



Clinical trial results:

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients With Systemic Sclerosis

Summary

EudraCT number	2015-000424-28
Trial protocol	DK DE BE LT PT ES HU NL GR HR IE IT
Global end of trial date	04 February 2019

Results information

Result version number	v1 (current)
This version publication date	19 February 2020
First version publication date	19 February 2020

Trial information

Trial identification

Sponsor protocol code	WA29767
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02453256
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 February 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of tocilizumab compared with placebo in subjects with systemic sclerosis (SSc).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Bulgaria: 26
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Japan: 20
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Mexico: 21
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	United States: 39

Worldwide total number of subjects	210
EEA total number of subjects	116

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)	193
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall 212 participants were randomized on to the study, 107 to the placebo arm and 105 to the Tocilizumab arm. One participant in placebo arm withdrew consent prior to receiving any treatment and one participant in the tocilizumab arm was withdrawn due to randomization error prior to receiving any treatment.

Period 1

Period 1 title	Double Blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Placebo, then Open Label Tocilizumab

Arm description:

Participants received double-blind matching placebo from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.

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:

Subjects were administered a subcutaneous (SC) injection of matching placebo once weekly (QW) for 48 weeks during the double-blind period.

Arm title	Double-Blind Tocilizumab, then Open Label Tocilizumab
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Arm description:

Participants received double-blind tocilizumab from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.

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

Dosage and administration details:

Subjects were administered a subcutaneous (SC) injection of tocilizumab 162 mg once weekly (QW) for 48 weeks during the double-blind treatment period.

Number of subjects in period 1	Double-Blind Placebo, then Open Label Tocilizumab	Double-Blind Tocilizumab, then Open Label Tocilizumab
Started	106	104
Completed	93	95
Not completed	13	9
Adverse event, serious fatal	1	1
Consent withdrawn by subject	9	5
Adverse event, non-fatal	3	2
Not Specified	-	1

Period 2

Period 2 title	Open Label Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Placebo, then Open Label Tocilizumab

Arm description:

Participants received double-blind matching placebo from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.

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

Dosage and administration details:

Subjects were administered a subcutaneous (SC) injection of tocilizumab (TCZ) 162 mg once weekly (QW) during the open label period for up to 48 weeks. First dose of open-label TCZ was at Week 48.

Arm title	Double-Blind Tocilizumab, then Open Label Tocilizumab
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Arm description:

Participants received double-blind tocilizumab from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.

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

Dosage and administration details:

Subjects were administered a subcutaneous (SC) injection of tocilizumab (TCZ) 162 mg once weekly (QW) for 48 weeks during the open label period. First dose of open-label TCZ was at Week 48.

Number of subjects in period 2 ^[1]	Double-Blind Placebo, then Open Label Tocilizumab	Double-Blind Tocilizumab, then Open Label Tocilizumab
Started	89	92
Completed	82	85
Not completed	7	7
Adverse event, serious fatal	-	1
Consent withdrawn by subject	5	1
Adverse event, non-fatal	1	3
Not Specified	-	2
Lost to follow-up	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Some participants who completed the double-blind period did not start the open-label period.

Baseline characteristics

Reporting groups

Reporting group title	Double-Blind Placebo, then Open Label Tocilizumab
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Reporting group description:

Participants received double-blind matching placebo from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.

Reporting group title	Double-Blind Tocilizumab, then Open Label Tocilizumab
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Reporting group description:

Participants received double-blind tocilizumab from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.

Reporting group values	Double-Blind Placebo, then Open Label Tocilizumab	Double-Blind Tocilizumab, then Open Label Tocilizumab	Total
Number of subjects	106	104	210
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	49.3 ± 12.6	47.0 ± 12.2	-
Sex: Female, Male Units: Participants			
Female	90	81	171
Male	16	23	39

End points

End points reporting groups

Reporting group title	Double-Blind Placebo, then Open Label Tocilizumab
Reporting group description: Participants received double-blind matching placebo from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.	
Reporting group title	Double-Blind Tocilizumab, then Open Label Tocilizumab
Reporting group description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.	
Reporting group title	Double-Blind Placebo, then Open Label Tocilizumab
Reporting group description: Participants received double-blind matching placebo from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.	
Reporting group title	Double-Blind Tocilizumab, then Open Label Tocilizumab
Reporting group description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Placebo, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind matching placebo from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Tocilizumab, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants then received open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind matching placebo from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Tocilizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Tocilizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Tocilizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Tocilizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	

Subject analysis set title	Double-Blind Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind matching placebo from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind matching placebo from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Placebo, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who received placebo during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Tocilizumab, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who received tocilizumab during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Double-Blind Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind matching placebo from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Double-Blind Tocilizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	
Subject analysis set title	Placebo, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who received placebo during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Tocilizumab, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who received tocilizumab during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Placebo, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who received placebo during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Tocilizumab, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who received tocilizumab during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Double-Blind Tocilizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received double-blind tocilizumab from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.	

Subject analysis set title	Placebo, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who received placebo during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Tocilizumab, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who received tocilizumab during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Placebo, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who received placebo during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	
Subject analysis set title	Tocilizumab, then Tocilizumab Open Label
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who received tocilizumab during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.	

Primary: Change in Modified Rodnan Skin Score (mRSS) During Double-blind Period

End point title	Change in Modified Rodnan Skin Score (mRSS) During Double-blind Period
End point description:	
The efficacy of TCZ vs placebo is evaluated in terms of in mean change in mRSS. Skin thickness will be assessed by palpation and rated using an mRSS that ranges from 0 (normal) to 3 (severe skin thickening) across 17 different body sites. The total score is the sum of the individual skin scores from all of these sites and ranges from 0 to 51 units. The analysis was conducted in the Intent-to-treat (ITT) population, i.e. all participants who were randomized and received any study drug.	
End point type	Primary
End point timeframe:	
From baseline to week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: Units on a scale				
least squares mean (confidence interval 95%)	-4.41 (-5.96 to -2.86)	-6.14 (-7.71 to -4.57)		

Statistical analyses

Statistical analysis title	Placebo versus Tocilizumab
Statistical analysis description:	
Difference in least square means between the TCZ group and the Placebo group at week 48. Null hypothesis: There is no difference between the TCZ group and the placebo group in mean change in mRSS from baseline to Week 48.	
Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0983
Method	Repeated Measure
Parameter estimate	Difference in least square means
Point estimate	-1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.78
upper limit	0.32

Secondary: Percentage of Participants with Greater Than or Equal to (\geq) 20%, 40%, or 60% Improvement in mRSS During Double-blind Period

End point title	Percentage of Participants with Greater Than or Equal to (\geq) 20%, 40%, or 60% Improvement in mRSS During Double-blind Period
End point description:	The proportion of participants with threshold improvements in mRSS at Week 48 relative to baseline. The analysis was conducted in the Intent-to-treat (ITT) population, i.e. all participants who were randomized and received any study drug.
End point type	Secondary
End point timeframe:	From Baseline to Week 48

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: Percentage of Participants				
number (confidence interval 95%)				
$\geq 20\%$	50.0 (40.01 to 59.99)	72.1 (63.02 to 81.21)		
$\geq 40\%$	37.7 (28.04 to 47.44)	42.3 (32.33 to 52.28)		
$\geq 60\%$	22.6 (14.20 to 31.08)	17.3 (9.56 to 25.06)		

Statistical analyses

Statistical analysis title	Placebo versus Tocilizumab
Statistical analysis description:	This statistical analysis applies to participants with $\geq 20\%$ improvement in mRSS.
Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	21.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.2
upper limit	34.6

Statistical analysis title	Placebo versus Tocilizumab
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Statistical analysis description:

This statistical analysis applies to participants with $\geq 40\%$ improvement in mRSS.

Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5139
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	4.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	17.3

Statistical analysis title	Placebo versus Tocilizumab
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Statistical analysis description:

This statistical analysis applies to participants with $\geq 60\%$ improvement in mRSS.

Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3276
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	-5.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	5.4

Secondary: Change from baseline in percent predicted FVC (ppFVC) During Double-blind Period

End point title	Change from baseline in percent predicted FVC (ppFVC) During Double-blind Period
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End point description:

FVC is pulmonary function test and will be conducted as per the study Pulmonary Function Manual, which is based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement. FVC is the maximum amount of air exhaled from the lungs after taking the deepest breath possible. Patients perform three to eight exhalations into a spirometer with the highest value recorded. The analysis was conducted in the Intent-to-treat (ITT) population, i.e. all participants who were randomized and received any study drug.

End point type	Secondary
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End point timeframe:

Baseline to week 48

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: Percent Predicted FVC				
median (confidence interval 95%)	-3.910 (-4.820 to -1.620)	-0.600 (-2.380 to 0.880)		

Statistical analyses

Statistical analysis title	Placebo versus Tocilizumab
Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 ^[1]
Method	Van Elteren

Notes:

[1] - P-value from Van Elteren analysis stratified by IL-6 level (<10; >=10 pg/mL) at screening.

Secondary: Change in Forced Vital Capacity (FVC) During Double-blind Period

End point title	Change in Forced Vital Capacity (FVC) During Double-blind Period
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End point description:

FVC is pulmonary function test and will be conducted as per the study Pulmonary Function Manual, which is based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement. FVC is the maximum amount of air exhaled from the lungs after taking the deepest breath possible. Patients perform three to eight exhalations into a spirometer with the highest value recorded. The analysis was conducted in the Intent-to-treat (ITT) population, i.e. all participants who were randomized and received any study drug.

End point type	Secondary
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End point timeframe:
From Baseline to Week 48

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: Liters of air				
least squares mean (confidence interval 95%)	-0.19 (-0.25 to -0.13)	-0.02 (-0.09 to 0.04)		

Statistical analyses

Statistical analysis title	Placebo versus Tocilizumab
Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Repeated Measure
Parameter estimate	Difference in least square means
Point estimate	0.167
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.083
upper limit	0.25

Secondary: Change in Health Assessment Questionnaire Disability Index (HAQ-DI) Score During Double-blind Period

End point title	Change in Health Assessment Questionnaire Disability Index (HAQ-DI) Score During Double-blind Period
End point description:	<p>The Health Assessment Questionnaire Disability Index (HAQ-DI) consists of 20 questions referring to eight component sets consisting of dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each item is scored on a 4-point scale from 0 to 3: 0 = Without any difficulty; 1 = With some difficulty; 2 = With much difficulty; 3 = Unable to do. Overall score was computed as the sum of component set scores and divided by the number of component sets answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty. The total score indicates the patient's self-assessed level of disability. This outcome measure represents the change in mean score from baseline. A negative change from baseline indicates improvement. The analysis was conducted in the Intent-to-treat (ITT) population, i.e. all participants who were randomized and received any study drug.</p>
End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	-0.06 (-0.16 to 0.05)	-0.11 (-0.22 to -0.01)		

Statistical analyses

Statistical analysis title	Placebo versus Tocilizumab
Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4489
Method	Repeated Measure
Parameter estimate	Difference in least square means
Point estimate	-0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.192
upper limit	0.085

Secondary: Change in Patient Global Assessment Score During Double-blind Period

End point title	Change in Patient Global Assessment Score During Double-blind Period
End point description: The Patient's Global Assessment represents the patient's overall assessment of current SSc status on a 100-mm horizontal visual analogue scale (VAS), ranging from 0 on the extreme left end of the scale indicating "has no effect at all" (symptom free), and 100 on the extreme right end indicating "worst possible effect". The analysis was conducted in the Intent-to-treat (ITT) population, i.e. all participants who were randomized and received any study drug.	
End point type	Secondary
End point timeframe: From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: mm				
least squares mean (confidence interval 95%)	-7.66 (-12.31 to -3.02)	-10.10 (-14.79 to -5.41)		

Statistical analyses

Statistical analysis title	Placebo versus Tocilizumab
Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4339
Method	Repeated Measure
Parameter estimate	Difference in least square means
Point estimate	-2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.57
upper limit	3.7

Secondary: Change in Physician Global Assessment Score During Double-blind Period

End point title	Change in Physician Global Assessment Score During Double-blind Period
End point description: The Physician's Global Assessment is to be completed on the basis of examination and overall assessment of the patient. The physician's assessment of the patient's SSc status will be scored on a 100-mm horizontal visual analogue scale (VAS), ranging from 0 on the extreme left end of the scale indicating "has no effect at all" (symptom free), and 100 on the extreme right end indicating "worst possible effect". The analysis was conducted in the Intent-to-treat (ITT) population, i.e. all participants who were randomized and received any study drug.	
End point type	Secondary
End point timeframe: From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: mm				
least squares mean (confidence interval 95%)	-19.99 (-24.76 to -15.22)	-22.45 (-27.33 to -17.57)		

Statistical analyses

Statistical analysis title	Placebo versus Tocilizumab
Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4378
Method	Repeated Measure
Parameter estimate	Difference in least square means
Point estimate	-2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.72
upper limit	3.79

Secondary: Time to Treatment Failure According to mRSS, FVC, or Protocol-Specified Event During Double-blind Period

End point title	Time to Treatment Failure According to mRSS, FVC, or Protocol-Specified Event During Double-blind Period
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End point description:

Time to treatment failure is defined as the time from randomization to the time of death, decline in percent-predicted FVC > 10% relative to baseline, > 20% increase in mRSS and an increase in mRSS of equal to or more than 5 points, or occurrence of a predefined SSc-related complication as adjudicated by the Clinical Adjudication Committee (whichever occurs first) during the 48-week double-blind treatment period. The median TTF was not estimable and is not presented for either treatment arm because of the low number of patients with events at Week 48. The analysis was conducted in the Intent-to-treat (ITT) population, i.e. all participants who were randomized and received any study drug. 99999 = not evaluable.

End point type	Secondary
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End point timeframe:

From Baseline to Week 48

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: months				
median (confidence interval 95%)	99999 (48.7 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Placebo versus Tocilizumab
Comparison groups	Double-Blind Placebo v Double-Blind Tocilizumab
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0821
Method	Cox-proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.06

Secondary: Frequency of Serious Systemic Sclerosis (SSC) Related Complications During Double-blind Period

End point title	Frequency of Serious Systemic Sclerosis (SSC) Related Complications During Double-blind Period
End point description:	
Adverse event terms coded using MedDRA 20.1. Includes only those serious events adjudicated as SSC-related complications by an independent external committee.	
End point type	Secondary
End point timeframe:	
From Baseline up to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	104		
Units: Number of Participants				
CARDIAC FAILURE	0	1		
CARDIAC FAILURE CHRONIC	1	0		
MICROVASCULAR CORONARY ARTERY DISEASE	1	0		
MYOCARDITIS	1	0		
INFECTED SKIN ULCER	1	0		
OSTEOMYELITIS	0	1		
WOUND INFECTION	0	1		

ILEUS PARALYTIC	1	0		
PAIN	1	0		
WEIGHT DECREASED	0	1		
SCLERODERMA	1	0		
HYPOKINESIA	0	1		
ADJUSTMENT DISORDER	1	0		
SCLERODERMA RENAL CRISIS	0	1		
DIGITAL PITTING SCAR	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Anti-Tocilizumab Antibody Status and Outcome Measures Pertaining to the Efficacy, Safety, and Pharmacokinetics of Tocilizumab

End point title	Correlation Between Anti-Tocilizumab Antibody Status and Outcome Measures Pertaining to the Efficacy, Safety, and Pharmacokinetics of Tocilizumab
End point description:	
Pre-specified analysis of the relationship between Anti-Tocilizumab Antibody status and safety, efficacy, and PK endpoints were not analyzed via subgroup analyses as there was only 1 participant with anti-tocilizumab antibody-positive status.	
End point type	Secondary
End point timeframe:	
Baseline; during Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: Units on a scale				
median (full range (min-max))	(to)	(to)		

Notes:

[2] - Correlation not analyzed as there was only one anti-TCZ antibody positive participant in the study.

[3] - Correlation not analyzed as there was only one anti-TCZ antibody positive participant in the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Low Serum Tocilizumab Exposure and Mean Modified Rodnan Skin Score (mRSS) From Baseline to Week 48

End point title	Correlation Between Low Serum Tocilizumab Exposure and Mean Modified Rodnan Skin Score (mRSS) From Baseline to Week 48
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End point description:

In order to characterize exposure-efficacy relationships, mRSS scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.

End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	30		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	20.4 (± 6.95)	20.3 (± 5.56)		
Week 8	18.6 (± 7.78)	17.9 (± 5.84)		
Week 16	17.9 (± 8.71)	16.2 (± 5.58)		
Week 24	16.9 (± 9.38)	14.7 (± 5.61)		
Week 36	16.2 (± 10.24)	13.2 (± 4.97)		
Week 48	14.8 (± 9.89)	12.2 (± 6.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Low Serum Tocilizumab Exposure and Median Modified Rodnan Skin Score (mRSS) From Baseline to Week 48

End point title	Correlation Between Low Serum Tocilizumab Exposure and Median Modified Rodnan Skin Score (mRSS) From Baseline to Week 48
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End point description:

In order to characterize exposure-efficacy relationships, mRSS scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.

End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	30		
Units: Units on a scale				
median (full range (min-max))				
Baseline	19.0 (10 to 40)	20.0 (11 to 31)		
Week 8	18.0 (4 to 43)	16.0 (9 to 34)		
Week 16	17.0 (0 to 38)	15.0 (8 to 30)		
Week 24	16.0 (0 to 42)	14.0 (6 to 29)		
Week 36	14.0 (0 to 47)	13.5 (5 to 27)		

Week 48	14.0 (0 to 43)	12.5 (2 to 30)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Medium Serum Tocilizumab Exposure and Mean Modified Rodnan Skin Score (mRSS) From Baseline to Week 48

End point title	Correlation Between Medium Serum Tocilizumab Exposure and Mean Modified Rodnan Skin Score (mRSS) From Baseline to Week 48
End point description: In order to characterize exposure-efficacy relationships, mRSS scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.	
End point type	Secondary
End point timeframe: From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	29		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	20.4 (± 6.95)	19.1 (± 6.24)		
Week 8	18.6 (± 7.78)	17.2 (± 6.17)		
Week 16	17.9 (± 8.71)	16.2 (± 6.10)		
Week 24	16.9 (± 9.38)	14.6 (± 6.66)		
Week 36	16.2 (± 10.24)	13.4 (± 6.20)		
Week 48	14.8 (± 9.89)	11.6 (± 5.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Medium Serum Tocilizumab Exposure and Median Modified Rodnan Skin Score (mRSS) From Baseline to Week 48

End point title	Correlation Between Medium Serum Tocilizumab Exposure and Median Modified Rodnan Skin Score (mRSS) From Baseline to Week 48
End point description: In order to characterize exposure-efficacy relationships, mRSS scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to	

placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.

End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	29		
Units: Units on a scale				
median (full range (min-max))				
Baseline	19.0 (10 to 40)	18.0 (10 to 35)		
Week 8	18.0 (4 to 43)	17.0 (5 to 31)		
Week 16	17.0 (0 to 38)	16.0 (5 to 27)		
Week 24	16.0 (0 to 42)	14.0 (3 to 28)		
Week 36	14.0 (0 to 47)	13.0 (2 to 25)		
Week 48	14.0 (0 to 43)	11.0 (0 to 24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between High Serum Tocilizumab Exposure and Mean Modified Rodnan Skin Score (mRSS) From Baseline to Week 48

End point title	Correlation Between High Serum Tocilizumab Exposure and Mean Modified Rodnan Skin Score (mRSS) From Baseline to Week 48
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End point description:

In order to characterize exposure-efficacy relationships, mRSS scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.

End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	29		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	20.4 (± 6.95)	19.8 (± 6.82)		
Week 8	18.6 (± 7.78)	17.9 (± 7.35)		
Week 16	17.9 (± 8.71)	16.7 (± 7.31)		

Week 24	16.9 (± 9.38)	15.6 (± 7.50)		
Week 36	16.2 (± 10.24)	13.7 (± 7.07)		
Week 48	14.8 (± 9.89)	12.8 (± 7.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between High Serum Tocilizumab Exposure and Median Modified Rodnan Skin Score (mRSS) From Baseline to Week 48

End point title	Correlation Between High Serum Tocilizumab Exposure and Median Modified Rodnan Skin Score (mRSS) From Baseline to Week 48
End point description: In order to characterize exposure-efficacy relationships, mRSS scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.	
End point type	Secondary
End point timeframe: From Baseline to Week 48	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106	29		
Units: Units on a scale				
median (full range (min-max))				
Baseline	19.0 (10 to 40)	19.0 (11 to 33)		
Week 8	18.0 (4 to 43)	17.5 (5 to 32)		
Week 16	17.0 (0 to 38)	15.0 (6 to 33)		
Week 24	16.0 (0 to 42)	15.0 (2 to 31)		
Week 36	14.0 (0 to 47)	11.0 (4 to 30)		
Week 48	14.0 (0 to 43)	11.0 (4 to 34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Mean Modified Rodnan Skin Score (mRSS) at Low, Medium and High Serum Tocilizumab Exposure From Baseline to Week 48

End point title	Change in Mean Modified Rodnan Skin Score (mRSS) at Low, Medium and High Serum Tocilizumab Exposure From Baseline to Week 48
End point description: In order to characterize exposure-efficacy relationships, mRSS scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to	

placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.

End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	Double-Blind Tocilizumab	Double-Blind Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	92		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Low Exposure	-8.0 (± 5.85)	-5.3 (± 7.77)		
Medium Exposure	-7.5 (± 5.06)	-5.3 (± 7.77)		
High Exposure	-7.0 (± 6.26)	-5.3 (± 7.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Median Modified Rodnan Skin Score (mRSS), at Low, Medium and High Serum Tocilizumab Exposure From Baseline to Week 48

End point title	Change in Median Modified Rodnan Skin Score (mRSS), at Low, Medium and High Serum Tocilizumab Exposure From Baseline to Week 48
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End point description:

In order to characterize exposure-efficacy relationships, mRSS scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.

End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	Double-Blind Tocilizumab	Double-Blind Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	92		
Units: Units on a scale				
median (full range (min-max))				
Low Exposure	-8.0 (-19 to 4)	-5.5 (-25 to 22)		
Medium Exposure	-7.0 (-18 to 2)	-5.5 (-25 to 22)		
High Exposure	-6.0 (-20 to 6)	-5.5 (-25 to 22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Mean Percent Predicted Forced Vital Capacity (ppFVC), at Low, Medium and High Serum Tocilizumab Exposure From Baseline to Week 48

End point title	Change in Mean Percent Predicted Forced Vital Capacity (ppFVC), at Low, Medium and High Serum Tocilizumab Exposure From Baseline to Week 48
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End point description:

In order to characterize exposure-efficacy relationships, ppFVC scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.

End point type	Secondary
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End point timeframe:

From Baseline to Week 48

End point values	Double-Blind Tocilizumab	Double-Blind Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	91		
Units: Percent				
arithmetic mean (standard deviation)				
Low Exposure	0.144 (± 6.474)	-4.264 (± 8.155)		
Medium Exposure	-0.161 (± 6.440)	-4.264 (± 8.155)		
High Exposure	-0.297 (± 7.895)	-4.264 (± 8.155)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Median Percent Predicted Forced Vital Capacity (ppFVC), at Low, Medium and High Serum Tocilizumab Exposure From Baseline to Week 48

End point title	Change in Median Percent Predicted Forced Vital Capacity (ppFVC), at Low, Medium and High Serum Tocilizumab Exposure From Baseline to Week 48
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End point description:

In order to characterize exposure-efficacy relationships, ppFVC scores are summarized based on TCZ exposure tertiles (high, medium, and low exposures) in the active treatment group and compared to placebo patients. Low Exposure = 0-<41 ug/ml, Medium = 41-<=61.1 ug/ml, High = 61.1-<=145 ug/ml.

ug/ml.

End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	Double-Blind Tocilizumab	Double-Blind Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	91		
Units: Percent				
median (full range (min-max))				
Low Exposure	0.525 (-14.25 to 11.38)	-3.910 (-31.47 to 13.47)		
Medium Exposure	-1.600 (-13.83 to 17.00)	-3.910 (-31.47 to 13.47)		
High Exposure	0.000 (-10.55 to 19.69)	-3.910 (-31.47 to 13.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Adverse Events Up to Week 96

End point title	Summary of Adverse Events Up to Week 96
End point description:	
Summary of key safety results including Adverse Events of Special Interest (AESI). All adverse events categorized according to MedDRA version 21.1. NMSC = Non-Melanoma Skin Cancer. The analysis was conducted in the safety population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment.	
End point type	Secondary
End point timeframe:	
Up to Week 96	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label	Tocilizumab, then Tocilizumab Open Label
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	106	104	89	92
Units: Percentage of participants				
number (not applicable)				
At least one Adverse Event (AE)	77.4	85.6	77.5	71.7
Withdrawn from study due to an AE	12.3	6.7	1.1	1.1
Fatal AE	2.8	1.0	1.1	1.1
Serious Adverse Events (SAEs)	17.0	12.5	7.9	10.9
SAE leading to withdrawal from treatment	5.7	4.8	1.1	1.1

SAE leading to dose modification/interruption	5.7	2.9	4.5	3.3
SAE related to study drug	6.6	1.0	3.4	3.3
AE leading to withdrawal from treatment	12.3	6.7	1.1	1.1
AE leading to dose modification/interruption	26.4	19.2	28.1	22.8
AE related to study drug	34.0	46.2	33.7	34.8
Related AE leading to withdrawal from treatment	1.9	1.0	1.1	1.1
Related AE with dose modification/interruption	17.0	11.5	12.4	14.1
Serious Infections and Infestations AEs	6.6	1.9	3.4	1.1
Infections and Infestations AEs	50.0	52.9	46.1	39.1
Opportunistic Infections AEs	0.9	1.0	0	1.1
Malignancy AEs	0.9	1.9	0	1.1
Malignancy AEs (excluding NMSC)	0.9	1.9	0	1.1
Serious Hepatic AEs	0	0	0	0
Serious Stroke AEs	0	0	0	0
Serious Myocardial Infarction AEs	1.9	0	0	0
Anaphylactic Reaction AEs	0	0	0	0
Anaphylactic Reaction AEs (Sampson's Criteria)	0	0	0	0
Serious Gastrointestinal Perforation AEs	0	0	0	0
Serious Bleeding AEs	0.9	0	0	0
Serious Demyelinating AEs	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and Severity of Adverse Events Up to Week 96

End point title	Incidence and Severity of Adverse Events Up to Week 96
End point description:	
Adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) severity grade: 1 = mild, 2 = moderate, 3 = severe and/or requiring medical intervention but not life-threatening, 4 = life-threatening consequences, and 5 = death. The analysis was conducted in the safety population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment.	
End point type	Secondary
End point timeframe:	
Up to Week 96	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label	Tocilizumab, then Tocilizumab Open Label
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	106	104	89	92
Units: Number of participants				
Grade 1	61	78	60	53

Grade 2	63	53	41	35
Grade 3	21	18	9	8
Grade 4	7	0	4	5
Grade 5	3	1	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events Leading to Death Up to Week 96

End point title	Number of Participants With Adverse Events Leading to Death Up to Week 96
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End point description:

The analysis was conducted in the safety population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment.

End point type	Secondary
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End point timeframe:

Up to Week 96

End point values	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label	Tocilizumab, then Tocilizumab Open Label
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	106	104	89	92
Units: Number of participants				
CARDIAC FAILURE CHRONIC	1	0	0	0
MYOCARDITIS	1	0	0	0
MYOCARDIAL INFARCTION	1	0	0	0
DEATH	0	1	0	0
BRAIN INJURY	0	0	1	0
PULMONARY HYPERTENSION	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Change in Digital Ulcer Count at Week 96

End point title	Percentage of Participants With Change in Digital Ulcer Count at Week 96
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End point description:

A digital ulcer is defined as an ulcer at or distal to the MCP joint on either the dorsal or volar surface, with loss of surface epithelialization. This does not include fissures, cracks, or calcium extrusions from calcinosis cutis. The number of fingers (0–10) with digital ulcers and the number of digital (or finger) ulcers will be counted and recorded by the investigator. The analysis was conducted in the safety

population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment.

End point type	Secondary
End point timeframe:	
From Baseline to Week 96	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label	Tocilizumab, then Tocilizumab Open Label
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	106	104	89	92
Units: Percentage of participants				
number (not applicable)				
No change	0	0	91.1	83.3
Increase by 1	0	0	0	4.8
Increase by 2	0	0	0	1.2
Increase by 3	0	0	0	1.2
Increase by 4	0	0	0	0
Increase by >4	0	0	0	1.2
Decrease by 1	0	0	3.8	4.8
Decrease by 2	0	0	2.5	0
Decrease by 3	0	0	1.3	1.2
Decrease by 4	0	0	1.3	1.2
Decrease by >4	0	0	0	0
Baseline missing	0	0	0	1.2

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Positive Anti-Tocilizumab Assay Up to Week 96

End point title	Percentage of Participants with Positive Anti-Tocilizumab Assay Up to Week 96
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End point description:

Reported were the percentage of participants with anti-TCZ antibodies. Positive samples underwent additional analyses: a neutralizing assay for the ability to inhibit the activity of TCZ and a test for anti - TCZ of the IgE isotype. Safety population: received at least one dose of study drug and provide data from at least one post dose safety assessment. 9999 = not evaluated

End point type	Secondary
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End point timeframe:

Baseline, double-blind period (up to Week 48), open label period (from Week 48 to Week 96)

End point values	Double-Blind Placebo, then Tocilizumab Open Label	Double-Blind Tocilizumab, then Tocilizumab Open Label		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	104		
Units: Percentage of Participants				
number (not applicable)				
Baseline	5.9	2.9		
Double-blind: Positive anti-TCZ assay	0.0	2.9		
Double-blind: Positive confirmation assay	0.0	1.0		
Double-blind: Positive neutralizing assay	0.0	1.0		
Double-blind: Positive IgE assay	0.0	0.0		
Open label: Positive anti-TCZ assay	9999	0.0		
Open label: Positive neutralizing assay	9999	0.0		
Open label: Positive IgE assay	9999	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Erythrocyte Sedimentation Rate (ESR) Up to Week 96

End point title	Erythrocyte Sedimentation Rate (ESR) Up to Week 96
End point description:	
Erythrocyte Sedimentation Rate (ESR) levels predose at baseline and at subsequent time points after initiation of study drug. The analysis was conducted in the safety population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment. 9999 indicates that 0 participants were analyzed for the specific arm and time point. n indicates the number of participants analyzed for the specific time point per arm.	
End point type	Secondary
End point timeframe:	
Up to Week 96	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label	Tocilizumab, then Tocilizumab Open Label
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103	100	82	89
Units: mm/hr				
arithmetic mean (standard deviation)				
Baseline: n=103,100,0,0	34.72 (± 18.49)	34.83 (± 16.29)	9999 (± 9999)	9999 (± 9999)
Week 4: n=96,98,0,0	31.38 (± 19.00)	14.29 (± 12.98)	9999 (± 9999)	9999 (± 9999)
Week 24: n=98,94,0,0	28.49 (± 20.86)	8.46 (± 8.63)	9999 (± 9999)	9999 (± 9999)
Week 48: n=91,93,0,0	26.23 (± 18.53)	10.89 (± 15.39)	9999 (± 9999)	9999 (± 9999)

Week 72: n=0,0,82,89	9999 (± 9999)	9999 (± 9999)	9.54 (± 9.47)	8.29 (± 10.13)
Week 96: n=0,0,79,85	9999 (± 9999)	9999 (± 9999)	9.67 (± 8.67)	8.06 (± 8.86)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Interleukin (IL)-6 Level, Mean, From Baseline to Week 96

End point title	Serum Interleukin (IL)-6 Level, Mean, From Baseline to Week 96
End point description: Serum Interleukin (IL)-6 levels predose at baseline and at subsequent time points after initiation of study drug. The analysis was conducted in the safety population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment. 9999 indicates that 0 participants were analyzed for the specific arm and time point. n indicates the number of participants analyzed for the specific time point per arm.	
End point type	Secondary
End point timeframe: Up to Week 96	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label	Tocilizumab, then Tocilizumab Open Label
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	106	104	79	79
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline: n=106,104,0,0	11.85 (± 19.73)	13.86 (± 43.78)	9999 (± 9999)	9999 (± 9999)
Week 4: n=95,98,0,0	13.41 (± 29.98)	144.75 (± 429.14)	9999 (± 9999)	9999 (± 9999)
Week 8: n=95,94,0,0	14.21 (± 26.82)	111.44 (± 280.34)	9999 (± 9999)	9999 (± 9999)
Week 16: n=93,88,0,0	15.40 (± 24.26)	66.20 (± 70.50)	9999 (± 9999)	9999 (± 9999)
Week 24: n=85,85,0,0	11.81 (± 24.05)	62.74 (± 53.40)	9999 (± 9999)	9999 (± 9999)
Week 36: n=73,83,0,0	9.32 (± 15.23)	62.15 (± 68.08)	9999 (± 9999)	9999 (± 9999)
Week 48: n=81,82,0,0	9.10 (± 14.88)	53.34 (± 56.80)	9999 (± 9999)	9999 (± 9999)
Week 96: n=0,0,79,79	9999 (± 9999)	9999 (± 9999)	62.60 (± 57.21)	52.03 (± 46.51)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Soluble Interleukin (IL)-6 Receptor Level, Mean, Up to Week 96

End point title	Serum Soluble Interleukin (IL)-6 Receptor Level, Mean, Up to Week 96
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End point description:

Serum Soluble Interleukin (IL)-6 receptor levels predose at baseline and at subsequent time points after initiation of study drug. The analysis was conducted in the safety population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment. 9999 indicates that 0 participants were analyzed for the specific arm and time point. n indicates the number of participants analyzed for the specific time point per arm.

End point type	Secondary
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End point timeframe:

Up to Week 96

End point values	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label	Tocilizumab, then Tocilizumab Open Label
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103	102	79	85
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline: n=100,102,0,0	42.23 (± 32.56)	42.15 (± 14.50)	9999 (± 9999)	9999 (± 9999)
Week 4: n=103,101,0,0	46.07 (± 73.52)	487.70 (± 123.02)	9999 (± 9999)	9999 (± 9999)
Week 8: n=103,101,0,0	45.71 (± 57.95)	546.59 (± 142.58)	9999 (± 9999)	9999 (± 9999)
Week 16: n=102,96,0,0	47.81 (± 68.22)	583.87 (± 164.36)	9999 (± 9999)	9999 (± 9999)
Week 24: n=95,95,0,0	41.35 (± 15.17)	587.28 (± 153.90)	9999 (± 9999)	9999 (± 9999)
Week 36: n=89,93,0,0	38.13 (± 11.22)	589.59 (± 140.63)	9999 (± 9999)	9999 (± 9999)
Week 48: n=93,92,0,0	49.51 (± 76.17)	566.49 (± 175.25)	9999 (± 9999)	9999 (± 9999)
Week 96: n=0,0,79,85	9999 (± 9999)	9999 (± 9999)	558.38 (± 256.86)	565.31 (± 159.82)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum C-Reactive Protein (CRP) Level, Mean, Up to Week 96

End point title	Serum C-Reactive Protein (CRP) Level, Mean, Up to Week 96
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End point description:

Serum C-Reactive Protein (CRP) levels predose at baseline and at subsequent time points after initiation of study drug. The analysis was conducted in the safety population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment. 9999 indicates that 0 participants were analyzed for the specific arm and time point. n indicates the number of participants analyzed for the specific time point per arm.

End point type	Secondary
End point timeframe:	
From Baseline up to Week 96	

End point values	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label	Tocilizumab, then Tocilizumab Open Label
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	106	104	83	90
Units: mg/L				
arithmetic mean (standard deviation)				
Baseline: n=106,104,0,0	7.42 (± 12.62)	8.99 (± 14.76)	9999 (± 9999)	9999 (± 9999)
Week 4: n=103,103,0,0	10.05 (± 20.82)	0.85 (± 2.50)	9999 (± 9999)	9999 (± 9999)
Week 24: n=100,97,0,0	9.89 (± 13.99)	0.56 (± 1.19)	9999 (± 9999)	9999 (± 9999)
Week 48: n=93,96,0,0	7.40 (± 12.62)	1.75 (± 6.43)	9999 (± 9999)	9999 (± 9999)
Week 72: n=0,0,82,90	9999 (± 9999)	9999 (± 9999)	0.57 (± 0.80)	0.92 (± 3.61)
Week 96: n=0,0,83,86	9999 (± 9999)	9999 (± 9999)	0.90 (± 2.73)	0.97 (± 5.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Tocilizumab Concentration, Mean, Up to Week 96

End point title	Serum Tocilizumab Concentration, Mean, Up to Week 96 ^[4]
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End point description:

Predose observed serum TCZ concentration at baseline and at specified timepoints thereafter. The PK population included all participants who received at least one TCZ injection and had at least one PK sample with detectable results. Only samples from the Double Blind TCZ, then Open Label TCZ were measured by the lab after week 48. Data for the Double Blind Period were reported at the time in separate endpoint up to Week 48. n indicates the number of participants analyzed for the specific time point per arm.

End point type	Secondary
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End point timeframe:

Up to Week 96

Notes:

[4] - 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: Serum tocilizumab was only measured after Week 48 in participants treated with tocilizumab throughout the study.

End point values	Double-Blind Tocilizumab, then Open Label Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: ug/mL				
arithmetic mean (standard deviation)				

Baseline: n=101	0.00 (\pm 0.03)			
Week 4: n=101	30.76 (\pm 15.23)			
Week 8: n=100	41.82 (\pm 17.66)			
Week 16: n=93	50.98 (\pm 23.33)			
Week 24: n=93	54.34 (\pm 26.24)			
Week 36: n=91	53.55 (\pm 29.25)			
Week 48: n=89	54.87 (\pm 29.69)			
Week 96: n=82	49.99 (\pm 26.19)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 96

Adverse event reporting additional description:

The analysis was conducted in the safety population i.e. received at least one dose of study drug and provide data from at least one post dose safety assessment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Double-Blind Placebo
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Reporting group description:

Participants received double-blind matching placebo from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.

Reporting group title	Double-Blind Tocilizumab
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Reporting group description:

Participants received double-blind tocilizumab from Baseline to Week 48. Participants may then receive open-label tocilizumab from Weeks 48 to 96.

Reporting group title	Placebo, then Tocilizumab Open Label
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Reporting group description:

Participants who received placebo during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.

Reporting group title	Tocilizumab, then Tocilizumab Open Label
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Reporting group description:

Participants who received tocilizumab during the double blind period from Baseline to Week 48, received tocilizumab from Week 48 to Week 96.

Serious adverse events	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 106 (16.98%)	13 / 104 (12.50%)	7 / 89 (7.87%)
number of deaths (all causes)	3	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-CELL LYMPHOMA			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
BENIGN BONE NEOPLASM			

subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST CANCER			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
LUNG ADENOCARCINOMA			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PAIN			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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

PULMONARY HYPERTENSION			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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
Psychiatric disorders			
ADJUSTMENT DISORDER			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEPRESSION			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
Injury, poisoning and procedural complications			
LIMB TRAUMATIC AMPUTATION			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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
SPINAL CORD INJURY			

subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA PECTORIS			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
CARDIAC FAILURE CHRONIC			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
MICROVASCULAR CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
MYOCARDITIS			

subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
ARRHYTHMIA			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONGESTIVE CARDIOMYOPATHY			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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
Nervous system disorders			
BRAIN INJURY			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
SYNCOPE			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
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			
ANAEMIA MEGALOBLASTIC			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHADENOPATHY MEDIASTINAL			

subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
RETINAL VEIN THROMBOSIS			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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			
ILEUS PARALYTIC			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS EROSIVE			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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
RECTAL PROLAPSE			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
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			
DIGITAL PITTING SCAR			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ECCHYMOSIS			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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

SKIN ULCER			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROLITHIASIS			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
SCLERODERMA RENAL CRISIS			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
Musculoskeletal and connective tissue disorders			
SCLERODERMA			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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
JOINT STIFFNESS			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
TENDONITIS			

subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENOSYNOVITIS			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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
TRIGGER FINGER			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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			
PNEUMONIA			
subjects affected / exposed	3 / 106 (2.83%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTED SKIN ULCER			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
PELVIC INFLAMMATORY DISEASE			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
PYELONEPHRITIS CHRONIC			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			

subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOFT TISSUE INFECTION			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	0 / 89 (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
INFECTIVE TENOSYNOVITIS			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OTITIS MEDIA			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	0 / 89 (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
Metabolism and nutrition disorders			
DIABETIC KETOACIDOSIS			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tocilizumab, then		
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	Tocilizumab Open Label		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 92 (10.87%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-CELL LYMPHOMA			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BENIGN BONE NEOPLASM			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BREAST CANCER			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LUNG ADENOCARCINOMA			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PAIN			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			

subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMOTHORAX			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PULMONARY HYPERTENSION			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Psychiatric disorders			
ADJUSTMENT DISORDER			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DEPRESSION			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
LIMB TRAUMATIC AMPUTATION			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RADIUS FRACTURE			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SPINAL CORD INJURY			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ANGINA PECTORIS			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CARDIAC FAILURE			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CARDIAC FAILURE CHRONIC			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MICROVASCULAR CORONARY			

ARTERY DISEASE			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MYOCARDITIS			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ARRHYTHMIA			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CONGESTIVE CARDIOMYOPATHY			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
BRAIN INJURY			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SYNCOPE			

subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA MEGALOBLASTIC			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LYMPHADENOPATHY MEDIASTINAL			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
RETINAL VEIN THROMBOSIS			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ILEUS PARALYTIC			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GASTRITIS EROSIVE			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RECTAL PROLAPSE			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
DIGITAL PITTING SCAR			

subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ECCHYMOSIS			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SKIN ULCER			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
NEPHROLITHIASIS			
subjects affected / exposed	0 / 92 (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 / 92 (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 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
JOINT STIFFNESS			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
TENDONITIS			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
TENOSYNOVITIS			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
TRIGGER FINGER			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
INFECTED SKIN ULCER			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
OSTEOMYELITIS			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

PELVIC INFLAMMATORY DISEASE subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 92 (0.00%) 0 / 0 0 / 0		
PYELONEPHRITIS CHRONIC subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 92 (0.00%) 0 / 0 0 / 0		
RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 92 (0.00%) 0 / 0 0 / 0		
SEPSIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 92 (0.00%) 0 / 0 0 / 0		
SOFT TISSUE INFECTION subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 92 (0.00%) 0 / 0 0 / 0		
WOUND INFECTION subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 92 (0.00%) 0 / 0 0 / 0		
INFECTIVE TENOSYNOVITIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 92 (0.00%) 0 / 0 0 / 0		
OTITIS MEDIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 92 (1.09%) 0 / 1 0 / 0		
Metabolism and nutrition disorders			

DIABETIC KETOACIDOSIS			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double-Blind Placebo	Double-Blind Tocilizumab	Placebo, then Tocilizumab Open Label
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 106 (55.66%)	60 / 104 (57.69%)	46 / 89 (51.69%)
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	6 / 106 (5.66%)	2 / 104 (1.92%)	1 / 89 (1.12%)
occurrences (all)	6	2	1
Nervous system disorders			
HEADACHE			
subjects affected / exposed	6 / 106 (5.66%)	3 / 104 (2.88%)	1 / 89 (1.12%)
occurrences (all)	6	3	1
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	6 / 106 (5.66%)	2 / 104 (1.92%)	1 / 89 (1.12%)
occurrences (all)	6	2	1
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	7 / 106 (6.60%)	8 / 104 (7.69%)	0 / 89 (0.00%)
occurrences (all)	8	9	0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	7 / 106 (6.60%)	6 / 104 (5.77%)	6 / 89 (6.74%)
occurrences (all)	7	7	7
NAUSEA			

subjects affected / exposed	6 / 106 (5.66%)	3 / 104 (2.88%)	2 / 89 (2.25%)
occurrences (all)	6	3	2
GASTROESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	6 / 106 (5.66%)	4 / 104 (3.85%)	8 / 89 (8.99%)
occurrences (all)	6	4	8
Respiratory, thoracic and mediastinal disorders			
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	8 / 106 (7.55%)	2 / 104 (1.92%)	1 / 89 (1.12%)
occurrences (all)	8	2	1
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	4 / 106 (3.77%)	6 / 104 (5.77%)	2 / 89 (2.25%)
occurrences (all)	5	6	3
RASH			
subjects affected / exposed	7 / 106 (6.60%)	2 / 104 (1.92%)	3 / 89 (3.37%)
occurrences (all)	8	2	3
SKIN ULCER			
subjects affected / exposed	12 / 106 (11.32%)	15 / 104 (14.42%)	16 / 89 (17.98%)
occurrences (all)	22	28	28
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	13 / 106 (12.26%)	12 / 104 (11.54%)	6 / 89 (6.74%)
occurrences (all)	14	14	6
Infections and infestations			
GASTROENTERITIS			
subjects affected / exposed	2 / 106 (1.89%)	7 / 104 (6.73%)	0 / 89 (0.00%)
occurrences (all)	2	7	0
NASOPHARYNGITIS			
subjects affected / exposed	8 / 106 (7.55%)	13 / 104 (12.50%)	9 / 89 (10.11%)
occurrences (all)	9	14	10
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	11 / 106 (10.38%)	12 / 104 (11.54%)	10 / 89 (11.24%)
occurrences (all)	15	13	16
URINARY TRACT INFECTION			

subjects affected / exposed	10 / 106 (9.43%)	5 / 104 (4.81%)	7 / 89 (7.87%)
occurrences (all)	14	5	8

Non-serious adverse events	Tocilizumab, then Tocilizumab Open Label		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 92 (30.43%)		
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
NAUSEA			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		

Skin and subcutaneous tissue disorders PRURITUS subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all) SKIN ULCER subjects affected / exposed occurrences (all)	1 / 92 (1.09%) 1 2 / 92 (2.17%) 2 11 / 92 (11.96%) 22		
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	5 / 92 (5.43%) 5		
Infections and infestations GASTROENTERITIS subjects affected / exposed occurrences (all) NASOPHARYNGITIS subjects affected / exposed occurrences (all) UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all) URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	3 / 92 (3.26%) 3 4 / 92 (4.35%) 4 4 / 92 (4.35%) 5 1 / 92 (1.09%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2015	The screening high-resolution computed tomography (HRCT) assessment was moved to the Day 1 visit as it is required only for subjects who are randomized. For the digital ulcer count, the definition of a digital ulcer was amended to include an additional joint (the metacarpal phalangeal [MCP]) and to clarify that the volar and dorsal surfaces are included. For the pulmonary function tests, the testing methods for FVC and diffusion capacity of the lung for carbon monoxide were clarified. Also, the reference value for the diffusion capacity of the lung for carbon monoxide was added. Whole blood for RNA extraction was added.
12 July 2015	The options for female contraception were amended to state that the double-barrier method is an acceptable form of contraception. An addition was made to specify that, in participants who are inadequate responders to methotrexate or hydroxychloroquine, other disease-modifying anti-rheumatic drugs (such as mycophenolate mofetil) may be used after discussion with the Medical Monitor. The guidance on when to report adverse events of worsening systemic sclerosis was amended to remove references to "unexpected" and "unanticipated" worsening to remove ambiguity in determining if a participant's systemic sclerosis has worsened. Body weight was added as a Day 1 assessment.
17 December 2015	Reduction of the time period for baseline HRCT scans performed prior to screening from 12 months to 3 months; Introduction of the option for participants who discontinued study medication during the 48-week double-blind treatment period to participate in the 48-week open-label treatment period and receive TCZ if they met specified criteria; Addition of Health Assessment Questionnaire-Disability Index (HAQ-DI) assessments up to Week 48 for participants who discontinued the study drug; Stipulation that C-reactive protein (CRP) results were not to be reported in the electronic case report form (eCRF) to avoid potential unblinding of the Sponsor to treatment assignment; Modification of the methotrexate (MTX) dose to be used as escape therapy from 10 to ≤ 25 mg/week to accommodate country-specific requirements; Clarification that the interim (futility) analysis was no longer optional and addition of details on the timing and stopping criteria for the analysis.
06 September 2016	Clarification of the exclusion criterion for limited cutaneous SSc to also exclude patients with skin involvement of the face from the study; Clarification of the exclusion criterion for corticosteroids to exclude patients who were treated with all routes of corticosteroids prior to baseline; Addition of the acceptable use of immuno-modulating drugs beyond Week 24 to allow patients with other significant SSc complications to be treated appropriately without being required to discontinue study medication; Addition of further details on the timing of the interim (futility) analysis; Addition of a HAQ-DI assessment at Week 36 of the double-blind treatment period to align with the schedule of assessments for patients who discontinued the study drug.

05 May 2017	Clarification of the timing of follow-up assessments after study drug discontinuation; Addition of language permitting participants who were on escape therapy during the 48-week double-blind treatment period to continue to do so during the 48-week open-label treatment period. Participants were also allowed to initiate escape therapy during the open-label treatment period if they met the specified criteria; Deletion of the criterion on washout times to allow participants who discontinued the study drug during the double-blind treatment period to participate in the open-label treatment period without having to undergo washout of other SSc treatments. Participants who were started on other SSc medications after study drug discontinuation were allowed to continue these medications during the 48-week open-label treatment period; Clarification that participants who discontinued the study drug prior to Week 48 and did not continue to the open-label treatment period were to complete a reduced schedule of assessments; Clarification that participants who discontinued prior to Week 48 and were eligible to continue to the open-label treatment period were to complete all Week 48 assessments; Revisions were made to ensure consistency of the mRSS assessments, emphasizing that the same assessor was to conduct the evaluations for a given participant at all visits; A stipulation was made that specified pulmonary function tests were to be repeated within 4 weeks if rejected by the over-readers; Addition of details for tuberculosis screening and clarification of the testing requirements for CRP.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported