



## Clinical trial results:

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

#### Summary

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

#### Results information

|                                |                                                                                                                                                      |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                                                         |
| This version publication date  | 25 June 2016                                                                                                                                         |
| First version publication date | 06 March 2016                                                                                                                                        |
| Version creation reason        | <ul style="list-style-type: none"><li>• New data added to full data set</li></ul> Interim results previously provided. Final result update required. |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | WA27788 |
|-----------------------|---------|

##### Additional study identifiers

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

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                |
|------------------------------------------------------|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 05 August 2015 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 16 June 2015   |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The study was designed to evaluate the efficacy and safety of tocilizumab (TCZ) at a subcutaneous (SC) dose of 162 milligrams (mg) for 96 weeks (Week 0 to Week 48 of blinded-treatment period and Week 48 to Week 96 of open-label period) in participants with systemic sclerosis.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 13 March 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 19 |
| Country: Number of subjects enrolled | France: 8          |
| Country: Number of subjects enrolled | Germany: 19        |
| Country: Number of subjects enrolled | Canada: 5          |
| Country: Number of subjects enrolled | United States: 36  |
| Worldwide total number of subjects   | 87                 |
| EEA total number of subjects         | 46                 |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 74 |

|                     |    |
|---------------------|----|
| From 65 to 84 years | 13 |
| 85 years and over   | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Randomization was stratified by joint involvement at baseline ( $\geq 4$  or  $< 4$  tender joints of 28 tender joint count [TJC]). The study consisted of double-blind (Week 0 to Week 48) and open-label (Week 48 to Week 96) periods. Data analyzed up to Weeks 24 and 48 (data cut-off: 11 July 2014), and up to Week 96 (data cut-off: 05 August 2015) are reported.

### Period 1

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

### Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | Placebo (Up to Week 24) |

Arm description:

Participants received TCZ matched placebo by SC injection every week (qw) for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 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:

TCZ matched placebo was administered SC qw for Week 0 to Week 48 (blinded-treatment period), followed by TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Tocilizumab (Up to Week 24) |
|------------------|-----------------------------|

Arm description:

Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.

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

Dosage and administration details:

TCZ was administered at a dose of 162 mg by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.

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

## Period 2

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

## Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | No                      |
| <b>Arm title</b>             | Placebo (Up to Week 48) |

### Arm description:

Participants received TCZ matched placebo by SC injection every week (qw) for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 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:

TCZ matched placebo was administered SC qw for Week 0 to Week 48 (blinded-treatment period) followed by TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Tocilizumab (Up to Week 48) |
|------------------|-----------------------------|

### Arm description:

Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.

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

**Dosage and administration details:**

TCZ was administered at a dose of 162 mg by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.

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

**Period 3**

|                              |                                        |
|------------------------------|----------------------------------------|
| Period 3 title               | Open-label Period (Week 48 to Week 96) |
| Is this the baseline period? | No                                     |
| Allocation method            | Not applicable                         |
| Blinding used                | Not blinded                            |

**Arms**

|                              |                                        |
|------------------------------|----------------------------------------|
| Are arms mutually exclusive? | Yes                                    |
| <b>Arm title</b>             | Placebo to Tocilizumab (Up to Week 96) |

**Arm description:**

Participants received TCZ matched placebo by SC injection every week (qw) for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96.

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

**Dosage and administration details:**

TCZ matched placebo was administered SC qw for Week 0 to Week 48 (blinded-treatment period), followed by TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96.

|                  |                                            |
|------------------|--------------------------------------------|
| <b>Arm title</b> | Tocilizumab to Tocilizumab (Up to Week 96) |
|------------------|--------------------------------------------|

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**Arm description:**

Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.

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

**Dosage and administration details:**

TCZ was administered at a dose of 162 mg by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.

| <b>Number of subjects in period 3</b> | Placebo to<br>Tocilizumab (Up to<br>Week 96) | Tocilizumab to<br>Tocilizumab (Up to<br>Week 96) |
|---------------------------------------|----------------------------------------------|--------------------------------------------------|
| Started                               | 31                                           | 30                                               |
| Completed                             | 24                                           | 27                                               |
| Not completed                         | 7                                            | 3                                                |
| Adverse event, non-fatal              | 4                                            | 1                                                |
| Non-compliance                        | 1                                            | -                                                |
| Lack of efficacy                      | 1                                            | 1                                                |
| Withdrawal by subject                 | 1                                            | 1                                                |

## Baseline characteristics

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Placebo (Up to Week 24) |
|-----------------------|-------------------------|

Reporting group description:

Participants received TCZ matched placebo by SC injection every week (qw) for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Tocilizumab (Up to Week 24) |
|-----------------------|-----------------------------|

Reporting group description:

Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.

| Reporting group values             | Placebo (Up to Week 24) | Tocilizumab (Up to Week 24) | Total |
|------------------------------------|-------------------------|-----------------------------|-------|
| Number of subjects                 | 44                      | 43                          | 87    |
| Age categorical<br>Units: Subjects |                         |                             |       |

|                                                                         |                |                |    |
|-------------------------------------------------------------------------|----------------|----------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 48.1<br>± 12.9 | 51.2<br>± 11.7 | -  |
| Gender categorical<br>Units: Subjects                                   |                |                |    |
| Female                                                                  | 35             | 32             | 67 |
| Male                                                                    | 9              | 11             | 20 |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                                            |                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                      | Placebo (Up to Week 24)                    |
| Reporting group description:<br>Participants received TCZ matched placebo by SC injection every week (qw) for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96  |                                            |
| Reporting group title                                                                                                                                                                                                                                      | Tocilizumab (Up to Week 24)                |
| Reporting group description:<br>Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.                                                           |                                            |
| Reporting group title                                                                                                                                                                                                                                      | Placebo (Up to Week 48)                    |
| Reporting group description:<br>Participants received TCZ matched placebo by SC injection every week (qw) for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96. |                                            |
| Reporting group title                                                                                                                                                                                                                                      | Tocilizumab (Up to Week 48)                |
| Reporting group description:<br>Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.                                                           |                                            |
| Reporting group title                                                                                                                                                                                                                                      | Placebo to Tocilizumab (Up to Week 96)     |
| Reporting group description:<br>Participants received TCZ matched placebo by SC injection every week (qw) for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96. |                                            |
| Reporting group title                                                                                                                                                                                                                                      | Tocilizumab to Tocilizumab (Up to Week 96) |
| Reporting group description:<br>Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96.                                                           |                                            |

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

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

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

## Statistical analyses

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

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

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

End point description:

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

up to Week 48

Notes:

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

Justification: Only descriptive data was planned to be reported.

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 24 and 48

| End point values                             | Placebo (Up to Week 48) | Tocilizumab (Up to Week 48) |  |  |
|----------------------------------------------|-------------------------|-----------------------------|--|--|
| Subject group type                           | Reporting group         | Reporting group             |  |  |
| Number of subjects analysed                  | 42                      | 41                          |  |  |
| Units: mm                                    |                         |                             |  |  |
| least squares mean (confidence interval 95%) |                         |                             |  |  |
| Week 24: Intestinal VAS Score (n=42, 41)     | 5.81 (-1.43 to 13.06)   | 5.38 (-1.98 to 12.74)       |  |  |
| Week 24: Breathing VAS Scores (n=42, 41)     | 8.54 (0.81 to 16.27)    | 4.42 (-3.47 to 12.31)       |  |  |
| Week 24: Raynaud syndrome (n=42, 41)         | 2.41 (-6.96 to 11.78)   | 1.13 (-8.47 to 10.73)       |  |  |
| Week 24: Finger ulcers VAS Score (n=42, 41)  | 9.2 (-0.22 to 18.61)    | 14.09 (4.45 to 23.73)       |  |  |
| Week 24: Overall disease (n=42, 41)          | 1.89 (-4.99 to 8.77)    | 1.81 (-5.21 to 8.84)        |  |  |
| Week 48: Intestinal VAS Score (n=41, 41)     | 7.91 (-0.37 to 16.18)   | 1.11 (-6.88 to 9.1)         |  |  |

|                                             |                      |                        |  |  |
|---------------------------------------------|----------------------|------------------------|--|--|
| Week 48: Breathing VAS Scores (n=41, 41)    | 0.55 (-7.09 to 8.19) | 2.09 (-5.39 to 9.57)   |  |  |
| Week 48: Raynaud syndrome (n=41, 41)        | 0.3 (-9.51 to 10.12) | -4.18 (-13.87 to 5.51) |  |  |
| Week 48: Finger ulcers VAS Score (n=41, 41) | 4.97 (-3.15 to 13.1) | -0.83 (-8.83 to 7.17)  |  |  |
| Week 48: Overall disease (n=41, 41)         | 3.46 (-4.5 to 11.41) | -4.36 (-12.27 to 3.55) |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                                                   | Physical Function Assessed by SHAQ-DI                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                            |                                                       |
| Change From Baseline in Intestinal VAS Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                            | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                      | 83                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                       | Pre-specified                                         |
| Analysis type                                                                                                                                                                                                                                                                                                                                | superiority                                           |
| P-value                                                                                                                                                                                                                                                                                                                                      | = 0.9336                                              |
| Method                                                                                                                                                                                                                                                                                                                                       | Mixed models analysis                                 |
| Parameter estimate                                                                                                                                                                                                                                                                                                                           | Difference in LS mean                                 |
| Point estimate                                                                                                                                                                                                                                                                                                                               | -0.43                                                 |
| Confidence interval                                                                                                                                                                                                                                                                                                                          |                                                       |
| level                                                                                                                                                                                                                                                                                                                                        | 95 %                                                  |
| sides                                                                                                                                                                                                                                                                                                                                        | 2-sided                                               |
| lower limit                                                                                                                                                                                                                                                                                                                                  | -10.78                                                |
| upper limit                                                                                                                                                                                                                                                                                                                                  | 9.91                                                  |

| Statistical analysis title                                                                                                                                                                                                                                                                                                                  | Physical Function Assessed by SHAQ-DI                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                           |                                                       |
| Change From Baseline in Breathing VAS Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                           | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                     | 83                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                      | Pre-specified                                         |
| Analysis type                                                                                                                                                                                                                                                                                                                               | superiority                                           |
| P-value                                                                                                                                                                                                                                                                                                                                     | = 0.4609                                              |
| Method                                                                                                                                                                                                                                                                                                                                      | Mixed models analysis                                 |
| Parameter estimate                                                                                                                                                                                                                                                                                                                          | Difference in LS mean                                 |
| Point estimate                                                                                                                                                                                                                                                                                                                              | -4.12                                                 |
| Confidence interval                                                                                                                                                                                                                                                                                                                         |                                                       |
| level                                                                                                                                                                                                                                                                                                                                       | 95 %                                                  |
| sides                                                                                                                                                                                                                                                                                                                                       | 2-sided                                               |
| lower limit                                                                                                                                                                                                                                                                                                                                 | -15.21                                                |
| upper limit                                                                                                                                                                                                                                                                                                                                 | 6.96                                                  |

|                                                                                                                                                                                                                                                                                                                                                |                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                              | Physical Function Assessed by SHAQ-DI                 |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                              |                                                       |
| Change From Baseline in Raynaud Syndrome Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                              | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                        | 83                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                         | Pre-specified                                         |
| Analysis type                                                                                                                                                                                                                                                                                                                                  | superiority                                           |
| P-value                                                                                                                                                                                                                                                                                                                                        | = 0.8493                                              |
| Method                                                                                                                                                                                                                                                                                                                                         | Mixed models analysis                                 |
| Parameter estimate                                                                                                                                                                                                                                                                                                                             | Difference in LS mean                                 |
| Point estimate                                                                                                                                                                                                                                                                                                                                 | -1.28                                                 |
| Confidence interval                                                                                                                                                                                                                                                                                                                            |                                                       |
| level                                                                                                                                                                                                                                                                                                                                          | 95 %                                                  |
| sides                                                                                                                                                                                                                                                                                                                                          | 2-sided                                               |
| lower limit                                                                                                                                                                                                                                                                                                                                    | -14.7                                                 |
| upper limit                                                                                                                                                                                                                                                                                                                                    | 12.13                                                 |

|                                                                                                                                                                                                                                                                                                                                             |                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                           | Physical Function Assessed by SHAQ-DI                 |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                           |                                                       |
| Change From Baseline in Finger Ulcers Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                           | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                     | 83                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                      | Pre-specified                                         |
| Analysis type                                                                                                                                                                                                                                                                                                                               | superiority                                           |
| P-value                                                                                                                                                                                                                                                                                                                                     | = 0.4717                                              |
| Method                                                                                                                                                                                                                                                                                                                                      | Mixed models analysis                                 |
| Parameter estimate                                                                                                                                                                                                                                                                                                                          | Difference in LS mean                                 |
| Point estimate                                                                                                                                                                                                                                                                                                                              | 4.89                                                  |
| Confidence interval                                                                                                                                                                                                                                                                                                                         |                                                       |
| level                                                                                                                                                                                                                                                                                                                                       | 95 %                                                  |
| sides                                                                                                                                                                                                                                                                                                                                       | 2-sided                                               |
| lower limit                                                                                                                                                                                                                                                                                                                                 | -8.59                                                 |
| upper limit                                                                                                                                                                                                                                                                                                                                 | 18.37                                                 |

|                                                                                                                                                                                                                                                                                                                          |                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                        | Physical Function Assessed by SHAQ-DI |
| Statistical analysis description:                                                                                                                                                                                                                                                                                        |                                       |
| Change From Baseline in Overall Disease Score at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score- |                                       |

by-visit interaction.

|                                         |                                                       |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups                       | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis | 83                                                    |
| Analysis specification                  | Pre-specified                                         |
| Analysis type                           | superiority                                           |
| P-value                                 | = 0.9876                                              |
| Method                                  | Mixed models analysis                                 |
| Parameter estimate                      | Difference in LS mean                                 |
| Point estimate                          | -0.08                                                 |
| Confidence interval                     |                                                       |
| level                                   | 95 %                                                  |
| sides                                   | 2-sided                                               |
| lower limit                             | -9.93                                                 |
| upper limit                             | 9.78                                                  |

|                                                                                                                                                                                                                                                                                                                                                                                                           |                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                         | Physical Function Assessed by SHAQ-DI                 |
| Statistical analysis description:<br>Change From Baseline in Intestinal VAS Score at Week 48. A total of 82 participants were included in analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medication, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                         | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                   | 83                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                    | Pre-specified                                         |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                             | superiority <sup>[2]</sup>                            |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                   | = 0.2407                                              |
| Method                                                                                                                                                                                                                                                                                                                                                                                                    | Mixed models analysis                                 |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                        | Difference in LS mean                                 |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                            | -6.8                                                  |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                       |                                                       |
| level                                                                                                                                                                                                                                                                                                                                                                                                     | 95 %                                                  |
| sides                                                                                                                                                                                                                                                                                                                                                                                                     | 2-sided                                               |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                               | -18.3                                                 |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                               | 4.71                                                  |

Notes:

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

|                                                                                                                                                                                                                                                                                                                                                                                                           |                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                         | Physical Function Assessed by SHAQ-DI                 |
| Statistical analysis description:<br>Change From Baseline in Breathing VAS Score at Week 48. A total of 82 participants were included in analysis. One participant from placebo group, included at Week 24 analysis, was not included in Week 48 analysis because this participant had taken escape medications, and after censoring for Week 48 analyses, had no valid efficacy result for the endpoint. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                         | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 83                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | = 0.7742                   |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | Difference in LS mean      |
| Point estimate                          | 1.54                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -9.18                      |
| upper limit                             | 12.26                      |

Notes:

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

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Physical Function Assessed by SHAQ-DI |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

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

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

Notes:

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

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Physical Function Assessed by SHAQ-DI |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

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

|                                         |                                                       |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups                       | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis | 83                                                    |
| Analysis specification                  | Pre-specified                                         |
| Analysis type                           | superiority <sup>[5]</sup>                            |
| P-value                                 | = 0.3106                                              |
| Method                                  | Mixed models analysis                                 |
| Parameter estimate                      | Difference in LS mean                                 |
| Point estimate                          | -5.8                                                  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -17.2   |
| upper limit         | 5.59    |

Notes:

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

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Physical Function Assessed by SHAQ-DI |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

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

|                                         |                                                       |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups                       | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis | 83                                                    |
| Analysis specification                  | Pre-specified                                         |
| Analysis type                           | superiority <sup>[6]</sup>                            |
| P-value                                 | = 0.1717                                              |
| Method                                  | Mixed models analysis                                 |
| Parameter estimate                      | Difference in LS mean                                 |
| Point estimate                          | -7.82                                                 |

Confidence interval

|             |         |
|-------------|---------|
| level       | 95 %    |
| sides       | 2-sided |
| lower limit | -19.11  |
| upper limit | 3.48    |

Notes:

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

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 24 and 48



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

## Statistical analyses

| Statistical analysis title | HAQ-DI Score at Week 24 |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

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

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

Notes:

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

| Statistical analysis title | HAQ-DI Score at Week 48 |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

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

|                                         |                                                       |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups                       | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis | 83                                                    |
| Analysis specification                  | Pre-specified                                         |
| Analysis type                           | superiority <sup>[8]</sup>                            |
| P-value                                 | = 0.1212                                              |
| Method                                  | Mixed models analysis                                 |
| Parameter estimate                      | Difference in LS mean                                 |
| Point estimate                          | -2.07                                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -4.71   |
| upper limit         | 0.056   |

Notes:

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

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 24 and 48

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

## Statistical analyses

|                            |                                                 |
|----------------------------|-------------------------------------------------|
| Statistical analysis title | Clinician's Global Assessment at Week 24 and 48 |
|----------------------------|-------------------------------------------------|

Statistical analysis description:

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

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

|                                         |                       |
|-----------------------------------------|-----------------------|
| Number of subjects included in analysis | 81                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.8118              |
| Method                                  | Mixed models analysis |
| Parameter estimate                      | Difference in LS mean |
| Point estimate                          | -0.99                 |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -9.2                  |
| upper limit                             | 7.23                  |

|                                   |                                                 |
|-----------------------------------|-------------------------------------------------|
| <b>Statistical analysis title</b> | Clinician's Global Assessment at Week 24 and 48 |
|-----------------------------------|-------------------------------------------------|

Statistical analysis description:

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

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

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 24 and 48

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

## Statistical analyses

| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                   | Patient's Global Assessment at Week 24 and 48         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                   |                                                       |
| Change From Baseline in Patient's Global Assessment at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                                   | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                             | 84                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                              | Pre-specified                                         |
| Analysis type                                                                                                                                                                                                                                                                                                                                       | superiority                                           |
| P-value                                                                                                                                                                                                                                                                                                                                             | = 0.4063                                              |
| Method                                                                                                                                                                                                                                                                                                                                              | Mixed models analysis                                 |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                  | Difference in LS mean                                 |
| Point estimate                                                                                                                                                                                                                                                                                                                                      | -3.85                                                 |
| Confidence interval                                                                                                                                                                                                                                                                                                                                 |                                                       |
| level                                                                                                                                                                                                                                                                                                                                               | 95 %                                                  |
| sides                                                                                                                                                                                                                                                                                                                                               | 2-sided                                               |
| lower limit                                                                                                                                                                                                                                                                                                                                         | -13.04                                                |
| upper limit                                                                                                                                                                                                                                                                                                                                         | 5.34                                                  |

| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                   | Patient's Global Assessment at Week 24 and 48         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                   |                                                       |
| Change From Baseline in Patient's Global Assessment at Week 48. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                                   | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |

|                                         |                       |
|-----------------------------------------|-----------------------|
| Number of subjects included in analysis | 84                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.1371              |
| Method                                  | Mixed models analysis |
| Parameter estimate                      | Difference in LS mean |
| Point estimate                          | -8.3                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -19.31                |
| upper limit                             | 2.71                  |

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 24 and 48

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

### Statistical analyses

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

Statistical analysis description:

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

by-visit interaction.

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

### Statistical analysis title

FACIT-Fatigue Score at Week 24 and 48

Statistical analysis description:

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

|                                         |                                                       |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups                       | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis | 83                                                    |
| Analysis specification                  | Pre-specified                                         |
| Analysis type                           | superiority                                           |
| P-value                                 | = 0.1886                                              |
| Method                                  | Mixed models analysis                                 |
| Parameter estimate                      | Difference in LS mean                                 |
| Point estimate                          | 2.75                                                  |
| Confidence interval                     |                                                       |
| level                                   | 95 %                                                  |
| sides                                   | 2-sided                                               |
| lower limit                             | -1.38                                                 |
| upper limit                             | 6.88                                                  |

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

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

End point description:

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

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

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

## Statistical analyses

| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                      | 5-D Itch Scale at Week 24 and Week 48                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                      |                                                       |
| Change From Baseline in 5-D Itch Scale at Week 24. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                      | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                | 82                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                 | Pre-specified                                         |
| Analysis type                                                                                                                                                                                                                                                                                                                          | superiority                                           |
| P-value                                                                                                                                                                                                                                                                                                                                | = 0.3651                                              |
| Method                                                                                                                                                                                                                                                                                                                                 | Mixed models analysis                                 |
| Parameter estimate                                                                                                                                                                                                                                                                                                                     | Difference in LS mean                                 |
| Point estimate                                                                                                                                                                                                                                                                                                                         | 0.79                                                  |
| Confidence interval                                                                                                                                                                                                                                                                                                                    |                                                       |
| level                                                                                                                                                                                                                                                                                                                                  | 95 %                                                  |
| sides                                                                                                                                                                                                                                                                                                                                  | 2-sided                                               |
| lower limit                                                                                                                                                                                                                                                                                                                            | -0.94                                                 |
| upper limit                                                                                                                                                                                                                                                                                                                            | 2.51                                                  |

| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                      | 5-D Itch Scale at Week 24 and Week 48                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                      |                                                       |
| Change From Baseline in 5-D Itch Scale at Week 48. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                                                                      | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |

|                                         |                       |
|-----------------------------------------|-----------------------|
| Number of subjects included in analysis | 82                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.2841              |
| Method                                  | Mixed models analysis |
| Parameter estimate                      | Difference in LS mean |
| Point estimate                          | -1.11                 |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -3.16                 |
| upper limit                             | 0.94                  |

## Secondary: Change From Baseline in mRSS at Week 48

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

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

## Statistical analyses

|                                                                                                                                                                                                                                                                                     |                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                          | Change From Baseline in mRSS at Week 48               |
| Statistical analysis description:                                                                                                                                                                                                                                                   |                                                       |
| The analysis included the fixed, categorical effects of treatment, visit, the stratification factor of joint involvement at the baseline visit, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. |                                                       |
| Comparison groups                                                                                                                                                                                                                                                                   | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |



|                                         |                       |
|-----------------------------------------|-----------------------|
| Number of subjects included in analysis | 84                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.0579              |
| Method                                  | Mixed models analysis |
| Parameter estimate                      | Difference in LS mean |
| Point estimate                          | -3.55                 |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -7.23                 |
| upper limit                             | 0.12                  |

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

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

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

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                    |                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                         | Improvement in mRSS From Week 24 to 48 |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                  |                                        |
| Percentage of Participants Who Maintained or Improved in mRSS From Week 24 to Week 48. The logistic regression model included the fixed categorical effects of treatment and the stratification factor of joint involvement at the baseline visit. The continuous covariate of baseline mRSS score was also included in the model. |                                        |

|                                         |                                                       |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups                       | Placebo (Up to Week 48) v Tocilizumab (Up to Week 48) |
| Number of subjects included in analysis | 84                                                    |
| Analysis specification                  | Pre-specified                                         |
| Analysis type                           | superiority                                           |
| P-value                                 | = 0.2159                                              |
| Method                                  | Regression, Logistic                                  |
| Parameter estimate                      | Odds ratio (OR)                                       |
| Point estimate                          | 2.39                                                  |
| Confidence interval                     |                                                       |
| level                                   | 95 %                                                  |
| sides                                   | 2-sided                                               |
| lower limit                             | 0.6                                                   |
| upper limit                             | 9.5                                                   |
| Variability estimate                    | Standard error of the mean                            |
| Dispersion value                        | 0.704                                                 |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                               | Change From Baseline in Tender Joint Count 28 (TJC28) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                        |                                                       |
| Joint tenderness was evaluated as per assessment of 28 joints. Joints on both sides of the body, including shoulders, elbows, wrists, 10 metacarpal phalangeal (MCP) joints, 10 proximal interphalangeal joint (PIP) joints, and both knees, were assessed. Joints were classified as not tender = 0 or tender = 1. ITT population. Here n = evaluable for the specific item at specified time point in specified time frame. |                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                | Secondary                                             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                          |                                                       |
| Baseline, Weeks 3, 8, 16, 24, 32, 40, and 48                                                                                                                                                                                                                                                                                                                                                                                  |                                                       |

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No inter-group analysis was performed.

|                                              |                                |  |  |  |
|----------------------------------------------|--------------------------------|--|--|--|
| <b>End point values</b>                      | Tocilizumab<br>(Up to Week 24) |  |  |  |
| Subject group type                           | Reporting group                |  |  |  |
| Number of subjects analysed                  | 7                              |  |  |  |
| Units: $\mu\text{g}\cdot\text{hr}/\text{mL}$ |                                |  |  |  |
| arithmetic mean (standard deviation)         |                                |  |  |  |
| Baseline (n=7)                               | 686 ( $\pm$ 455)               |  |  |  |
| Week 16 (n=4)                                | 7508 ( $\pm$ 2369)             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values                         | Placebo (Up to Week 48) | Tocilizumab (Up to Week 48) |  |  |
|------------------------------------------|-------------------------|-----------------------------|--|--|
| Subject group type                       | Reporting group         | Reporting group             |  |  |
| Number of subjects analysed              | 43                      | 43                          |  |  |
| Units: picograms per milliliters (pg/mL) |                         |                             |  |  |
| arithmetic mean (standard deviation)     |                         |                             |  |  |
| Baseline (n=43, 42)                      | 15.02 (± 18.19)         | 13.57 (± 14.69)             |  |  |
| Week 1: Absolute values (n=43, 43)       | 17.24 (± 22.77)         | 158.91 (± 326.42)           |  |  |
| Week 1: Change From Baseline (n=42, 42)  | 1.33 (± 27.29)          | 147.37 (± 326.2)            |  |  |
| Week 2: Absolute values (n=43, 41)       | 12.6 (± 13.78)          | 107.1 (± 73.75)             |  |  |
| Week 2: Change From Baseline (n=42, 40)  | -3.07 (± 17.85)         | 94.54 (± 67.99)             |  |  |
| Week 3: Absolute values (n=42, 40)       | 12.47 (± 10.72)         | 116.58 (± 75.31)            |  |  |
| Week 3: Change From Baseline (n=41, 39)  | -3.6 (± 15.28)          | 104.44 (± 71.84)            |  |  |
| Week 8: Absolute values (n=42, 39)       | 15.39 (± 19.04)         | 115.31 (± 66.39)            |  |  |
| Week 8: Change From Baseline(n=41,38)    | 0.15 (± 18.65)          | 104.14 (± 62.95)            |  |  |
| Week 16: Absolute values (n=32,33)       | 12.51 (± 14.06)         | 98.36 (± 61.65)             |  |  |
| Week 16: Change From Baseline (n=31,32)  | -1.26 (± 11.34)         | 88.86 (± 59.77)             |  |  |
| Week 24: Absolute values (n=36,34)       | 10.19 (± 10.55)         | 84.67 (± 68.37)             |  |  |
| Week 24: Change From Baseline(n=35,33)   | -2.74 (± 12.43)         | 73.61 (± 68.07)             |  |  |
| Week 48: Absolute values (n=32,27)       | 10.5 (± 11.82)          | 65.3 (± 35.95)              |  |  |
| Week 48: Change From Baseline (n=31,26)  | -2.61 (± 14.92)         | 55.6 (± 35.86)              |  |  |

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values                         | Placebo (Up to Week 48) | Tocilizumab (Up to Week 48) |  |  |
|------------------------------------------|-------------------------|-----------------------------|--|--|
| Subject group type                       | Reporting group         | Reporting group             |  |  |
| Number of subjects analysed              | 44                      | 43                          |  |  |
| Units: pg/mL                             |                         |                             |  |  |
| arithmetic mean (standard deviation)     |                         |                             |  |  |
| Baseline (n=44, 42)                      | 37.61 (± 11.12)         | 39.39 (± 10.16)             |  |  |
| Week 1: Absolute values (n=44, 43)       | 51.03 (± 59.12)         | 237.34 (± 71.38)            |  |  |
| Week 1: Change From Baseline (n=44, 42)  | 13.42 (± 57.91)         | 198.39 (± 69.41)            |  |  |
| Week 2: Absolute values (n=43, 41)       | 44.07 (± 42.15)         | 329.9 (± 81.93)             |  |  |
| Week 2: Change From Baseline (n=43, 40)  | 6.13 (± 41.6)           | 291.38 (± 79.29)            |  |  |
| Week 3: Absolute values (n=44, 40)       | 41.64 (± 27.07)         | 384.88 (± 99.41)            |  |  |
| Week 3: Change From Baseline (n=44, 39)  | 4.03 (± 26)             | 346.68 (± 95.96)            |  |  |
| Week 8: Absolute values (n=42, 39)       | 38.66 (± 11.95)         | 486.62 (± 116.41)           |  |  |
| Week 8: Change From Baseline (n=42, 38)  | 0.91 (± 5.07)           | 447.77 (± 114.4)            |  |  |
| Week 16: Absolute values (n=32, 33)      | 37.71 (± 10.3)          | 525.48 (± 164.9)            |  |  |
| Week 16: Change From Baseline (n=32, 32) | -0.08 (± 5.71)          | 486.43 (± 163.32)           |  |  |
| Week 24: Absolute values (n=36, 34)      | 38.72 (± 13.06)         | 520.18 (± 167.97)           |  |  |
| Week 24: Change From Baseline (n=36, 33) | 1.11 (± 6.47)           | 482.1 (± 168.44)            |  |  |
| Week 48: Absolute values (n=32, 27)      | 36.52 (± 9.93)          | 491.44 (± 164.82)           |  |  |
| Week 48: Change From Baseline (n=32, 26) | -0.75 (± 5.2)           | 454.19 (± 163.93)           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Anti-Tocilizumab Antibody

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Percentage of Participants With Anti-Tocilizumab Antibody |
|-----------------|-----------------------------------------------------------|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 96 (reporting groups up to 24 Weeks and up to 48 Weeks present data as of the 11 July 2014 data cut-off date; reporting groups up to 96 weeks present data as of the 05 August 2015 data cut-off date).

Adverse event reporting additional description:

MedDRA 17.0 was utilized up to Week 48; MedDRA 18.0 was utilized for Week 48 up to Week 96

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Placebo (up to 24 Weeks) |
|-----------------------|--------------------------|

Reporting group description:

Participants received TCZ matched placebo by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96. The data analyzed for placebo up to Week 24 was presented in this arm group.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Tocilizumab (up to 24 Weeks) |
|-----------------------|------------------------------|

Reporting group description:

Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96. The data analyzed for TCZ up to Week 24 was presented in this arm group.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Placebo (up to 48 Weeks) |
|-----------------------|--------------------------|

Reporting group description:

Participants received TCZ matched placebo by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96. The data analyzed for placebo up to Week 48 was presented in this arm group.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Tocilizumab (up to 48 Weeks) |
|-----------------------|------------------------------|

Reporting group description:

Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96. The data analyzed for TCZ up to Week 48 was presented in this arm group.

|                       |                                         |
|-----------------------|-----------------------------------------|
| Reporting group title | Placebo to Tocilizumab (up to 96 Weeks) |
|-----------------------|-----------------------------------------|

Reporting group description:

Participants received TCZ matched placebo by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then received TCZ (162 mg) SC injection qw in the open-label period for Week 48 to Week 96. The data analyzed for double-blind placebo to open-label tocilizumab up to Week 96 are presented in this reporting group.

|                       |                                             |
|-----------------------|---------------------------------------------|
| Reporting group title | Tocilizumab to Tocilizumab (up to 96 Weeks) |
|-----------------------|---------------------------------------------|

Reporting group description:

Participants received TCZ (162 mg) by SC injection qw for Week 0 to Week 48 (blinded-treatment period) and then in the open-label period for Week 48 to Week 96. The data analyzed for double-blind tocilizumab to open-label tocilizumab up to Week 96 are presented in this reporting group.

| Serious adverse events                            | Placebo (up to 24 Weeks) | Tocilizumab (up to 24 Weeks) | Placebo (up to 48 Weeks) |
|---------------------------------------------------|--------------------------|------------------------------|--------------------------|
| Total subjects affected by serious adverse events |                          |                              |                          |
| subjects affected / exposed                       | 11 / 44 (25.00%)         | 9 / 43 (20.93%)              | 15 / 44 (34.09%)         |
| number of deaths (all causes)                     | 1                        | 1                            | 1                        |

|                                                                     |                |                |                |
|---------------------------------------------------------------------|----------------|----------------|----------------|
| number of deaths resulting from adverse events                      |                |                |                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |                |
| Breast cancer metastatic                                            |                |                |                |
| subjects affected / exposed                                         | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Uterine leiomyoma                                                   |                |                |                |
| subjects affected / exposed                                         | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                                                  |                |                |                |
| Hypertension                                                        |                |                |                |
| subjects affected / exposed                                         | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypertensive emergency                                              |                |                |                |
| subjects affected / exposed                                         | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Raynaud's phenomenon                                                |                |                |                |
| subjects affected / exposed                                         | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all                     | 0 / 2          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Peripheral ischaemia                                                |                |                |                |
| subjects affected / exposed                                         | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions                |                |                |                |
| Impaired healing                                                    |                |                |                |
| subjects affected / exposed                                         | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Multi-organ failure                                                 |                |                |                |



|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders        |                |                |                |
| Uterine haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Status asthmaticus                              |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Psychotic disorder                              |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure                                 |                |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| Cyanosis                                        |                |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arrhythmia                                      |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrioventricular block                          |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial flutter                                  |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Congestive cardiomyopathy                       |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Headache                                        |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Subarachnoid haemorrhage                        |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Haemolytic uraemic syndrome                     |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Iron deficiency anaemia                         |                |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eosinophilia                                    |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Gastrointestinal disorders</b>               |                |                |                |
| Colonic pseudo-obstruction                      |                |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastric antral vascular ectasia                 |                |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal distension                            |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Retroperitoneal fibrosis                        |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Skin and subcutaneous tissue disorders</b>   |                |                |                |
| Skin ulcer                                      |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin necrosis                                   |                |                |                |

|                                                 |                                                                                                                         |                |                |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 44 (0.00%)                                                                                                          | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                                                                                                                         |                |                |
| Renal failure acute                             | Additional description: The previous event Renal failure acute at Week 48 was updated to Acute kidney injury at Week 96 |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%)                                                                                                          | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1                                                                                                                   | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Scleroderma renal crisis                        |                                                                                                                         |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%)                                                                                                          | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1                                                                                                                   | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Acute kidney injury                             |                                                                                                                         |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%)                                                                                                          | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Endocrine disorders                             |                                                                                                                         |                |                |
| Autoimmune thyroiditis                          |                                                                                                                         |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%)                                                                                                          | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                                                                                                                         |                |                |
| Scleroderma                                     |                                                                                                                         |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%)                                                                                                          | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1                                                                                                                   | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Systemic sclerosis                              |                                                                                                                         |                |                |
| subjects affected / exposed                     | 1 / 44 (2.27%)                                                                                                          | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1                                                                                                                   | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Osteoarthritis                                  |                                                                                                                         |                |                |

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

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Pneumonia</b>                                |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Post procedural cellulitis</b>               |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Sepsis</b>                                   |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Appendicitis</b>                             |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Device related infection</b>                 |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Tuberculosis</b>                             |                |                |                |
| subjects affected / exposed                     | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | Tocilizumab (up to 48 Weeks) | Placebo to Tocilizumab (up to 96 Weeks) | Tocilizumab to Tocilizumab (up to 96 Weeks) |
|---------------------------------------------------|------------------------------|-----------------------------------------|---------------------------------------------|
| Total subjects affected by serious adverse events |                              |                                         |                                             |
| subjects affected / exposed                       | 14 / 43 (32.56%)             | 22 / 44 (50.00%)                        | 17 / 43 (39.53%)                            |
| number of deaths (all causes)                     | 2                            | 1                                       | 2                                           |
| number of deaths resulting from adverse events    |                              |                                         |                                             |

|                                                                     |                |                |                |
|---------------------------------------------------------------------|----------------|----------------|----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |                |
| Breast cancer metastatic                                            |                |                |                |
| subjects affected / exposed                                         | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Uterine leiomyoma                                                   |                |                |                |
| subjects affected / exposed                                         | 0 / 43 (0.00%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                                                  |                |                |                |
| Hypertension                                                        |                |                |                |
| subjects affected / exposed                                         | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypertensive emergency                                              |                |                |                |
| subjects affected / exposed                                         | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Raynaud's phenomenon                                                |                |                |                |
| subjects affected / exposed                                         | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Peripheral ischaemia                                                |                |                |                |
| subjects affected / exposed                                         | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| General disorders and administration site conditions                |                |                |                |
| Impaired healing                                                    |                |                |                |
| subjects affected / exposed                                         | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Multi-organ failure                                                 |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| Reproductive system and breast disorders        |                |                |                |
| Uterine haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Status asthmaticus                              |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Psychiatric disorders                           |                |                |                |
| Psychotic disorder                              |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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                                 |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Cyanosis                                        |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Arrhythmia                                      |                |                |                |



|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| Atrioventricular block                          |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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 flutter                                  |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Congestive cardiomyopathy                       |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Headache                                        |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Subarachnoid haemorrhage                        |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Blood and lymphatic system disorders            |                |                |                |
| Haemolytic uraemic syndrome                     |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Iron deficiency anaemia                         |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Eosinophilia                                    |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| <b>Gastrointestinal disorders</b>               |                |                |                |
| Colonic pseudo-obstruction                      |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Gastric antral vascular ectasia                 |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal distension                            |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Retroperitoneal fibrosis                        |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| <b>Skin and subcutaneous tissue disorders</b>   |                |                |                |
| Skin ulcer                                      |                |                |                |
| subjects affected / exposed                     | 2 / 43 (4.65%) | 1 / 44 (2.27%) | 2 / 43 (4.65%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin necrosis                                   |                |                |                |

|                                                 |                                                                                                                         |                |                |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                          | 1 / 44 (2.27%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                   | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                                                                                                                         |                |                |
| Renal failure acute                             | Additional description: The previous event Renal failure acute at Week 48 was updated to Acute kidney injury at Week 96 |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                          | 0 / 44 (0.00%) | 0 / 43 (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          |
| Scleroderma renal crisis                        |                                                                                                                         |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                          | 2 / 44 (4.55%) | 0 / 43 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                   | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Acute kidney injury                             |                                                                                                                         |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                          | 1 / 44 (2.27%) | 0 / 43 (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          |
| Endocrine disorders                             |                                                                                                                         |                |                |
| Autoimmune thyroiditis                          |                                                                                                                         |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                          | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                   | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                                                                                                                         |                |                |
| Scleroderma                                     |                                                                                                                         |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                          | 1 / 44 (2.27%) | 0 / 43 (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          |
| Systemic sclerosis                              |                                                                                                                         |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%)                                                                                                          | 1 / 44 (2.27%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1                                                                                                                   | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                   | 0 / 0          | 0 / 0          |
| Osteoarthritis                                  |                                                                                                                         |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Infections and infestations                     |                |                |                |
| Osteomyelitis                                   |                |                |                |
| subjects affected / exposed                     | 2 / 43 (4.65%) | 2 / 44 (4.55%) | 2 / 43 (4.65%) |
| occurrences causally related to treatment / all | 2 / 2          | 2 / 2          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchitis                                      |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Infected skin ulcer                             |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 2 / 44 (4.55%) | 2 / 43 (4.65%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 3          | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lower respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Lung infection                                  |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          | 1 / 1          |
| Oesophageal candidiasis                         |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 1 / 44 (2.27%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural cellulitis                      |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis                                          |                |                |                |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 0 / 44 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tuberculosis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 44 (2.27%) | 0 / 43 (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          |

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

| <b>Non-serious adverse events</b>                     | Placebo (up to 24 Weeks) | Tocilizumab (up to 24 Weeks) | Placebo (up to 48 Weeks) |
|-------------------------------------------------------|--------------------------|------------------------------|--------------------------|
| Total subjects affected by non-serious adverse events |                          |                              |                          |
| subjects affected / exposed                           | 26 / 44 (59.09%)         | 28 / 43 (65.12%)             | 32 / 44 (72.73%)         |
| Injury, poisoning and procedural complications        |                          |                              |                          |
| Fall                                                  |                          |                              |                          |
| subjects affected / exposed                           | 0 / 44 (0.00%)           | 0 / 43 (0.00%)               | 0 / 44 (0.00%)           |
| occurrences (all)                                     | 0                        | 0                            | 0                        |
| Vascular disorders                                    |                          |                              |                          |
| Raynaud's phenomenon                                  |                          |                              |                          |
| subjects affected / exposed                           | 1 / 44 (2.27%)           | 3 / 43 (6.98%)               | 2 / 44 (4.55%)           |
| occurrences (all)                                     | 1                        | 3                            | 2                        |
| Hypertension                                          |                          |                              |                          |
| subjects affected / exposed                           | 0 / 44 (0.00%)           | 0 / 43 (0.00%)               | 3 / 44 (6.82%)           |
| occurrences (all)                                     | 0                        | 0                            | 3                        |
| Nervous system disorders                              |                          |                              |                          |
| Dizziness                                             |                          |                              |                          |
| subjects affected / exposed                           | 2 / 44 (4.55%)           | 3 / 43 (6.98%)               | 2 / 44 (4.55%)           |
| occurrences (all)                                     | 2                        | 3                            | 2                        |
| Headache                                              |                          |                              |                          |
| subjects affected / exposed                           | 2 / 44 (4.55%)           | 3 / 43 (6.98%)               | 3 / 44 (6.82%)           |
| occurrences (all)                                     | 2                        | 5                            | 3                        |
| General disorders and administration site conditions  |                          |                              |                          |
| Asthenia                                              |                          |                              |                          |
| subjects affected / exposed                           | 3 / 44 (6.82%)           | 0 / 43 (0.00%)               | 3 / 44 (6.82%)           |
| occurrences (all)                                     | 3                        | 0                            | 3                        |
| Fatigue                                               |                          |                              |                          |
| subjects affected / exposed                           | 2 / 44 (4.55%)           | 4 / 43 (9.30%)               | 2 / 44 (4.55%)           |
| occurrences (all)                                     | 2                        | 7                            | 2                        |
| Oedema peripheral                                     |                          |                              |                          |
| subjects affected / exposed                           | 1 / 44 (2.27%)           | 3 / 43 (6.98%)               | 1 / 44 (2.27%)           |
| occurrences (all)                                     | 1                        | 3                            | 1                        |
| Injection site erythema                               |                          |                              |                          |
| subjects affected / exposed                           | 0 / 44 (0.00%)           | 0 / 43 (0.00%)               | 0 / 44 (0.00%)           |
| occurrences (all)                                     | 0                        | 0                            | 0                        |
| Gastrointestinal disorders                            |                          |                              |                          |

|                                                 |  |                                                                                                                                                                                                      |                 |                 |
|-------------------------------------------------|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|
| Abdominal Pain                                  |  | Additional description: One case of abdominal pain was updated between Week 24 and 48 to diverticulum. The remaining 2 cases at week 48 fall below the 5% threshold and are therefore not presented. |                 |                 |
| subjects affected / exposed                     |  | 0 / 44 (0.00%)                                                                                                                                                                                       | 3 / 43 (6.98%)  | 0 / 44 (0.00%)  |
| occurrences (all)                               |  | 0                                                                                                                                                                                                    | 3               | 0               |
| Diarrhoea                                       |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 4 / 44 (9.09%)                                                                                                                                                                                       | 6 / 43 (13.95%) | 4 / 44 (9.09%)  |
| occurrences (all)                               |  | 4                                                                                                                                                                                                    | 7               | 4               |
| Gastrooesophageal reflux disease                |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 4 / 44 (9.09%)                                                                                                                                                                                       | 4 / 43 (9.30%)  | 5 / 44 (11.36%) |
| occurrences (all)                               |  | 4                                                                                                                                                                                                    | 4               | 5               |
| Vomiting                                        |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 0 / 44 (0.00%)                                                                                                                                                                                       | 3 / 43 (6.98%)  | 1 / 44 (2.27%)  |
| occurrences (all)                               |  | 0                                                                                                                                                                                                    | 3               | 1               |
| Dyspepsia                                       |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 0 / 44 (0.00%)                                                                                                                                                                                       | 0 / 43 (0.00%)  | 3 / 44 (6.82%)  |
| occurrences (all)                               |  | 0                                                                                                                                                                                                    | 0               | 3               |
| Nausea                                          |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 0 / 44 (0.00%)                                                                                                                                                                                       | 0 / 43 (0.00%)  | 3 / 44 (6.82%)  |
| occurrences (all)                               |  | 0                                                                                                                                                                                                    | 0               | 5               |
| Constipation                                    |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 0 / 44 (0.00%)                                                                                                                                                                                       | 0 / 43 (0.00%)  | 0 / 44 (0.00%)  |
| occurrences (all)                               |  | 0                                                                                                                                                                                                    | 0               | 0               |
| Mouth ulceration                                |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 0 / 44 (0.00%)                                                                                                                                                                                       | 0 / 43 (0.00%)  | 0 / 44 (0.00%)  |
| occurrences (all)                               |  | 0                                                                                                                                                                                                    | 0               | 0               |
| Respiratory, thoracic and mediastinal disorders |  |                                                                                                                                                                                                      |                 |                 |
| Dyspnoea                                        |  | Additional description: The Investigator removed an adverse event of dyspnoea between Week 24 and Week 48 reporting events.                                                                          |                 |                 |
| subjects affected / exposed                     |  | 4 / 44 (9.09%)                                                                                                                                                                                       | 2 / 43 (4.65%)  | 3 / 44 (6.82%)  |
| occurrences (all)                               |  | 4                                                                                                                                                                                                    | 2               | 3               |
| Cough                                           |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 0 / 44 (0.00%)                                                                                                                                                                                       | 0 / 43 (0.00%)  | 0 / 44 (0.00%)  |
| occurrences (all)                               |  | 0                                                                                                                                                                                                    | 0               | 0               |
| Oropharyngeal pain                              |  |                                                                                                                                                                                                      |                 |                 |
| subjects affected / exposed                     |  | 0 / 44 (0.00%)                                                                                                                                                                                       | 0 / 43 (0.00%)  | 0 / 44 (0.00%)  |
| occurrences (all)                               |  | 0                                                                                                                                                                                                    | 0               | 0               |
| Pulmonary hypertension                          |  |                                                                                                                                                                                                      |                 |                 |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 44 (0.00%)<br>0 | 0 / 43 (0.00%)<br>0 | 0 / 44 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders           |                     |                     |                     |
| Pruritus                                         |                     |                     |                     |
| subjects affected / exposed                      | 3 / 44 (6.82%)      | 7 / 43 (16.28%)     | 4 / 44 (9.09%)      |
| occurrences (all)                                | 3                   | 8                   | 4                   |
| Skin ulcer                                       |                     |                     |                     |
| subjects affected / exposed                      | 6 / 44 (13.64%)     | 6 / 43 (13.95%)     | 7 / 44 (15.91%)     |
| occurrences (all)                                | 7                   | 15                  | 11                  |
| Erythema                                         |                     |                     |                     |
| subjects affected / exposed                      | 0 / 44 (0.00%)      | 0 / 43 (0.00%)      | 0 / 44 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Pruritus generalised                             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 44 (0.00%)      | 0 / 43 (0.00%)      | 0 / 44 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Psychiatric disorders                            |                     |                     |                     |
| Sleep disorder                                   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 44 (0.00%)      | 0 / 43 (0.00%)      | 3 / 44 (6.82%)      |
| occurrences (all)                                | 0                   | 0                   | 3                   |
| Musculoskeletal and connective tissue disorders  |                     |                     |                     |
| Arthralgia                                       |                     |                     |                     |
| subjects affected / exposed                      | 6 / 44 (13.64%)     | 6 / 43 (13.95%)     | 8 / 44 (18.18%)     |
| occurrences (all)                                | 7                   | 6                   | 11                  |
| Back pain                                        |                     |                     |                     |
| subjects affected / exposed                      | 3 / 44 (6.82%)      | 5 / 43 (11.63%)     | 3 / 44 (6.82%)      |
| occurrences (all)                                | 4                   | 5                   | 4                   |
| Pain in extremity                                |                     |                     |                     |
| subjects affected / exposed                      | 1 / 44 (2.27%)      | 5 / 43 (11.63%)     | 2 / 44 (4.55%)      |
| occurrences (all)                                | 1                   | 5                   | 2                   |
| Musculoskeletal pain                             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 44 (0.00%)      | 0 / 43 (0.00%)      | 0 / 44 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Infections and infestations                      |                     |                     |                     |
| Infected skin ulcer                              |                     |                     |                     |
| subjects affected / exposed                      | 5 / 44 (11.36%)     | 0 / 43 (0.00%)      | 5 / 44 (11.36%)     |
| occurrences (all)                                | 6                   | 0                   | 7                   |



|                                                                                       |                     |                     |                      |
|---------------------------------------------------------------------------------------|---------------------|---------------------|----------------------|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 44 (4.55%)<br>3 | 3 / 43 (6.98%)<br>3 | 4 / 44 (9.09%)<br>5  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 3 / 44 (6.82%)<br>3 | 2 / 43 (4.65%)<br>2 | 3 / 44 (6.82%)<br>3  |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 44 (0.00%)<br>0 | 0 / 43 (0.00%)<br>0 | 2 / 44 (4.55%)<br>2  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 44 (0.00%)<br>0 | 0 / 43 (0.00%)<br>0 | 6 / 44 (13.64%)<br>8 |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 44 (0.00%)<br>0 | 0 / 43 (0.00%)<br>0 | 0 / 44 (0.00%)<br>0  |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 44 (0.00%)<br>0 | 0 / 43 (0.00%)<br>0 | 0 / 44 (0.00%)<br>0  |

| <b>Non-serious adverse events</b>                                                                                                                                      | Tocilizumab (up to 48 Weeks)                    | Placebo to Tocilizumab (up to 96 Weeks)        | Tocilizumab to Tocilizumab (up to 96 Weeks)     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------|-------------------------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                                                                   | 34 / 43 (79.07%)                                | 39 / 44 (88.64%)                               | 38 / 43 (88.37%)                                |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)                                                             | 0 / 43 (0.00%)<br>0                             | 0 / 44 (0.00%)<br>0                            | 3 / 43 (6.98%)<br>3                             |
| Vascular disorders<br>Raynaud's phenomenon<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypertension<br>subjects affected / exposed<br>occurrences (all) | 5 / 43 (11.63%)<br>5<br><br>2 / 43 (4.65%)<br>2 | 2 / 44 (4.55%)<br>2<br><br>4 / 44 (9.09%)<br>4 | 6 / 43 (13.95%)<br>6<br><br>3 / 43 (6.98%)<br>3 |
| Nervous system disorders<br>Dizziness                                                                                                                                  |                                                 |                                                |                                                 |

|                                                      |                                                                                                                                                                                                      |                 |                  |
|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------|
| subjects affected / exposed                          | 3 / 43 (6.98%)                                                                                                                                                                                       | 2 / 44 (4.55%)  | 5 / 43 (11.63%)  |
| occurrences (all)                                    | 3                                                                                                                                                                                                    | 2               | 5                |
| Headache                                             |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 5 / 43 (11.63%)                                                                                                                                                                                      | 5 / 44 (11.36%) | 8 / 43 (18.60%)  |
| occurrences (all)                                    | 7                                                                                                                                                                                                    | 6               | 12               |
| General disorders and administration site conditions |                                                                                                                                                                                                      |                 |                  |
| Asthenia                                             |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 0 / 43 (0.00%)                                                                                                                                                                                       | 3 / 44 (6.82%)  | 0 / 43 (0.00%)   |
| occurrences (all)                                    | 0                                                                                                                                                                                                    | 3               | 0                |
| Fatigue                                              |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 5 / 43 (11.63%)                                                                                                                                                                                      | 3 / 44 (6.82%)  | 6 / 43 (13.95%)  |
| occurrences (all)                                    | 9                                                                                                                                                                                                    | 3               | 10               |
| Oedema peripheral                                    |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 3 / 43 (6.98%)                                                                                                                                                                                       | 3 / 44 (6.82%)  | 4 / 43 (9.30%)   |
| occurrences (all)                                    | 3                                                                                                                                                                                                    | 3               | 4                |
| Injection site erythema                              |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 0 / 43 (0.00%)                                                                                                                                                                                       | 2 / 44 (4.55%)  | 3 / 43 (6.98%)   |
| occurrences (all)                                    | 0                                                                                                                                                                                                    | 3               | 3                |
| Gastrointestinal disorders                           |                                                                                                                                                                                                      |                 |                  |
| Abdominal Pain                                       | Additional description: One case of abdominal pain was updated between Week 24 and 48 to diverticulum. The remaining 2 cases at week 48 fall below the 5% threshold and are therefore not presented. |                 |                  |
| subjects affected / exposed                          | 0 / 43 (0.00%)                                                                                                                                                                                       | 2 / 44 (4.55%)  | 4 / 43 (9.30%)   |
| occurrences (all)                                    | 0                                                                                                                                                                                                    | 2               | 4                |
| Diarrhoea                                            |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 7 / 43 (16.28%)                                                                                                                                                                                      | 5 / 44 (11.36%) | 12 / 43 (27.91%) |
| occurrences (all)                                    | 9                                                                                                                                                                                                    | 5               | 16               |
| Gastrooesophageal reflux disease                     |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 5 / 43 (11.63%)                                                                                                                                                                                      | 7 / 44 (15.91%) | 5 / 43 (11.63%)  |
| occurrences (all)                                    | 5                                                                                                                                                                                                    | 7               | 5                |
| Vomiting                                             |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 3 / 43 (6.98%)                                                                                                                                                                                       | 2 / 44 (4.55%)  | 3 / 43 (6.98%)   |
| occurrences (all)                                    | 4                                                                                                                                                                                                    | 4               | 5                |
| Dyspepsia                                            |                                                                                                                                                                                                      |                 |                  |
| subjects affected / exposed                          | 3 / 43 (6.98%)                                                                                                                                                                                       | 3 / 44 (6.82%)  | 3 / 43 (6.98%)   |
| occurrences (all)                                    | 3                                                                                                                                                                                                    | 3               | 3                |
| Nausea                                               |                                                                                                                                                                                                      |                 |                  |

|                                                 |                                                                                                                             |                 |                  |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------|------------------|
| subjects affected / exposed                     | 2 / 43 (4.65%)                                                                                                              | 5 / 44 (11.36%) | 3 / 43 (6.98%)   |
| occurrences (all)                               | 2                                                                                                                           | 7               | 3                |
| Constipation                                    |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                              | 4 / 44 (9.09%)  | 2 / 43 (4.65%)   |
| occurrences (all)                               | 0                                                                                                                           | 4               | 2                |
| Mouth ulceration                                |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                              | 3 / 44 (6.82%)  | 2 / 43 (4.65%)   |
| occurrences (all)                               | 0                                                                                                                           | 3               | 2                |
| Respiratory, thoracic and mediastinal disorders |                                                                                                                             |                 |                  |
| Dyspnoea                                        | Additional description: The Investigator removed an adverse event of dyspnoea between Week 24 and Week 48 reporting events. |                 |                  |
| subjects affected / exposed                     | 4 / 43 (9.30%)                                                                                                              | 3 / 44 (6.82%)  | 5 / 43 (11.63%)  |
| occurrences (all)                               | 4                                                                                                                           | 3               | 5                |
| Cough                                           |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                              | 1 / 44 (2.27%)  | 4 / 43 (9.30%)   |
| occurrences (all)                               | 0                                                                                                                           | 1               | 4                |
| Oropharyngeal pain                              |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                              | 0 / 44 (0.00%)  | 3 / 43 (6.98%)   |
| occurrences (all)                               | 0                                                                                                                           | 0               | 3                |
| Pulmonary hypertension                          |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                              | 1 / 44 (2.27%)  | 3 / 43 (6.98%)   |
| occurrences (all)                               | 0                                                                                                                           | 1               | 3                |
| Skin and subcutaneous tissue disorders          |                                                                                                                             |                 |                  |
| Pruritus                                        |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 8 / 43 (18.60%)                                                                                                             | 9 / 44 (20.45%) | 12 / 43 (27.91%) |
| occurrences (all)                               | 9                                                                                                                           | 9               | 13               |
| Skin ulcer                                      |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 7 / 43 (16.28%)                                                                                                             | 9 / 44 (20.45%) | 8 / 43 (18.60%)  |
| occurrences (all)                               | 17                                                                                                                          | 15              | 22               |
| Erythema                                        |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                              | 3 / 44 (6.82%)  | 1 / 43 (2.33%)   |
| occurrences (all)                               | 0                                                                                                                           | 5               | 2                |
| Pruritus generalised                            |                                                                                                                             |                 |                  |
| subjects affected / exposed                     | 0 / 43 (0.00%)                                                                                                              | 0 / 44 (0.00%)  | 3 / 43 (6.98%)   |
| occurrences (all)                               | 0                                                                                                                           | 0               | 3                |
| Psychiatric disorders                           |                                                                                                                             |                 |                  |

|                                                                                       |                      |                        |                       |
|---------------------------------------------------------------------------------------|----------------------|------------------------|-----------------------|
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 43 (2.33%)<br>1  | 3 / 44 (6.82%)<br>3    | 1 / 43 (2.33%)<br>1   |
| Musculoskeletal and connective tissue disorders                                       |                      |                        |                       |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                        | 6 / 43 (13.95%)<br>6 | 10 / 44 (22.73%)<br>13 | 6 / 43 (13.95%)<br>8  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                         | 6 / 43 (13.95%)<br>6 | 3 / 44 (6.82%)<br>5    | 8 / 43 (18.60%)<br>8  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                 | 5 / 43 (11.63%)<br>7 | 2 / 44 (4.55%)<br>2    | 7 / 43 (16.28%)<br>11 |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)              | 0 / 43 (0.00%)<br>0  | 3 / 44 (6.82%)<br>3    | 2 / 43 (4.65%)<br>2   |
| Infections and infestations                                                           |                      |                        |                       |
| Infected skin ulcer<br>subjects affected / exposed<br>occurrences (all)               | 1 / 43 (2.33%)<br>1  | 7 / 44 (15.91%)<br>11  | 3 / 43 (6.98%)<br>3   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 5 / 43 (11.63%)<br>6 | 5 / 44 (11.36%)<br>6   | 8 / 43 (18.60%)<br>9  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 3 / 43 (6.98%)<br>3  | 5 / 44 (11.36%)<br>5   | 6 / 43 (13.95%)<br>9  |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 43 (6.98%)<br>3  | 2 / 44 (4.55%)<br>2    | 4 / 43 (9.30%)<br>4   |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 43 (2.33%)<br>1  | 8 / 44 (18.18%)<br>10  | 3 / 43 (6.98%)<br>5   |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 43 (0.00%)<br>0  | 3 / 44 (6.82%)<br>3    | 0 / 43 (0.00%)<br>0   |
| Lower respiratory tract infection                                                     |                      |                        |                       |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 43 (0.00%) | 3 / 44 (6.82%) | 0 / 43 (0.00%) |
| occurrences (all)           | 0              | 3              | 0              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 09 March 2012    | <ul style="list-style-type: none"><li>- To clarify that participants were required to have uninvolved skin at at least one of 3 locations to ensure application of SC study drug in uninvolved skin. The area for SC injection had been expanded in one area from the lower abdomen to the entire abdomen except for the 2-inch area directly around the navel.</li><li>- To add a lipid panel at Week 8.</li><li>- To clarify that investigators must draw immunogenicity labs in participants with hypersensitivity reactions leading to withdrawal from study drug, not just in the case of serious hypersensitivity leading to withdrawal from study drug.</li><li>- To clarify that Sponsor company requested a review of liver biopsy slides and report if the investigator deemed a liver biopsy necessary but Sponsor company did not request a liver biopsy. The investigators might have deemed a liver biopsy necessary in the management of persistently elevated liver enzymes. In that case, Sponsor company was requesting a biopsy report and slides of the biopsied tissue.</li></ul>                                                                                                                                                                  |
| 02 November 2012 | <ul style="list-style-type: none"><li>- To remove recruitment barriers to allow for completion and closeout of recruiting for this study.</li><li>- To provide clarification on the use of SSc medications, including those initiated after baseline, specifically allowing modification of the dose regimen after Week 24 if clinically warranted.</li><li>- To provide clarification that after the baseline visit, per the Principal Investigator's clinical judgment, if angiotensin-converting enzyme inhibitors, calcium-channel blockers, proton-pump inhibitors, and/or vasodilators need to be initiated for chronic use, the dose regimen should remain stable up to and including Week 24, unless dose adjustments are required for safety reasons or cytochrome P450 (CYP450) interactions.</li><li>- To allow safety assessments to be done before efficacy assessments if necessary due to clinical assessor availability since this does not compromise data quality and subsequent analysis.</li><li>- To replace the reporting time frame for serious adverse events, AEs of special interest, and pregnancies from within "1 working day" to "24 hours."</li><li>- To update safety information from Actemra SC studies as of October 2012.</li></ul> |
| 20 November 2012 | <ul style="list-style-type: none"><li>- To add back in the Schedule of Sampling from the PK Substudy, which was inadvertently removed from the protocol during the previous amendment.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported