
A Phase II/III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study To Assess the Efficacy and Safety of Tocilizumab Versus Placebo In Patients With Systemic Sclerosis

Summary

EudraCT number	2011-001460-22
Trial protocol	GB DE
Global end of trial date	16 June 2015

Results information

Result version number	v1
This version publication date	06 March 2016
First version publication date	06 March 2016

Trial information

Trial identification

Sponsor protocol code	WA27788

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01532869
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
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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	Interim
Date of interim/final analysis	11 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study was designed to evaluate the efficacy and safety of tocilizumab (TCZ) at a subcutaneous (SC) dose of 162 milligrams (mg) for 96 weeks (48 weeks of blinded-treatment period and another 48 weeks of open-label period) in participants with systemic sclerosis.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 2012
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	United Kingdom: 19
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	87
EEA total number of subjects	46

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)	74

From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The randomization of participants were stratified by joint involvement at baseline (>=4 or <4 tender joints of 28 tender joint count [TJC]). The study consisted of 2 treatment period: Blinded-treatment (first 48 weeks) and Open-label (another 48 weeks) period. The data analyzed up to Week 24 and 48 (data cut-off, 11 July 2014) were reported here.

Period 1

Period 1 title	Blinded-Treatment Period (Up to Week 24)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Up to Week 24)

Arm description:

Participants received TCZ matched placebo by SC injection every week (qw) for up to 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

TCZ matched placebo was administered SC qw for 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks.

Arm title	Tocilizumab (Up to Week 24)

Arm description:

Participants received TCZ (162 mg) by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks.

Arm type	Experimental
Investigational medicinal product name	TCZ
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

TCZ was administered at a dose of 162 mg by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks.

Number of subjects in period 1	Placebo (Up to Week 24)	Tocilizumab (Up to Week 24)
Started	44	43
Completed	36	35
Not completed	8	8
Adverse event, non-fatal	2	3
Death	-	1
Non-compliance	1	-
Lost to follow-up	-	1
Lack of efficacy	1	1
Withdrawal by subject	4	2

Period 2

Period 2 title	Blinded-Treatment Period (Up to Week 48)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Placebo (Up to Week 48)

Arm description:

Participants received TCZ matched placebo by SC injection every week (qw) for up to 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

TCZ matched placebo was administered SC qw for 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks.

Arm title	Tocilizumab (Up to Week 48)

Arm description:

Participants received TCZ (162 mg) by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks.

Arm type	Experimental
Investigational medicinal product name	TCZ
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

TCZ was administered at a dose of 162 mg by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks.

Number of subjects in period 2	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)
Started	44	43
Completed	33	30
Not completed	11	13
Physician decision	1	-
Adverse event, non-fatal	4	5
Death	-	3
Non-compliance	1	-
Lost to follow-up	-	1
Withdrawal by subject	5	3
Lack of efficacy	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo (Up to Week 24)

Reporting group description:

Participants received TCZ matched placebo by SC injection every week (qw) for up to 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks.

Reporting group title	Tocilizumab (Up to Week 24)

Reporting group description:

Participants received TCZ (162 mg) by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks.

Reporting group values	Placebo (Up to Week 24)	Tocilizumab (Up to Week 24)	Total
Number of subjects	44	43	87
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	48.1	51.2	
standard deviation	± 12.9	± 11.7	-
Gender categorical			
Units: Subjects			
Female	35	32	67
Male	9	11	20

End points

End points reporting groups

Reporting group title	Placebo (Up to Week 24)
Reporting group description:	
Participants received TCZ matched placebo by SC injection every week (qw) for up to 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks.	
Reporting group title	Tocilizumab (Up to Week 24)
Reporting group description:	
Participants received TCZ (162 mg) by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks.	
Reporting group title	Placebo (Up to Week 48)
Reporting group description:	
Participants received TCZ matched placebo by SC injection every week (qw) for up to 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks.	
Reporting group title	Tocilizumab (Up to Week 48)
Reporting group description:	
Participants received TCZ (162 mg) by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks.	

Primary: Change From Baseline in Modified Rodnan Skin Score (mRSS) at Week 24

End point title	Change From Baseline in Modified Rodnan Skin Score (mRSS) at Week 24
End point description:	
Skin thickness was assessed by the mRSS. The mRSS was rated with scores ranging from 0 (normal) to 3 (severe skin thickening) across 17 different sites. The total score was the sum of the individual skin scores in the 17 body areas (e.g., face, hands, fingers; proximal area of the arms, distal area of the arms, thorax, abdomen; proximal area of the legs, and distal area of the legs, feet), giving a range of 0–51 units and had been validated for participants with systemic sclerosis (SSc). A negative change from baseline showed improvement. Intent-to-treat (ITT) population included all participants randomized who had received any study drug at the time of the Week 24 cutoff date (14 January 2014). Here, number of participants analyzed included only those participants who were evaluable for this outcome measure at any time point up to Week 24.	
End point type	Primary
End point timeframe:	
Baseline, and Week 24	

End point values	Placebo (Up to Week 24)	Tocilizumab (Up to Week 24)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	41		
Units: units on a scale				
least squares mean (confidence interval 95%)	-1.22 (-3.42 to 0.98)	-3.92 (-6.17 to -1.67)		

Statistical analyses

Statistical analysis title	Change From Baseline in mRSS at Week 24
Comparison groups	Placebo (Up to Week 24) v Tocilizumab (Up to Week 24)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0915
Method	Mixed models analysis
Parameter estimate	Difference in Least Square (LS) mean
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.85
upper limit	0.45

Primary: Percentage of Participants With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

An AE was any untoward medical occurrence attributed to study drug in a participant who received study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to Week 8 after last dose that were absent before treatment or that worsened relative to pretreatment state. Safety population included all participants who received any study drug and provided at least one post-dose safety assessment (withdrawal, AE, death, laboratory assessment, vital signs).

End point type	Primary

End point timeframe:

up to Week 48

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: percentage of participants				
number (not applicable)				
Treatment-emergent AEs	90.9	97.7		
Treatment-emergent SAEs	34.1	32.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physical Function Assessed by Scleroderma Health Assessment Questionnaire Disability Index (SHAQ-DI)

End point title	Change From Baseline in Physical Function Assessed by Scleroderma Health Assessment Questionnaire Disability Index (SHAQ-DI)

End point description:

SHAQ-DI assessed five scleroderma-specific visual analogue scale (VAS) items to explore the impact of participant's disease. These items were developed to measure the effect of scleroderma on five elements of disease that could have a great impact on a participant's daily activities. Each VAS item was rated separately (0−100 millimeters [mm]), with higher scores indicating more severe disease. The five items were: 1) intestinal disease, 2) breathing problem, 3) Raynaud syndrome, 4) finger ulcers, and 5) overall disease. ITT population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure and "n" included those who were evaluable for the specific item at specified time point in specified timeframe.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: mm				
least squares mean (confidence interval 95%)				
Week 24: Intestinal VAS Score (n=42, 41)	5.81 (-1.43 to 13.06)	5.38 (-1.98 to 12.74)		
Week 24: Breathing VAS Scores (n=42, 41)	8.54 (0.81 to 16.27)	4.42 (-3.47 to 12.31)		
Week 24: Raynaud syndrome (n=42, 41)	2.41 (-6.96 to 11.78)	1.13 (-8.47 to 10.73)		
Week 24: Finger ulcers VAS Score (n=42, 41)	9.2 (-0.22 to 18.61)	14.09 (4.45 to 23.73)		
Week 24: Overall disease (n=42, 41)	1.89 (-4.99 to 8.77)	1.81 (-5.21 to 8.84)		
Week 48: Intestinal VAS Score (n=41, 41)	7.91 (-0.37 to 16.18)	1.11 (-6.88 to 9.1)		
Week 48: Breathing VAS Scores (n=41, 41)	0.55 (-7.09 to 8.19)	2.09 (-5.39 to 9.57)		
Week 48: Raynaud syndrome (n=41, 41)	0.3 (-9.51 to 10.12)	-4.18 (-13.87 to 5.51)		
Week 48: Finger ulcers VAS Score (n=41, 41)	4.97 (-3.15 to 13.1)	-0.83 (-8.83 to 7.17)		
Week 48: Overall disease (n=41, 41)	3.46 (-4.5 to 11.41)	-4.36 (-12.27 to 3.55)		

Statistical analyses

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Intestinal VAS Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9336
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.78
upper limit	9.91

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Breathing VAS Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4609
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-4.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.21
upper limit	6.96

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Raynaud Syndrome Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8493
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	12.13

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Finger Ulcers Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4717
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	4.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.59
upper limit	18.37

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Overall Disease Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9876
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-0.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.93
upper limit	9.78

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Intestinal VAS Score at Week 48. A total of 82 participants were included in analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medication, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.2407
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.3
upper limit	4.71

Notes:

[2] - The analysis included fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at baseline visit, and treatment-by-visit interaction, as well as continuous covariates of baseline score and baseline score-by-visit interaction.

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Breathing VAS Score at Week 48. A total of 82 participants were included in analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medications, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.7742
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.18
upper limit	12.26

Notes:

[3] - The analysis included fixed, categorical effects of treatment, visit, stratification factor of joint involvement at baseline visit, and treatment-by-visit interaction, as well as continuous covariates of baseline score and baseline score-by-visit interaction.

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Raynaud Syndrome Score at Week 48. A total of 82 participants were included in the analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medication, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.5182
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-4.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.28
upper limit	9.31

Notes:

[4] - The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Finger Ulcers Score at Week 48. A total of 82 participants were included in the analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medication, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.3106
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.2
upper limit	5.59

Notes:

[5] - The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Statistical analysis title	Physical Function Assessed by SHAQ-DI

Statistical analysis description:

Change From Baseline in Overall Disease Score at Week 48. A total of 82 participants were included in

the

analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medication, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.1717
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-7.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.11
upper limit	3.48

Notes:

[6] - The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Secondary: Change From Baseline in HAQ-DI Score at Week 24 and Week 48

End point title	Change From Baseline in HAQ-DI Score at Week 24 and Week 48

End point description:

The HAQ-DI scale consisted of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. The total score indicated the participant's self-assessed level of disability. There were four possible responses for each component: 0 = without any difficulty; 1 = with some difficulty; 2 = with much difficulty; 3 = unable to do. The HAQ-DI was the sum of the domain scores, divided by the number of domains that had a score (i.e. the average score), with total range of 0 to 3, higher scores showing larger functional limitation. ITT population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure and "n" included those who were evaluable for the specific item at specified time point in specified time frame.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 24 (n=42, 41)	0.118 (-0.026 to 0.262)	0.137 (-0.01 to 0.285)		
Week 48 (n=41, 41)	0.205 (0.017 to 0.393)	-0.002 (-0.188 to 0.183)		

Statistical analyses

Statistical analysis title	HAQ-DI Score at Week 24

Statistical analysis description:

Change From Baseline in HAQ-DI Score at Week 24. A total of 82 participants were included in the analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medication, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.8503
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.186
upper limit	0.225

Notes:

[7] - The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Statistical analysis title	HAQ-DI Score at Week 48

Statistical analysis description:

Change From Baseline in HAQ-DI Score at Week 48. A total of 82 participants were included in the analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medication, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.1212
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.71
upper limit	0.056

Notes:

[8] - The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Secondary: Change From Baseline in Clinician's Global Assessment at Week 24 and Week 48

End point title	Change From Baseline in Clinician's Global Assessment at Week 24 and Week 48

End point description:

The Clinician's Global Assessment evaluated the overall impact of SSc on the participant as assessed by

the physician on a VAS with scores ranging from 0 to 100 mm, with higher scores indicating worse disease in terms of severity, damage, or overall disease, but there was no standardization for the scale.ITT population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure and "n" included those who were evaluable for the specific item at specified time point.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 24 and 48	

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: mm				
least squares mean (confidence interval 95%)				
Week 24 (n=41, 39)	-7.25 (-12.99 to -1.51)	-8.24 (-14.06 to -2.41)		
Week 48 (n=41, 40)	-9.39 (-16.66 to -2.12)	-18.41 (-25.3 to -11.52)		

Statistical analyses

Statistical analysis title	Clinician's Global Assessment at Week 24 and 48
Statistical analysis description:	
Change From Baseline in Clinician's Global Assessment at Week 24.The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.	
Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8118
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	7.23

Statistical analysis title	Clinician's Global Assessment at Week 24 and 48
Statistical analysis description:	
Change From Baseline in Clinician's Global Assessment at Week 48. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit,	

and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0768
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-9.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.04
upper limit	1

Secondary: Change From Baseline in Patient's Global Assessment at Week 24 and Week 48

End point title	Change From Baseline in Patient's Global Assessment at Week 24 and Week 48

End point description:

The Patient's Global Assessment was a patient's reported outcome that represented the participant's overall assessment of his or her current SSc on a 100 mm horizontal VAS scale (0 mm to 100 mm), with higher scores indicating worsening disease. ITT population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure and "n" included those who were evaluable for the specific item at specified time point in specified time frame.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: mm				
least squares mean (confidence interval 95%)				
Week 24 (n=42, 42)	1.53 (-4.93 to 7.98)	-2.33 (-8.87 to 4.22)		
Week 48 (n=41, 42)	-2.7 (-10.56 to 5.16)	-11 (-18.69 to -3.31)		

Statistical analyses

Statistical analysis title	Patient's Global Assessment at Week 24 and 48

Statistical analysis description:

Change From Baseline in Patient's Global Assessment at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4063
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-3.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.04
upper limit	5.34

Statistical analysis title	Patient's Global Assessment at Week 24 and 48

Statistical analysis description:

Change From Baseline in Patient's Global Assessment at Week 48. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1371
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.31
upper limit	2.71

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy−Fatigue (FACIT-Fatigue) Score at Week 24 and Week 48

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy−Fatigue (FACIT-Fatigue) Score at Week 24 and Week 48

End point description:

This FACIT-Fatigue Scale was a 13-item measure with participants scoring each item on a 5-point scale (0 to 4) up to 52 points. The endpoint measured was fatigue. On this scale, a numerical increase indicated an improvement in the participant's condition. ITT population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure and "n" included those who were evaluable for the specific item at specified time point in specified time frame.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	42		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 24 (n=41, 42)	1.26 (-1.85 to 4.37)	2.68 (-0.41 to 5.77)		
Week 48 (n=40, 42)	0.36 (-2.64 to 3.37)	3.11 (0.28 to 5.95)		

Statistical analyses

Statistical analysis title	FACIT-Fatigue Score at Week 24 and 48

Statistical analysis description:

Change From Baseline in FACIT-Fatigue Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5197
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	5.82

Statistical analysis title	FACIT-Fatigue Score at Week 24 and 48

Statistical analysis description:

Change From Baseline in FACIT-Fatigue Score at Week 48. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1886
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	2.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.38
upper limit	6.88

Secondary: Change From Baseline in 5-D Itch Scale at Week 24 and Week 48

End point title	Change From Baseline in 5-D Itch Scale at Week 24 and Week 48

End point description:

The 5-D Itch Scale contained five domains of duration, degree, direction, disability, and distribution. The endpoint of the scale was pruritus. Each domain was scored on a 5-point scale, the scores of each of the five domains were achieved separately and then summed together to obtain a total 5-D score. 5-D scores ranged between 5 (no pruritus) and 25 (most severe pruritus). ITT population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure and "n" included those who were evaluable for the specific item at specified time point in specified time frame.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	41		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 24 (n=41, 41)	-1.73 (-2.95 to -0.5)	-0.94 (-2.15 to 0.28)		
Week 48 (n=40, 41)	-1.08 (-2.6 to 0.43)	-2.19 (-3.58 to -0.8)		

Statistical analyses

Statistical analysis title	5-D Itch Scale at Week 24 and Week 48

Statistical analysis description:

Change From Baseline in 5-D Itch Scale at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit

interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3651
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	2.51

Statistical analysis title	5-D Itch Scale at Week 24 and Week 48

Statistical analysis description:

Change From Baseline in 5-D Itch Scale at Week 48. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2841
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.16
upper limit	0.94

Secondary: Change From Baseline in mRSS at Week 48

End point title	Change From Baseline in mRSS at Week 48

End point description:

Skin thickness was assessed by the mRSS. The mRSS was rated with scores ranging from 0 (normal) to 3 (severe skin thickening) across 17 different sites. The total score was the sum of the individual skin scores in the 17 body areas (e.g., face, hands, fingers; proximal area of the arms, distal area of the arms, thorax, abdomen; proximal area of the legs, and distal area of the legs, feet), giving a range of 0–51 units and had been validated for participants SSc. A negative change from baseline showed improvement. ITT population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure at specified time point up to 48 weeks.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	41		
Units: units on a scale				
least squares mean (confidence interval 95%)	-2.77 (-5.44 to -0.11)	-6.33 (-8.86 to -3.79)		

Statistical analyses

Statistical analysis title	Change From Baseline in mRSS at Week 48

Statistical analysis description:

The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0579
Method	Mixed models analysis
Parameter estimate	Difference in LS mean
Point estimate	-3.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.23
upper limit	0.12

Secondary: Percentage of Participants Who Maintained or Improved in mRSS From Week 24 to Week 48

End point title	Percentage of Participants Who Maintained or Improved in mRSS From Week 24 to Week 48

End point description:

Skin thickness was assessed by the mRSS. The mRSS was rated with scores ranging from 0 (normal) to 3 (severe skin thickening) across 17 different sites. The total score was the sum of the individual skin scores in the 17 body areas (e.g., face, hands, fingers; proximal area of the arms, distal area of the arms, thorax, abdomen; proximal area of the legs, and distal area of the legs, feet), giving a range of 0–51 units and had been validated for participants with SSc. A negative change from baseline showed improvement. Percentage of participants with an improvement in mRSS at Week 24 (change from baseline <0) that maintained or further improved at Week 48 were reported as "Yes" and "No" with Yes = improvers at Week 24 that had a change from baseline in MRSS at Week 48 <= change from baseline at Week 24. ITT population. Here number of participants analyzed included those with mRSS change from baseline <0 at Week 24 and with non-missing change from baseline in mRSS at Week 48.

End point type	Secondary

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	41		
Units: percentage of participants				
number (not applicable)	44.4	68.2		

Statistical analyses

Statistical analysis title	Improvement in mRSS From Week 24 to 48
Statistical analysis description:	
Percentage of Participants Who Maintained or Improved in mRSS From Week 24 to Week 48. The logistic regression model included the fixed categorical effects of treatment and the stratification factor of joint involvement at the baseline visit. The continuous covariate of baseline mRSS score was also included in the model.	
Comparison groups	Placebo (Up to Week 48) v Tocilizumab (Up to Week 48)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2159
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	9.5
Variability estimate	Standard error of the mean
Dispersion value	0.704

Secondary: Change From Baseline in Tender Joint Count 28 (TJC28)

End point title	Change From Baseline in Tender Joint Count 28 (TJC28)
End point description:	
Joint tenderness was evaluated as per assessment of 28 joints. Joints on both sides of the body, including shoulders, elbows, wrists, 10 metacarpal phalangeal (MCP) joints, 10 proximal interphalangeal joint (PIP) joints, and both knees, were assessed. Joints were classified as not tender = 0 or tender = 1. ITT population. Here n = evaluable for the specific item at specified time point in specified time frame.	
End point type	Secondary

End point timeframe:

Baseline, Weeks 3, 8, 16, 24, 32, 40, and 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: joint count				
arithmetic mean (standard deviation)				
Week 3 (n=20, 19)	-2.75 (± 4.27)	-2.32 (± 5.55)		
Week 8 (n=18, 19)	-3.06 (± 6.67)	-4 (± 6.16)		
Week 16 (n=18, 17)	-3.5 (± 6)	-3.65 (± 7.59)		
Week 24 (n=17, 16)	-2.06 (± 6.28)	-4.31 (± 7.34)		
Week 32 (n=12, 11)	-3.33 (± 6.62)	-3.18 (± 7.4)		
Week 40 (n=10, 10)	-3.8 (± 6.76)	-4.3 (± 8.23)		
Week 48 (n=12, 10)	-2.92 (± 7.08)	-5.1 (± 7.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve (AUC) From Time 0 to 168 Hour (AUC0-168)

End point title	Area Under the Concentration-Time Curve (AUC) From Time 0 to 168 Hour (AUC0-168)[9]

End point description:

AUC was a measure of the serum concentration of the drug over time which was measured in micrograms times (*) hour per milliliter (μg*hr/mL). It is used to characterize drug absorption. Pharmacokinetic (PK) population included all participants who received at least one TCZ injection and had at least one PK sample with detectable results. Here, "n" = participants evaluable for the specific item at specified time point in specified time frame.

End point type	Secondary

End point timeframe:

Pre-dose, 24, 48, 72, 96, 120 or 144, and 168 hours post dose for Baseline and Week 16

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data for placebo group was not collected as it was not planned to measure AUC for placebo.

End point values	Tocilizumab (Up to Week 24)			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: μg*hr/mL				
arithmetic mean (standard deviation)				
Baseline (n=7)	686 (± 455)			
Week 16 (n=4)	7508 (± 2369)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Serum Concentrations of Interleukin (IL)-6 by Visit

End point title	Mean Serum Concentrations of Interleukin (IL)-6 by Visit

End point description:

Observed data was presented for this outcome measure. Safety population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure and "n" included those who were evaluable for the specific item at specified time point in specified time frame.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 3, 8, 16, 24, and 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: picograms per milliliters (pg/mL)				
arithmetic mean (standard deviation)				
Baseline (n=43, 42)	15.02 (± 18.19)	13.57 (± 14.69)		
Week 1: Absolute values (n=43, 43)	17.24 (± 22.77)	158.91 (± 326.42)		
Week 1: Change From Baseline (n=42, 42)	1.33 (± 27.29)	147.37 (± 326.2)		
Week 2: Absolute values (n=43, 41)	12.6 (± 13.78)	107.1 (± 73.75)		
Week 2: Change From Baseline (n=42, 40)	-3.07 (± 17.85)	94.54 (± 67.99)		
Week 3: Absolute values (n=42, 40)	12.47 (± 10.72)	116.58 (± 75.31)		
Week 3: Change From Baseline (n=41, 39)	-3.6 (± 15.28)	104.44 (± 71.84)		
Week 8: Absolute values (n=42, 39)	15.39 (± 19.04)	115.31 (± 66.39)		
Week 8: Change From Baseline(n=41,38)	0.15 (± 18.65)	104.14 (± 62.95)		
Week 16: Absolute values (n=32,33)	12.51 (± 14.06)	98.36 (± 61.65)		
Week 16: Change From Baseline (n=31,32)	-1.26 (± 11.34)	88.86 (± 59.77)		
Week 24: Absolute values (n=36,34)	10.19 (± 10.55)	84.67 (± 68.37)		
Week 24: Change From Baseline(n=35,33)	-2.74 (± 12.43)	73.61 (± 68.07)		

Week 48: Absolute values (n=32,27)	10.5 (± 11.82)	65.3 (± 35.95)	
Week 48: Change From Baseline (n=31,26)	-2.61 (± 14.92)	55.6 (± 35.86)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Serum Concentrations of Soluble IL-6 Receptor (R) by Visit

End point title	Mean Serum Concentrations of Soluble IL-6 Receptor (R) by Visit

End point description:

Observed data was presented for this outcome measure. Safety population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure and "n" included those who were evaluable for the specific item at specified time point in specified time frame.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 3, 8, 16, 24, and 48

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline (n=44, 42)	37.61 (± 11.12)	39.39 (± 10.16)		
Week 1: Absolute values (n=44, 43)	51.03 (± 59.12)	237.34 (± 71.38)		
Week 1: Change From Baseline (n=44, 42)	13.42 (± 57.91)	198.39 (± 69.41)		
Week 2: Absolute values (n=43, 41)	44.07 (± 42.15)	329.9 (± 81.93)		
Week 2: Change From Baseline (n=43, 40)	6.13 (± 41.6)	291.38 (± 79.29)		
Week 3: Absolute values (n=44, 40)	41.64 (± 27.07)	384.88 (± 99.41)		
Week 3: Change From Baseline (n=44, 39)	4.03 (± 26)	346.68 (± 95.96)		
Week 8: Absolute values (n=42, 39)	38.66 (± 11.95)	486.62 (± 116.41)		
Week 8: Change From Baseline (n=42, 38)	0.91 (± 5.07)	447.77 (± 114.4)		
Week 16: Absolute values (n=32, 33)	37.71 (± 10.3)	525.48 (± 164.9)		
Week 16: Change From Baseline (n=32, 32)	-0.08 (± 5.71)	486.43 (± 163.32)		
Week 24: Absolute values (n=36, 34)	38.72 (± 13.06)	520.18 (± 167.97)		

Week 24: Change From Baseline (n=36, 33)	1.11 (± 6.47)	482.1 (± 168.44)	
Week 48: Absolute values (n=32, 27)	36.52 (± 9.93)	491.44 (± 164.82)	
Week 48: Change From Baseline (n=32, 26)	-0.75 (± 5.2)	454.19 (± 163.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Tocilizumab Antibody

End point title	Percentage of Participants With Anti-Tocilizumab Antibody

End point description:

Safety population. Here, number of participants analyzed included only those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, and post-baseline (up to Week 48)

End point values	Placebo (Up to Week 48)	Tocilizumab (Up to Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: percentage of participants				
number (not applicable)				
Baseline	7	2.4		
Post-Baseline	0	2.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Up to Week 48 (data cut-off date of 11 July 2014)	
Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo (up to 24 Weeks)

Reporting group description:

Participants received TCZ matched placebo by SC injection qw for up to 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks. The data analyzed for placebo up to Week 24 was presented in this arm group.

Reporting group title	Tocilizumab (up to 24 Weeks)

Reporting group description:

Participants received TCZ (162 mg) by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks. The data analyzed for TCZ up to Week 24 was presented in this arm group.

Reporting group title	Placebo (up to 48 Weeks)

Reporting group description:

Participants received TCZ matched placebo by SC injection qw for up to 48 weeks (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for another 48 weeks. The data analyzed for placebo up to Week 48 was presented in this arm group.

Reporting group title	Tocilizumab (up to 48 Weeks)

Reporting group description:

Participants received TCZ (162 mg) by SC injection qw for up to 48 weeks (blinded-treatment period) and then in the open-label period for another 48 weeks. The data analyzed for TCZ up to Week 48 was presented in this arm group.

Serious adverse events	Placebo (up to 24 Weeks)	Tocilizumab (up to 24 Weeks)	Placebo (up to 48 Weeks)
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 44 (25.00%)	9 / 43 (20.93%)	15 / 44 (34.09%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Raynaud's phenomenon

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders

Acute myocardial infarction

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Cyanosis

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arrhythmia

subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrioventricular block

subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders

Headache

subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Subarachnoid haemorrhage

subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colonic pseudo-obstruction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal fibrosis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma renal crisis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Scleroderma			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic sclerosis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 44 (0.00%)	2 / 43 (4.65%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tocilizumab (up to 48 Weeks)		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 43 (32.56%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive emergency			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Raynaud's phenomenon			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders

Acute myocardial infarction			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac failure			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cyanosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Arrhythmia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Atrioventricular block			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders

Headache			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Subarachnoid haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Colonic pseudo-obstruction			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric antral vascular ectasia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal distension			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal fibrosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scleroderma renal crisis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Scleroderma			

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Systemic sclerosis				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Osteomyelitis				
subjects affected / exposed	2 / 43 (4.65%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected skin ulcer				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Oesophageal candidiasis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural cellulitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo (up to 24 Weeks)	Tocilizumab (up to 24 Weeks)	Placebo (up to 48 Weeks)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 44 (59.09%)	28 / 43 (65.12%)	32 / 44 (72.73%)
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	1 / 44 (2.27%)	3 / 43 (6.98%)	2 / 44 (4.55%)
occurrences (all)	1	3	2
Hypertension			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	3 / 44 (6.82%)
occurrences (all)	0	0	3
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 44 (4.55%)	3 / 43 (6.98%)	2 / 44 (4.55%)
occurrences (all)	2	3	2
Headache			
subjects affected / exposed	2 / 44 (4.55%)	3 / 43 (6.98%)	3 / 44 (6.82%)
occurrences (all)	2	5	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 43 (0.00%)	3 / 44 (6.82%)
occurrences (all)	3	0	3
Fatigue			
subjects affected / exposed	2 / 44 (4.55%)	4 / 43 (9.30%)	2 / 44 (4.55%)
occurrences (all)	2	7	2
Oedema peripheral			
subjects affected / exposed	1 / 44 (2.27%)	3 / 43 (6.98%)	1 / 44 (2.27%)
occurrences (all)	1	3	1
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 44 (0.00%)	3 / 43 (6.98%)	0 / 44 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			
subjects affected / exposed	4 / 44 (9.09%)	6 / 43 (13.95%)	4 / 44 (9.09%)
occurrences (all)	4	7	4
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 44 (9.09%)	4 / 43 (9.30%)	5 / 44 (11.36%)
occurrences (all)	4	4	5
Vomiting			
subjects affected / exposed	0 / 44 (0.00%)	3 / 43 (6.98%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Dyspepsia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	3 / 44 (6.82%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	3 / 44 (6.82%)
occurrences (all)	0	0	5
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	4 / 44 (9.09%)	2 / 43 (4.65%)	3 / 44 (6.82%)
occurrences (all)	4	2	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 44 (6.82%)	7 / 43 (16.28%)	4 / 44 (9.09%)
occurrences (all)	3	8	4
Skin ulcer			
subjects affected / exposed	6 / 44 (13.64%)	6 / 43 (13.95%)	7 / 44 (15.91%)
occurrences (all)	7	15	11
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	3 / 44 (6.82%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 44 (13.64%)	6 / 43 (13.95%)	8 / 44 (18.18%)
occurrences (all)	7	6	11
Back pain			
subjects affected / exposed	3 / 44 (6.82%)	5 / 43 (11.63%)	3 / 44 (6.82%)
occurrences (all)	4	5	4
Pain in extremity			
subjects affected / exposed	1 / 44 (2.27%)	5 / 43 (11.63%)	2 / 44 (4.55%)
occurrences (all)	1	5	2
Infections and infestations			
Infected skin ulcer			
subjects affected / exposed	5 / 44 (11.36%)	0 / 43 (0.00%)	5 / 44 (11.36%)
occurrences (all)	6	0	7
Nasopharyngitis			
subjects affected / exposed	2 / 44 (4.55%)	3 / 43 (6.98%)	4 / 44 (9.09%)
occurrences (all)	3	3	5
Urinary tract infection			
subjects affected / exposed	3 / 44 (6.82%)	2 / 43 (4.65%)	3 / 44 (6.82%)
occurrences (all)	3	2	3
Herpes zoster			

subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	6 / 44 (13.64%)
occurrences (all)	0	0	8

Non-serious adverse events	Tocilizumab (up to 48 Weeks)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 43 (79.07%)		
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Hypertension			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	7		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	9		
Oedema peripheral			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal Pain			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	9		
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 43 (18.60%)		
occurrences (all)	9		
Skin ulcer			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	17		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	6		

Back pain			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	7		
Infections and infestations			
Infected skin ulcer			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Herpes zoster			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2012	- To clarify that participants were required to have uninvolved skin at at least one of 3 locations to ensure application of SC study drug in uninvolved skin. The area for SC injection had been expanded in one area from the lower abdomen to the entire abdomen except for the 2-inch area directly around the navel. - To add a lipid panel at Week 8. - To clarify that investigators must draw immunogenicity labs in participants with hypersensitivity reactions leading to withdrawal from study drug, not just in the case of serious hypersensitivity leading to withdrawal from study drug. - To clarify that Sponsor company requested a review of liver biopsy slides and report if the investigator deemed a liver biopsy necessary but Sponsor company did not request a liver biopsy. The investigators might have deemed a liver biopsy necessary in the management of persistently elevated liver enzymes. In that case, Sponsor company was requesting a biopsy report and slides of the biopsied tissue.
02 November 2012	- To remove recruitment barriers to allow for completion and closeout of recruiting for this study. - To provide clarification on the use of SSc medications, including those initiated after baseline, specifically allowing modification of the dose regimen after Week 24 if clinically warranted. - To provide clarification that after the baseline visit, per the Principal Investigator's clinical judgment, if angiotensin-converting enzyme inhibitors, calcium-channel blockers, proton-pump inhibitors, and/or vasodilators need to be initiated for chronic use, the dose regimen should remain stable up to and including Week 24, unless dose adjustments are required for safety reasons or cytochrome P450 (CYP450) interactions. - To allow safety assessments to be done before efficacy assessments if necessary due to clinical assessor availability since this does not compromise data quality and subsequent analysis. - To replace the reporting time frame for serious adverse events, AEs of special interest, and pregnancies from within "1 working day" to "24 hours." - To update safety information from Actemra SC studies as of October 2012.
20 November 2012	- To add back in the Schedule of Sampling from the PK Substudy, which was inadvertently removed from the protocol during the previous amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported