



## Clinical trial results:

**A randomised, double-blind, parallel-group study of safety and the effect on clinical outcome of tocilizumab subcutaneous (SC) versus placebo SC in combination with traditional disease modifying anti-rheumatic drugs (DMARDs), in patients with moderate to severe active rheumatoid arthritis.**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2010-019912-18   |
| Trial protocol           | ES GR HU BG      |
| Global end of trial date | 27 November 2013 |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 22 April 2016  |
| First version publication date | 08 August 2015 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | NA25220 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01232569 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | F. Hoffmann-La Roche AG   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070  |
| Public contact               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, <a href="mailto:global.trial_information@roche.com">global.trial_information@roche.com</a> |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, <a href="mailto:global.trial_information@roche.com">global.trial_information@roche.com</a> |

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                       | 27 November 2013 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 28 May 2012      |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 27 November 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

This randomised, parallel-group, placebo-controlled, multicenter study will evaluate the reduction in disease activity and the safety of tocilizumab (RoActemra/Actemra) in combination with traditional disease-modifying anti-rheumatic drugs (DMARDs) in patients with active, moderate to severe rheumatoid arthritis. In the double-blind part of the study, patients will be randomised to receive either 162 mg tocilizumab or placebo subcutaneously every 2 weeks for 24 weeks using a pre-filled syringe. In the open-label part of the study, patients who reach Week 24 on their randomised treatment will be rerandomised to receive 162 mg tocilizumab subcutaneously every 2 weeks from Week 24 to Week 96 using a pre-filled syringe or an auto-injector. Patients with inadequate efficacy had the option to escape to treatment with tocilizumab 162 mg subcutaneously once weekly. The analysis of the endpoints occurred at Week 24. No analyses were planned at Week 96, so none are presented.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 23 February 2011 |
| 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 | Poland: 99    |
| Country: Number of subjects enrolled | Spain: 11     |
| Country: Number of subjects enrolled | Bulgaria: 27  |
| Country: Number of subjects enrolled | Greece: 2     |
| Country: Number of subjects enrolled | Hungary: 10   |
| Country: Number of subjects enrolled | Argentina: 29 |
| Country: Number of subjects enrolled | Australia: 6  |
| Country: Number of subjects enrolled | Brazil: 98    |
| Country: Number of subjects enrolled | Canada: 20    |
| Country: Number of subjects enrolled | Colombia: 17  |
| Country: Number of subjects enrolled | Guatemala: 9  |
| Country: Number of subjects enrolled | Israel: 13    |
| Country: Number of subjects enrolled | Malaysia: 7   |
| Country: Number of subjects enrolled | Mexico: 106   |
| Country: Number of subjects enrolled | Panama: 6     |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Philippines: 11        |
| Country: Number of subjects enrolled | Russian Federation: 48 |
| Country: Number of subjects enrolled | South Africa: 11       |
| Country: Number of subjects enrolled | Switzerland: 1         |
| Country: Number of subjects enrolled | Thailand: 11           |
| Country: Number of subjects enrolled | United States: 114     |
| Worldwide total number of subjects   | 656                    |
| EEA total number of subjects         | 149                    |

Notes:

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### 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)                      | 575 |
| From 65 to 84 years                       | 81  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Of the 656 patients randomised into the study (437 to the tocilizumab arm and 219 to the placebo arm), 438 patients received tocilizumab as their first dose and 218 received placebo as their first dose because of a dose administration error with 1 patient.

### Pre-assignment

Screening details:

The target population for this study was patients with moderate to severe rheumatoid arthritis who were inadequate responders to disease-modifying anti-rheumatic drugs that may include one or more anti-tumor necrosis factor- $\alpha$  agents.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Double-blind treatment period   |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Double blind                    |
| Roles blinded                | Subject, Investigator, Assessor |

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes                   |
| <b>Arm title</b>             | Tocilizumab 162 mg sc |

Arm description:

Patients received tocilizumab 162 mg subcutaneously (sc) every 2 weeks for 24 weeks.

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

Dosage and administration details:

Tocilizumab was supplied in a ready-to-use, single-use, pre-filled syringe. Patients and/or caregivers were trained to administer the injection.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Placebo sc |
|------------------|------------|

Arm description:

Patients received placebo sc every 2 weeks for 24 weeks.

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

Dosage and administration details:

Placebo was supplied in a ready-to-use, single-use, pre-filled syringe. Patients and/or caregivers were trained to administer the injection.

| <b>Number of subjects in period 1</b> | Tocilizumab 162 mg sc | Placebo sc |
|---------------------------------------|-----------------------|------------|
| Started                               | 438                   | 218        |
| Completed                             | 410                   | 209        |
| Not completed                         | 28                    | 9          |
| Physician decision                    | 1                     | -          |
| Death                                 | 2                     | -          |
| Withdrawal by Subject                 | 9                     | 2          |
| Escape                                | 2                     | 2          |
| Lost to follow-up                     | 4                     | -          |
| Adverse Event (Except Anaphylaxis)    | 9                     | 3          |
| Lack of efficacy                      | 1                     | 2          |

## Period 2

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

## Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | Tocilizumab pre-filled syringe |

### Arm description:

Patients received tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 72 weeks.

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

### Dosage and administration details:

Tocilizumab was supplied in a ready-to-use, single-use, pre-filled syringe. Patients and/or caregivers were trained to administer the injection.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Tocilizumab auto-injector |
|------------------|---------------------------|

### Arm description:

Patients received tocilizumab 162 mg sc via auto-injector every 2 weeks for 72 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Tocilizumab                              |
| Investigational medicinal product code |  |
| Other name                             | RoActemra, Actemra                       |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

### Dosage and administration details:

Tocilizumab was supplied in a ready-to-use, single-use, auto-injector. Patients and/or caregivers were trained to administer the injection.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Tocilizumab pre-filled syringe | Tocilizumab auto-injector |
|---|--------------------------------|---------------------------|
| Started   | 230                            | 227                       |
| Completed   | 203                            | 200                       |
| Not completed                                       | 27                             | 27                        |
| Reason not specified                                | 27                             | 27                        |

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Notes:

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

Justification: Some participants who completed the double-blind treatment period did not enter the open-label period. Only participants who reached week 24 on their randomised treatment were rerandomised into the open-label period.

## Baseline characteristics

### Reporting groups

|  |                       |
|--|-----------------------|
| Reporting group title  | Tocilizumab 162 mg sc |
| Reporting group description:<br>Patients received tocilizumab 162 mg subcutaneously (sc) every 2 weeks for 24 weeks. |                       |
| Reporting group title  | Placebo sc            |
| Reporting group description:<br>Patients received placebo sc every 2 weeks for 24 weeks.                             |                       |

| Reporting group values  | Tocilizumab 162 mg sc | Placebo sc  | Total |
|---|-----------------------|-------------|-------|
| Number of subjects  | 438                   | 218         | 656   |
| Age categorical<br>Units: Subjects  |                       |             |       |
| Adults (18-64 years)  | 383                   | 192         | 575   |
| From 65-84 years  | 55                    | 26          | 81    |
| Age continuous  |                       |             |       |
| Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population. |                       |             |       |
| Units: years<br>arithmetic mean<br>standard deviation   | 120<br>± 60           | 120<br>± 60 | -     |
| Gender categorical<br>Units: Subjects   |                       |             |       |
| Female  | 0                     | 0           | 0     |
| Male  | 0                     | 0           | 0     |
| Not recorded  | 438                   | 218         | 656   |

### Subject analysis sets

|  |                       |
|--|-----------------------|
| Subject analysis set title   | Tocilizumab 162 mg sc |
| Subject analysis set type  | Safety analysis       |
| Subject analysis set description:<br>Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population. |                       |
| Subject analysis set title   | Placebo sc            |
| Subject analysis set type  | Safety analysis       |
| Subject analysis set description:<br>Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population. |                       |

| Reporting group values             | Tocilizumab 162 mg sc | Placebo sc |  |
|------------------------------------|-----------------------|------------|--|
| Number of subjects                 | 437                   | 218        |  |
| Age categorical<br>Units: Subjects |                       |            |  |
| Adults (18-64 years)               |                       |            |  |

|   |                 |               |  |
|---|-----------------|---------------|--|
| From 65-84 years  |                 |               |  |
| Age continuous  |                 |               |  |
| Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population. |                 |               |  |
| Units: years<br>arithmetic mean<br>standard deviation   | 52.1<br>± 11.49 | 52<br>± 11.67 |  |
| Gender categorical<br>Units: Subjects   |                 |               |  |
| Female  | 375             | 180           |  |
| Male  | 62              | 38            |  |
| Not recorded  | 0               | 0             |  |



## End points

### End points reporting groups

|  |                                |
|--|--------------------------------|
| Reporting group title  | Tocilizumab 162 mg sc          |
| Reporting group description:<br>Patients received tocilizumab 162 mg subcutaneously (sc) every 2 weeks for 24 weeks.   |                                |
| Reporting group title  | Placebo sc                     |
| Reporting group description:<br>Patients received placebo sc every 2 weeks for 24 weeks.   |                                |
| Reporting group title  | Tocilizumab pre-filled syringe |
| Reporting group description:<br>Patients received tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 72 weeks.   |                                |
| Reporting group title  | Tocilizumab auto-injector      |
| Reporting group description:<br>Patients received tocilizumab 162 mg sc via auto-injector every 2 weeks for 72 weeks.  |                                |
| Subject analysis set title   | Tocilizumab 162 mg sc          |
| Subject analysis set type  | Safety analysis                |
| Subject analysis set description:<br>Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population. |                                |
| Subject analysis set title   | Placebo sc                     |
| Subject analysis set type  | Safety analysis                |
| Subject analysis set description:<br>Baseline Characteristics are reported for the safety population which included all patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population. |                                |

### Primary: Percentage of patients with an American College of Rheumatology 20 (ACR20) response at Week 24

|   |  |
|---|--|
| End point title   | Percentage of patients with an American College of Rheumatology 20 (ACR20) response at Week 24 |
| End point description:<br>A patient had an ACR20 response if there was at least a 20% improvement, ie, reduction from baseline, in tender and swollen joint counts (28 assessed joints) and in at least 3 of the following 5 parameters: Separate patient and physician assessments of patient disease activity in the previous 24 hours on a visual analog scale (VAS, left end=no disease activity [symptom-free and no arthritis symptoms], right end=maximum disease activity; patient assessment of pain in previous 24 hours on a VAS (left end=no pain and right end=unbearable pain); Health Assessment Questionnaire-Disability Index (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do); and acute-phase reactant (either C-reactive protein or erythrocyte sedimentation rate). |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline to Week 24   |  |

| End point values                 | Tocilizumab<br>162 mg sc | Placebo sc             |  |  |
|----------------------------------|--------------------------|------------------------|--|--|
| Subject group type               | Subject analysis set     | Subject analysis set   |  |  |
| Number of subjects analysed      | 437                      | 219                    |  |  |
| Units: Percentage of patients    |                          |                        |  |  |
| number (confidence interval 95%) | 60.9 (56.3 to<br>65.4)   | 31.5 (25.4 to<br>37.7) |  |  |

### Statistical analyses

| Statistical analysis title              | Tocilizumab vs placebo             |
|---|------------------------------------|
| Comparison groups                       | Tocilizumab 162 mg sc v Placebo sc |
| Number of subjects included in analysis | 656                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | < 0.0001                           |
| Method                                  | Cochran-Mantel-Haenszel            |
| Parameter estimate                      | Mean difference (final values)     |
| Point estimate                          | 29.5                               |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | 22                                 |
| upper limit                             | 37                                 |

### Secondary: Percentage of patients with ACR50 and ACR70 responses at Week 24

|   |  |
|---|--|
| End point title   | Percentage of patients with ACR50 and ACR70 responses at Week 24 |
| End point description:  |  |
| A patient had an ACR50 response if there was at least a 50% improvement in the ACR scores. A patient had an ACR70 response if there was at least a 70% improvement in the ACR scores. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline to Week 24   |  |

| End point values                 | Tocilizumab<br>162 mg sc | Placebo sc           |  |  |
|----------------------------------|--------------------------|----------------------|--|--|
| Subject group type               | Subject analysis set     | Subject analysis set |  |  |
| Number of subjects analysed      | 437                      | 219                  |  |  |
| Units: Percentage of patients    |                          |                      |  |  |
| number (confidence interval 95%) |                          |                      |  |  |
| ACR50                            | 39.8 (35.2 to<br>44.4)   | 12.3 (8 to<br>16.7)  |  |  |
| ACR70                            | 19.7 (16 to<br>23.4)     | 5 (2.1 to 7.9)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to onset of ACR20, ACR50, and ACR70 responses

|                 |  |
|-----------------|--|
| End point title | Time to onset of ACR20, ACR50, and ACR70 responses |
|-----------------|--|

End point description:

Time to first ACR response was calculated as the number of days between the date of the first ACR response minus the date of the first dose of study drug.

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

End point timeframe:

Baseline to Week 24

| End point values                 | Tocilizumab<br>162 mg sc | Placebo sc           |  |  |
|----------------------------------|--------------------------|----------------------|--|--|
| Subject group type               | Subject analysis set     | Subject analysis set |  |  |
| Number of subjects analysed      | 437 <sup>[1]</sup>       | 219 <sup>[2]</sup>   |  |  |
| Units: Days                      |                          |                      |  |  |
| median (confidence interval 95%) |                          |                      |  |  |
| ACR20                            | 57 (57 to 58)            | 86 (85 to 113)       |  |  |
| ACR50                            | 115 (113 to 141)         | 999 (999 to 999)     |  |  |
| ACR70                            | 174 (172 to 999)         | 999 (999 to 999)     |  |  |

Notes:

[1] - Only patients with available data were included in the analysis. 999.0 = NA due to too few events

[2] - 999.0 = Not calculable due to too few events.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in tender joint count (TJC) and swollen joint count (SJC) at Week 24

|                 |   |
|-----------------|---|
| End point title | Change from baseline in tender joint count (TJC) and swollen joint count (SJC) at Week 24 |
|-----------------|---|

End point description:

Joints (28 joints) will be assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination.

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

End point timeframe:

Baseline to Week 24

| End point values                     | Tocilizumab<br>162 mg sc | Placebo sc           |  |  |
|--------------------------------------|--------------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set     | Subject analysis set |  |  |
| Number of subjects analysed          | 432 <sup>[3]</sup>       | 219                  |  |  |
| Units: Joint count                   |                          |                      |  |  |
| arithmetic mean (standard deviation) |                          |                      |  |  |
| Tender joint count                   | -14.8 (± 15)             | -8.1 (± 14.2)        |  |  |
| Swollen joint count                  | -9.6 (± 9.7)             | -5.9 (± 10.2)        |  |  |

Notes:

[3] - Only patients with available data were included in the analysis.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in C-reactive protein at Week 24

|                        |   |
|------------------------|---|
| End point title        | Change from baseline in C-reactive protein at Week 24 |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 24    |   |

| End point values                     | Tocilizumab<br>162 mg sc | Placebo sc         |  |  |
|--------------------------------------|--------------------------|--------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group    |  |  |
| Number of subjects analysed          | 345 <sup>[4]</sup>       | 124 <sup>[5]</sup> |  |  |
| Units: mg/dL                         |                          |                    |  |  |
| arithmetic mean (standard deviation) | -1.7 (± 2.6)             | -0.1 (± 1.8)       |  |  |

Notes:

[4] - Only patients with available data were included in the analysis.

[5] - Only patients with available data were included in the analysis.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in erythrocyte sedimentation rate at Week 24

|                        |   |
|------------------------|---|
| End point title        | Change from baseline in erythrocyte sedimentation rate at Week 24 |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 24    |   |

| End point values                     | Tocilizumab<br>162 mg sc | Placebo sc         |  |  |
|--------------------------------------|--------------------------|--------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group    |  |  |
| Number of subjects analysed          | 347 <sup>[6]</sup>       | 124 <sup>[7]</sup> |  |  |
| Units: mm/hrmm/hr                    |                          |                    |  |  |
| arithmetic mean (standard deviation) | -36.4 (± 23.6)           | -9.5 (± 22.7)      |  |  |

Notes:

[6] - Only patients with available data were included in the analysis.

[7] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in the patient's and the physician's global assessment of disease activity visual analog score

|                 |   |
|-----------------|---|
| End point title | Change from baseline in the patient's and the physician's global assessment of disease activity visual analog score |
|-----------------|---|

End point description:

Patients and physicians assessed the patient's disease activity in the previous 24 hours on a 100 mm visual analog scale, where the extreme left end of the line represented "no disease activity" (symptom-free and no arthritis symptoms) and the extreme right end represented "maximum disease activity". Scores ranged from 0 to 100 with a higher score indicating more disease activity. A negative change score indicated less disease activity.

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

End point timeframe:

Baseline to Week 24

| End point values                                 | Tocilizumab<br>162 mg sc | Placebo sc         |  |  |
|--|--------------------------|--------------------|--|--|
| Subject group type                               | Reporting group          | Reporting group    |  |  |
| Number of subjects analysed                      | 348 <sup>[8]</sup>       | 124 <sup>[9]</sup> |  |  |
| Units: Units on a scale                          |                          |                    |  |  |
| arithmetic mean (standard deviation)             |                          |                    |  |  |
| Patient's Global Assessment VAS,<br>N=346, 123   | -32 (± 27.6)             | -20.9 (± 25.2)     |  |  |
| Physician's Global Assessment VAS,<br>N=348, 124 | -36.9 (± 22.5)           | -30.7 (± 25.8)     |  |  |

Notes:

[8] - Only patients with available data were included in the analysis.

[9] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in the patient's pain visual analog score

|                 |  |
|-----------------|--|
| End point title | Change from baseline in the patient's pain visual analog score |
|-----------------|--|

**End point description:**

Patients assessed their pain in the previous 24 hours on a visual analog scale, where the extreme left end of the line represented "no pain" and the extreme right end represented "unbearable pain". Scores ranged from 0 to 100 with a higher score indicating more pain. A negative change score indicated less pain.

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

End point timeframe:

Baseline to Week 24

| End point values                     | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
|--------------------------------------|--------------------------|---------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed          | 346 <sup>[10]</sup>      | 123 <sup>[11]</sup> |  |  |
| Units: Units on a scale              |                          |                     |  |  |
| arithmetic mean (standard deviation) | -28.1 (± 27.2)           | -15 (± 28.3)        |  |  |

Notes:

[10] - Only patients with available data were included in the analysis.

[11] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24

|                 |  |
|-----------------|--|
| End point title | Change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24 |
|-----------------|--|

**End point description:**

The HAQ-DI is a questionnaire specific for rheumatoid arthritis and consists of 20 questions referring to 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Patients completed the questionnaire by answering the 20 questions on a scale of 0 (without difficulty) to 3 (unable to do). The total score ranges from 0 (no disability) to 3 (completely disabled). A negative change score indicates improvement.

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

End point timeframe:

Baseline to Week 24

| End point values                     | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
|--------------------------------------|--------------------------|---------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed          | 348 <sup>[12]</sup>      | 124 <sup>[13]</sup> |  |  |
| Units: Units on a scale              |                          |                     |  |  |
| arithmetic mean (standard deviation) | -0.5 (± 0.6)             | -0.3 (± 0.6)        |  |  |

Notes:

[12] - Only patients with available data were included in the analysis.

[13] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of patients with an improvement of  $\geq 0.3$  units from baseline in the HAQ-DI score at Week 24**

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|                 |   |
|-----------------|---|
| End point title | Percentage of patients with an improvement of $\geq 0.3$ units from baseline in the HAQ-DI score at Week 24 |
|-----------------|---|

End point description:

The HAQ-DI is a questionnaire specific for rheumatoid arthritis and consists of 20 questions referring to 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Patients completed the questionnaire by answering the 20 questions on a scale of 0 (without difficulty) to 3 (unable to do). The total score ranges from 0 (no disability) to 3 (completely disabled). A negative change score indicates improvement.

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

End point timeframe:

Baseline to Week 24

---

| End point values                 | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
|----------------------------------|--------------------------|---------------------|--|--|
| Subject group type               | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed      | 348 <sup>[14]</sup>      | 124 <sup>[15]</sup> |  |  |
| Units: Percentage of patients    |                          |                     |  |  |
| number (confidence interval 95%) | 58 (52.9 to 63.2)        | 46.8 (38 to 55.6)   |  |  |

Notes:

[14] - Only patients with available data were included in the analysis.

[15] - Only patients with available data were included in the analysis.

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change from baseline in Disease Activity Score 28 (DAS28) at Week 24**

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|                 |  |
|-----------------|--|
| End point title | Change from baseline in Disease Activity Score 28 (DAS28) at Week 24 |
|-----------------|--|

End point description:

The DAS28 is a combined index for measuring disease activity in rheumatic arthritis (RA) and includes swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and general health (GH) status. The index is calculated with the following formula:  $\text{DAS28} = (0.56 \times \sqrt{(\text{TJC28})}) + (0.28 \times \sqrt{(\text{SJC28})}) + (0.7 \times \log(\text{ESR})) + (0.014 \times \text{GH})$ , where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints. GH = a patient's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]). When ESR equaled 0 mm/hr, it was set to 1 mm/hr. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. A negative change score indicates improvement.

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

End point timeframe:

Baseline to Week 24

---

|                                      |                          |                     |  |  |
|--------------------------------------|--------------------------|---------------------|--|--|
| <b>End point values</b>              | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
| Subject group type                   | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed          | 344 <sup>[16]</sup>      | 123 <sup>[17]</sup> |  |  |
| Units: Units on a scale              |                          |                     |  |  |
| arithmetic mean (standard deviation) | -3.3 (± 1.4)             | -1.8 (± 1.3)        |  |  |

Notes:

[16] - Only patients with available data were included in the analysis.

[17] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of patients with a DAS28 score ≤ 3.2 (DAS28 low disease activity) at Week 24

|                 |   |
|-----------------|---|
| End point title | Percentage of patients with a DAS28 score ≤ 3.2 (DAS28 low disease activity) at Week 24 |
|-----------------|---|

End point description:

The DAS28 is a combined index for measuring disease activity in rheumatic arthritis (RA) and includes swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and general health (GH) status. The index is calculated with the following formula:  $\text{DAS28} = (0.56 \times \sqrt{\text{TJC28}}) + (0.28 \times \sqrt{\text{SJC28}}) + (0.7 \times \log(\text{ESR})) + (0.014 \times \text{GH})$ , where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints. GH = a patient's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]). When ESR equaled 0 mm/hr, it was set to 1 mm/hr. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. A negative change score indicates improvement.

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

End point timeframe:

Baseline to Week 24

|                                  |                          |                     |  |  |
|----------------------------------|--------------------------|---------------------|--|--|
| <b>End point values</b>          | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
| Subject group type               | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed      | 347 <sup>[18]</sup>      | 124 <sup>[19]</sup> |  |  |
| Units: Percentage of patients    |                          |                     |  |  |
| number (confidence interval 95%) | 45.2 (40 to 50.5)        | 15.3 (9 to 21.7)    |  |  |

Notes:

[18] - Only patients with available data were included in the analysis.

[19] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of patients with a DAS28 score < 2.6 (DAS28 remission) at Week 24

|                 |  |
|-----------------|--|
| End point title | Percentage of patients with a DAS28 score < 2.6 (DAS28 remission) at Week 24 |
|-----------------|--|

End point description:

The DAS28 is a combined index for measuring disease activity in rheumatic arthritis (RA) and includes swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and general health (GH) status.



The index is calculated with the following formula:  $\text{DAS28} = (0.56 \times \sqrt{(\text{TJC28})}) + (0.28 \times \sqrt{(\text{SJC28})}) + (0.7 \times \log(\text{ESR})) + (0.014 \times \text{GH})$ , where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints. GH = a patient's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]). When ESR equaled 0 mm/hr, it was set to 1 mm/hr. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. A negative change score indicates improvement.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 24              |           |

| End point values                 | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
|----------------------------------|--------------------------|---------------------|--|--|
| Subject group type               | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed      | 347 <sup>[20]</sup>      | 124 <sup>[21]</sup> |  |  |
| Units: Percentage of patients    |                          |                     |  |  |
| number (confidence interval 95%) | 32 (27.1 to 36.9)        | 4 (0.6 to 7.5)      |  |  |

Notes:

[20] - Only patients with available data were included in the analysis.

[21] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of patients with good, moderate, or no European League Against Rheumatism (EULAR) responses at Week 24

|                 |   |
|-----------------|---|
| End point title | Percentage of patients with good, moderate, or no European League Against Rheumatism (EULAR) responses at Week 24 |
|-----------------|---|

End point description:

Change of the Disease Activity Score 28 score from baseline was used to determine EULAR responses of good, moderate, or no response. For a post-baseline score  $\leq 3.2$ , a change from baseline of  $< -1.2$  was a good response,  $< -0.6$  to  $\geq -1.2$  was a moderate response, and  $\geq -0.6$  was no response. For a post-baseline score  $> 3.2$  to  $\leq 5.1$ , a change from baseline of  $< -0.6$  was a moderate response and  $\geq -0.6$  was no response. For a post-baseline score  $> 5.1$ , a change from baseline  $< -1.2$  was a moderate response and  $\geq -1.2$  was no response. A good response could not be achieved for post-baseline scores  $> 3.2$ .

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline to Week 24  |           |

| End point values              | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
|-------------------------------|--------------------------|---------------------|--|--|
| Subject group type            | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed   | 374 <sup>[22]</sup>      | 138 <sup>[23]</sup> |  |  |
| Units: Percentage of patients |                          |                     |  |  |
| number (not applicable)       |                          |                     |  |  |
| Good Response                 | 41.7                     | 13.8                |  |  |
| Moderate Response             | 44.9                     | 54.3                |  |  |
| No Response                   | 13.4                     | 31.9                |  |  |

Notes:

[22] - Only patients with available data were included in the analysis.

[23] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in the van der Heijde modified Sharp radiographic score at Week 24

|                 |   |
|-----------------|---|
| End point title | Change from baseline in the van der Heijde modified Sharp radiographic score at Week 24 |
|-----------------|---|

End point description:

The degree of joint damage was assessed using the van der Heijde modified total Sharp score (mTSS). The methodology quantifies the extent of bone erosions for 44 joints and joint space narrowing (JSN) for 42 joints, with higher scores representing greater damage. The independent read of X-ray images was performed by 2 primary readers. In case of discrepancy between the 2 primary readers, an adjudicator was involved. The mTSS can range from 0 to 448 with a higher score indicating more joint damage. A negative change score indicates improvement.

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

End point timeframe:

Baseline to Week 24

| End point values                     | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
|--------------------------------------|--------------------------|---------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed          | 391 <sup>[24]</sup>      | 186 <sup>[25]</sup> |  |  |
| Units: Units on a scale              |                          |                     |  |  |
| arithmetic mean (standard deviation) | 0.62 (± 2.692)           | 1.23 (± 2.816)      |  |  |

Notes:

[24] - Only patients with available data were included in the analysis.

[25] - Only patients with available data were included in the analysis.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in the Physical and Mental Component Scores of the Short Form 36 (SF-36) Health Survey at Week 24

|                 |  |
|-----------------|--|
| End point title | Change from baseline in the Physical and Mental Component Scores of the Short Form 36 (SF-36) Health Survey at Week 24 |
|-----------------|--|

End point description:

The SF-36 Health Survey uses patient-reported symptoms on 8 subscales to assess health-related quality of life (HRQoL). The Physical Component Summary (PCS) score summarizes the subscales Physical Functioning, Role-Physical, Bodily Pain, and General Health. The Mental Component Summary (MCS) score summarizes the subscales Vitality, Social Functioning, Role-Emotional, and Mental Health. Each score was scaled from 0 to 100 with a higher score indicating better HRQoL. A positive change score indicates an improvement in HRQoL.

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

End point timeframe:

Baseline to Week 24

| End point values                     | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
|--------------------------------------|--------------------------|---------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed          | 347 <sup>[26]</sup>      | 123 <sup>[27]</sup> |  |  |
| Units: Units on a scale              |                          |                     |  |  |
| arithmetic mean (standard deviation) |                          |                     |  |  |
| Physical Component                   | 7.2 (± 8)                | 4.3 (± 5.9)         |  |  |
| Mental Component                     | 6.1 (± 10.8)             | 3 (± 9.7)           |  |  |

Notes:

[26] - Only patients with available data were included in the analysis.

[27] - Only patients with available data were included in the analysis.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in haemoglobin at Week 24

|                        |  |
|------------------------|--|
| End point title        | Change from baseline in haemoglobin at Week 24 |
| End point description: |  |
| End point type         | Secondary                                      |
| End point timeframe:   |  |
| Baseline to Week 24    |  |

| End point values                     | Tocilizumab<br>162 mg sc | Placebo sc          |  |  |
|--------------------------------------|--------------------------|---------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed          | 343 <sup>[28]</sup>      | 123 <sup>[29]</sup> |  |  |
| Units: g/L                           |                          |                     |  |  |
| arithmetic mean (standard deviation) | 11 (± 12.6)              | 0 (± 7.1)           |  |  |

Notes:

[28] - Only patients with available data were included in the analysis.

[29] - Only patients with available data were included in the analysis.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of each patient's randomization into the study until their last visit (up to 96 weeks).

Adverse event reporting additional description:

Safety population: All patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. One patient who received tocilizumab had no post-baseline safety data and was excluded from the safety population.

Due to the study design, some participants received tocilizumab throughout the study, others not.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Tocilizumab pre-filled syringe |
|-----------------------|--------------------------------|

Reporting group description:

Patients received tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 24 weeks. In addition, this reporting group includes participants rerandomised at Week 24 to tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 72 weeks (Weeks 25-96).

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Placebo pre-filled syringe |
|-----------------------|----------------------------|

Reporting group description:

Patients received placebo subcutaneously (sc) via a pre-filled syringe every 2 weeks for 24 weeks.

|                       |   |
|-----------------------|---|
| Reporting group title | Tocilizumab pre-filled syringe to tocilizumab auto-injector |
|-----------------------|---|

Reporting group description:

Patients received tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 24 weeks followed by tocilizumab 162 mg sc via an autoinjector every 2 weeks for 72 weeks.

|                       |  |
|-----------------------|--|
| Reporting group title | Placebo pre-filled syringe to tocilizumab pre-filled syringe |
|-----------------------|--|

Reporting group description:

Patients received placebo sc via a pre-filled syringe every 2 weeks for 24 weeks followed by tocilizumab 162 mg sc via a pre-filled syringe every 2 weeks for 72 weeks.

|                       |  |
|-----------------------|--|
| Reporting group title | Placebo pre-filled syringe to tocilizumab autoinjector |
|-----------------------|--|

Reporting group description:

Patients received placebo sc via a pre-filled syringe every 2 weeks for 24 weeks followed by tocilizumab 162 mg sc via an autoinjector every 2 weeks for 72 weeks.

| Serious adverse events  | Tocilizumab pre-filled syringe | Placebo pre-filled syringe | Tocilizumab pre-filled syringe to tocilizumab auto-injector |
|---|--------------------------------|----------------------------|---|
| Total subjects affected by serious adverse events                   |                                |                            |   |
| subjects affected / exposed   | 36 / 437 (8.24%)               | 8 / 218 (3.67%)            | 17 / 168 (10.12%)   |
| number of deaths (all causes)                                       | 4                              | 0                          | 3   |
| number of deaths resulting from adverse events                      | 3                              | 0                          | 1   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                |                            |   |
| Adenocarcinoma pancreas   |                                |                            |   |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal cancer  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal cancer   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Schwannoma   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Myelodysplastic syndrome                             |                 |                 |                 |
| subjects affected / exposed                          | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Ovarian epithelial cancer                            |                 |                 |                 |
| subjects affected / exposed                          | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                   |                 |                 |                 |
| Deep vein thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| Immune system disorders                         |                 |                 |                 |
| Drug hypersensitivity                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Ovarian cyst                                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 437 (0.46%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endometrial hypertrophy                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ovarian cyst torsion                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| 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 |                 |                 |                 |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 437 (0.46%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Bipolar disorder                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cervical vertebral fracture<br>subjects affected / exposed  | 0 / 437 (0.00%) | 1 / 218 (0.46%) | 0 / 168 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders   |                 |                 |                 |
| Acute myocardial infarction<br>subjects affected / exposed  | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 1           | 0 / 0           | 0 / 0           |
| Angina pectoris<br>subjects affected / exposed              | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to<br>treatment / all          | 1 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 1           |
| Atrial fibrillation<br>subjects affected / exposed          | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction<br>subjects affected / exposed        | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 1           |
| Supraventricular tachycardia<br>subjects affected / exposed | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                                    |                 |                 |                 |
| Grand mal convulsion<br>subjects affected / exposed         | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar radiculopathy<br>subjects affected / exposed         | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Neutropenia                                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 437 (0.46%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Cataract  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Pancreatitis acute                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 2 / 168 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal adhesions                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulum intestinal haemorrhagic            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 1 / 218 (0.46%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Pyoderma gangrenosum                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Calculus ureteric                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocrine disorders                             |                 |                 |                 |
| Adrenocortical insufficiency acute              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 1 / 218 (0.46%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Intervertebral disc protrusion                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 437 (0.00%) | 1 / 218 (0.46%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal chest pain                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 1 / 218 (0.46%) | 0 / 168 (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           |
| Spinal column stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 1 / 218 (0.46%) | 0 / 168 (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           |
| Synovial cyst                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 1 / 218 (0.46%) | 0 / 168 (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                     |                 |                 |                 |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 437 (0.46%) | 2 / 218 (0.92%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 437 (0.46%) | 1 / 218 (0.46%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 2 / 2           | 0 / 0           | 0 / 0           |
| Arthritis bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 437 (0.46%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0           |
| Osteomyelitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary tuberculosis                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 437 (0.46%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abscess   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchopneumonia                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coccidioidomycosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 1 / 218 (0.46%) | 0 / 168 (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           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint abscess                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Localised infection                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ludwig angina                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 1 / 168 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Postoperative wound infection                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 1 / 218 (0.46%) | 0 / 168 (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           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 437 (0.00%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Diabetic ketoacidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 437 (0.23%) | 0 / 218 (0.00%) | 0 / 168 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                     | Placebo pre-filled syringe to tocilizumab pre-filled syringe | Placebo pre-filled syringe to tocilizumab autoinjector |  |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 2 / 61 (3.28%)   | 0 / 59 (0.00%)   |  |
| number of deaths (all causes)                     | 1  | 0  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| number of deaths resulting from adverse events                      | 1              | 0              |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |  |
| Adenocarcinoma pancreas   |                |                |  |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Rectal cancer   |                |                |  |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Renal cancer  |                |                |  |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Schwannoma  |                |                |  |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Myelodysplastic syndrome  |                |                |  |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Ovarian epithelial cancer   |                |                |  |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Vascular disorders  |                |                |  |
| Deep vein thrombosis  |                |                |  |
| subjects affected / exposed   | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Hypertension  |                |                |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Pyrexia  |                |                |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Immune system disorders                              |                |                |  |
| Drug hypersensitivity                                |                |                |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Reproductive system and breast disorders             |                |                |  |
| Ovarian cyst   |                |                |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Endometrial hypertrophy                              |                |                |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Ovarian cyst torsion                                 |                |                |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders      |                |                |  |
| Pleural effusion                                     |                |                |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                                |                |                |  |
| Bipolar disorder                                     |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Cervical vertebral fracture                     |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Acute myocardial infarction                     |                |                |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| Angina pectoris                                 |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial fibrillation                             |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Myocardial infarction                           |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Supraventricular tachycardia                    |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Grand mal convulsion                            |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Lumbar radiculopathy                            |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Syncope   |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Transient ischaemic attack                      |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Neutropenia                                     |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Eye disorders                                   |                |                |  |
| Cataract  |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Pancreatitis acute                              |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Abdominal adhesions                             |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Constipation                                    |                |                |  |



|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diarrhoea                                       |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diverticulum intestinal haemorrhagic            |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Inguinal hernia                                 |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Cholelithiasis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                |                |  |
| Pyoderma gangrenosum                            |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Calculus ureteric                               |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Endocrine disorders                             |                |                |  |
| Adrenocortical insufficiency acute              |                |                |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                            | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |  |
| Intervertebral disc protrusion                         |                |                |  |
| subjects affected / exposed                            | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| Musculoskeletal chest pain                             |                |                |  |
| subjects affected / exposed                            | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| Osteoarthritis   |                |                |  |
| subjects affected / exposed                            | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| Spinal column stenosis                                 |                |                |  |
| subjects affected / exposed                            | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| Synovial cyst  |                |                |  |
| subjects affected / exposed                            | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| <b>Infections and infestations</b>                     |                |                |  |
| Pneumonia  |                |                |  |
| subjects affected / exposed                            | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |
| Sepsis   |                |                |  |
| subjects affected / exposed                            | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Arthritis bacterial                             |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lower respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Osteomyelitis                                   |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary tuberculosis                          |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Abscess   |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchitis                                      |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchopneumonia                                |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Coccidioidomycosis                              |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Erysipelas                                      |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Joint abscess                                   |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Localised infection                             |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ludwig angina                                   |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Postoperative wound infection                   |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Septic shock                                    |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Urinary tract infection                         |                |                |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Diabetic ketoacidosis                           |                |                |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 59 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Tocilizumab pre-filled syringe | Placebo pre-filled syringe | Tocilizumab pre-filled syringe to tocilizumab auto-injector |
|---|--------------------------------|----------------------------|---|
| Total subjects affected by non-serious adverse events |                                |                            |   |
| subjects affected / exposed                           | 212 / 437 (48.51%)             | 65 / 218 (29.82%)          | 89 / 168 (52.98%)   |
| Investigations  |                                |                            |   |
| Alanine aminotransferase increased                    |                                |                            |   |
| subjects affected / exposed                           | 67 / 437 (15.33%)              | 13 / 218 (5.96%)           | 24 / 168 (14.29%)   |
| occurrences (all)                                     | 85                             | 14                         | 29  |
| Aspartate aminotransferase increased                  |                                |                            |   |
| subjects affected / exposed                           | 40 / 437 (9.15%)               | 10 / 218 (4.59%)           | 14 / 168 (8.33%)  |
| occurrences (all)                                     | 53                             | 10                         | 21  |
| Vascular disorders                                    |                                |                            |   |
| Hypertension  |                                |                            |   |
| subjects affected / exposed                           | 26 / 437 (5.95%)               | 8 / 218 (3.67%)            | 9 / 168 (5.36%)   |
| occurrences (all)                                     | 30                             | 9                          | 11  |
| Nervous system disorders                              |                                |                            |   |
| Headache  |                                |                            |   |
| subjects affected / exposed                           | 28 / 437 (6.41%)               | 13 / 218 (5.96%)           | 8 / 168 (4.76%)   |
| occurrences (all)                                     | 35                             | 15                         | 9   |
| Blood and lymphatic system disorders                  |                                |                            |   |
| Neutropenia   |                                |                            |   |
| subjects affected / exposed                           | 25 / 437 (5.72%)               | 1 / 218 (0.46%)            | 8 / 168 (4.76%)   |
| occurrences (all)                                     | 33                             | 1                          | 14  |
| Leukopenia  |                                |                            |   |
| subjects affected / exposed                           | 13 / 437 (2.97%)               | 1 / 218 (0.46%)            | 5 / 168 (2.98%)   |
| occurrences (all)                                     | 17                             | 1                          | 5   |
| Gastrointestinal disorders                            |                                |                            |   |
| Diarrhoea   |                                |                            |   |
| subjects affected / exposed                           | 21 / 437 (4.81%)               | 3 / 218 (1.38%)            | 6 / 168 (3.57%)   |
| occurrences (all)                                     | 23                             | 3                          | 6   |
| Gastritis   |                                |                            |   |
| subjects affected / exposed                           | 6 / 437 (1.37%)                | 3 / 218 (1.38%)            | 1 / 168 (0.60%)   |
| occurrences (all)                                     | 6                              | 3                          | 1   |
| Musculoskeletal and connective tissue disorders       |                                |                            |   |

|   |                         |                        |                         |
|---|-------------------------|------------------------|-------------------------|
| Rheumatoid arthritis<br>subjects affected / exposed<br>occurrences (all)              | 14 / 437 (3.20%)<br>16  | 4 / 218 (1.83%)<br>4   | 12 / 168 (7.14%)<br>14  |
| Infections and infestations   |                         |                        |                         |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 52 / 437 (11.90%)<br>66 | 14 / 218 (6.42%)<br>14 | 21 / 168 (12.50%)<br>32 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 35 / 437 (8.01%)<br>40  | 5 / 218 (2.29%)<br>5   | 16 / 168 (9.52%)<br>19  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 26 / 437 (5.95%)<br>30  | 7 / 218 (3.21%)<br>8   | 15 / 168 (8.93%)<br>19  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 13 / 437 (2.97%)<br>16  | 1 / 218 (0.46%)<br>3   | 8 / 168 (4.76%)<br>12   |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 13 / 437 (2.97%)<br>15  | 2 / 218 (0.92%)<br>2   | 4 / 168 (2.38%)<br>4    |
| Metabolism and nutrition disorders  |                         |                        |                         |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all)             | 13 / 437 (2.97%)<br>15  | 2 / 218 (0.92%)<br>2   | 5 / 168 (2.98%)<br>5    |
| Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)                     | 6 / 437 (1.37%)<br>7    | 2 / 218 (0.92%)<br>2   | 2 / 168 (1.19%)<br>2    |

|   |   |   |  |
|---|---|---|--|
| <b>Non-serious adverse events</b>   | Placebo pre-filled<br>syringe to<br>tocilizumab pre-filled<br>syringe | Placebo pre-filled<br>syringe to<br>tocilizumab<br>autoinjector |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 35 / 61 (57.38%)  | 33 / 59 (55.93%)  |  |
| Investigations  |   |   |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)  | 6 / 61 (9.84%)<br>7   | 10 / 59 (16.95%)<br>13  |  |
| Aspartate aminotransferase<br>increased   |   |   |  |

|  |   |   |  |
|--|---|---|--|
| subjects affected / exposed<br>occurrences (all)   | 4 / 61 (6.56%)<br>5                               | 6 / 59 (10.17%)<br>9                            |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 2 / 61 (3.28%)<br>2                               | 2 / 59 (3.39%)<br>2                             |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 5 / 61 (8.20%)<br>5                               | 2 / 59 (3.39%)<br>2                             |  |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukopenia<br>subjects affected / exposed<br>occurrences (all)  | 5 / 61 (8.20%)<br>5<br><br>0 / 61 (0.00%)<br>0    | 7 / 59 (11.86%)<br>7<br><br>3 / 59 (5.08%)<br>3 |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastritis<br>subjects affected / exposed<br>occurrences (all)   | 3 / 61 (4.92%)<br>3<br><br>2 / 61 (3.28%)<br>2    | 5 / 59 (8.47%)<br>6<br><br>3 / 59 (5.08%)<br>3  |  |
| Musculoskeletal and connective tissue disorders<br>Rheumatoid arthritis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 61 (1.64%)<br>1                               | 3 / 59 (5.08%)<br>4                             |  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection | 12 / 61 (19.67%)<br>20<br><br>5 / 61 (8.20%)<br>7 | 6 / 59 (10.17%)<br>7<br><br>4 / 59 (6.78%)<br>4 |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                          | 2 / 61 (3.28%)<br>2 | 4 / 59 (6.78%)<br>5 |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)             | 5 / 61 (8.20%)<br>5 | 1 / 59 (1.69%)<br>1 |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)            | 1 / 61 (1.64%)<br>1 | 3 / 59 (5.08%)<br>3 |  |
| Metabolism and nutrition disorders  |                     |                     |  |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 61 (3.28%)<br>2 | 4 / 59 (6.78%)<br>5 |  |
| Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)         | 6 / 61 (9.84%)<br>6 | 1 / 59 (1.69%)<br>1 |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 24 February 2011  | <p>Amendment B</p> <ul style="list-style-type: none"><li>• Tocilizumab autoinjector, as a new investigational product, was made available for use in the open-label portion of the study.</li><li>• Additional details for the analyses of the radiographic endpoint were included.</li><li>• The required tests for the liver profile were clarified, liver profile testing was added at Week 36, and vital sign measurements were added at Weeks 10 and 36.</li><li>• The adjustment of the random element used to ensure a baseline randomization ratio of 2:1 was clarified.</li><li>• To prevent any potential unblinding, a dual assessor approach was used until the completion of Week 48 data analysis.</li><li>• The reporting period for adverse events, including non-serious adverse events to Roche Drug Safety was clarified (ie, within 24 hours of learning of the event).</li><li>• The requirement for an X-ray image at the initiation of escape therapy was clarified.</li></ul> |
| 26 April 2011     | <p>Amendment C</p> <ul style="list-style-type: none"><li>• An optional ease-of-use substudy was added to the open-label period for the sites in Canada and the United States in order to evaluate the ability of patients, caregivers and healthcare professionals to handle and use the pre-filled syringe or autoinjector.</li></ul>  |
| 12 September 2012 | <p>Amendments D and E</p> <ul style="list-style-type: none"><li>• In response to cases of fatal infections in patients participating in the trial, Protocol versions D (rest of world sites) and E (US sites) implemented an increase in the frequency of study visits for safety monitoring. Starting at Week 44, the frequency of study visits was changed from every 12 weeks to every 4 weeks. Vital signs, concomitant medications, and adverse events were required at these additional visits.</li></ul>   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported