



Clinical trial results:

A Randomized, Double-blind, Parallel Group Study of the Safety and Effect on Clinical Outcome of Tocilizumab SC Versus Tocilizumab IV, in Combination With Traditional Disease Modifying Anti-rheumatic Drugs (DMARDs), in Patients With Moderate to Severe Active Rheumatoid Arthritis

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2010-018375-22 |
| Trial protocol | ES GB IT DE LT BG |
| Global end of trial date | 19 August 2013 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 27 May 2016 |
| First version publication date | 27 May 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | WA22762 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|----------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01194414 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Other study name: SUMMACTA |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 19 August 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 August 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This randomised, double-blind, parallel group study compares the efficacy and safety of subcutaneous (sc) versus intravenous (iv) administration of tocilizumab (RoActemra/Actemra) in subjects with moderate to severe active rheumatoid arthritis. Subjects were randomised to receive either tocilizumab 162 mg sc weekly plus iv placebo every 4 weeks, or tocilizumab 8 mg/kg iv every 4 weeks plus sc placebo weekly during the double-blind period from baseline to Week 24. The double-blind period was followed by a 72-week open-label treatment with some switching of sc and iv administration. No placebo was administered in the open-label phase. Subjects continued on their stable dose of disease-modifying anti-rheumatic drugs (DMARDs) throughout the study. Anticipated time on study treatment was 2 years.

Protection of trial subjects:

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

Background therapy:

Subjects will continue on their stable dose of disease-modifying anti-rheumatic drugs (DMARDs) throughout the study.

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 18 August 2010 |
| 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 | Argentina: 43 |
| Country: Number of subjects enrolled | Australia: 40 |
| Country: Number of subjects enrolled | Brazil: 70 |
| Country: Number of subjects enrolled | Bulgaria: 40 |
| Country: Number of subjects enrolled | Canada: 96 |
| Country: Number of subjects enrolled | Colombia: 24 |
| Country: Number of subjects enrolled | France: 23 |
| Country: Number of subjects enrolled | Germany: 58 |
| Country: Number of subjects enrolled | United Kingdom: 52 |
| Country: Number of subjects enrolled | Guatemala: 14 |
| Country: Number of subjects enrolled | Hong Kong: 20 |
| Country: Number of subjects enrolled | Italy: 29 |
| Country: Number of subjects enrolled | Lithuania: 32 |
| Country: Number of subjects enrolled | Mexico: 135 |
| Country: Number of subjects enrolled | New Zealand: 11 |
| Country: Number of subjects enrolled | Peru: 24 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Philippines: 24 |
| Country: Number of subjects enrolled | Poland: 56 |
| Country: Number of subjects enrolled | Romania: 7 |
| Country: Number of subjects enrolled | Russian Federation: 45 |
| Country: Number of subjects enrolled | South Africa: 30 |
| Country: Number of subjects enrolled | Spain: 100 |
| Country: Number of subjects enrolled | Thailand: 24 |
| Country: Number of subjects enrolled | United States: 265 |
| Worldwide total number of subjects | 1262 |
| EEA total number of subjects | 397 |

Notes:

Subjects enrolled per age group

| | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 1041 |
| From 65 to 84 years | 219 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

A total of 1262 subjects at 209 centers in 25 countries were randomised into the study.

Pre-assignment

Screening details:

Rheumatoid arthritis (RA) of ≥ 6 months' duration, diagnosed according to the revised 1987 American College of Rheumatology (ACR) criteria. Swollen joint count (SJC) ≥ 4 (66 joint count) and tender joint count (TJC) ≥ 4 (68 joint count) at screening and baseline and taking at least one non-biologic disease-modifying anti-rheumatic drug (DMARD).

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | 24 Weeks Double Blind 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 |
| Arm title | Tocilizumab SC |

Arm description:

Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | tocilizumab SC |
| 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 supplied in a single-use pre-filled syringe, with a needle safety device, delivering 162 mg/0.9 mL solution for subcutaneous injection once a week.

| | |
|--|---------------------------|
| Investigational medicinal product name | placebo to tocilizumab IV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo to tocilizumab IV supplied as a solution in 10 mL vials containing polysorbate 80 and sucrose in water for infusion every 4 weeks.

| | |
|------------------|----------------|
| Arm title | Tocilizumab IV |
|------------------|----------------|

Arm description:

Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------------------|
| Investigational medicinal product name | tocilizumab IV |
| Investigational medicinal product code | |
| Other name | RoActemra/Actemra |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tocilizumab supplied in vials as a sterile solution for 8 mg/kg intravenous infusion every 4 weeks.

| | |
|--|--|
| Investigational medicinal product name | placebo to tocilizumab SC |
| 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 to tocilizumab SC supplied as a single-use pre-filled syringe with a needle safety device, delivering 0.9 mL sodium chloride for subcutaneous injection once a week.

| Number of subjects in period 1 | Tocilizumab SC | Tocilizumab IV |
|--|----------------|----------------|
| Started | 631 | 631 |
| Completed | 572 | 564 |
| Not completed | 59 | 67 |
| Adverse event, serious fatal | - | 1 |
| Subject/legal Guardian Decision | 9 | 5 |
| Adverse event, non-fatal | 28 | 40 |
| Other | - | 1 |
| Pregnancy | 2 | 2 |
| Physician Decision to Withdraw Subject | - | 5 |
| Anaphylaxis or Hypersensitivity Reaction | 2 | 1 |
| Lost to follow-up | 2 | 1 |
| Insufficient Therapeutic Response | 11 | 8 |
| Protocol deviation | 5 | 3 |

Period 2

| | |
|------------------------------|-------------------------------|
| Period 2 title | 72 Weeks Open Label Extension |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|--|
| Arm title | Tocilizumab SC |
| Arm description: Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study. | |
| Arm type | Experimental |
| Investigational medicinal product name | tocilizumab SC |
| 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 supplied in a single-use pre-filled syringe, with a needle safety device, delivering 162 mg/0.9 mL solution for subcutaneous injection once a week. | |
| Arm title | Tocilizumab IV |
| Arm description: Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study. | |
| Arm type | Experimental |
| Investigational medicinal product name | tocilizumab IV |
| Investigational medicinal product code | |
| Other name | RoActemra/Actemra |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Tocilizumab supplied in vials as a sterile solution for 8 mg/kg intravenous infusion every 4 weeks. | |
| Arm title | Tocilizumab SC Then Tocilizumab IV |
| Arm description: Subjects who received tocilizumab 162 mg subcutaneous (SC) injection weekly and placebo to tocilizumab IV every 4 weeks for 24 weeks in double blind treatment period switched to tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study. | |
| Arm type | Experimental |
| Investigational medicinal product name | tocilizumab IV |
| Investigational medicinal product code | |
| Other name | RoActemra/Actemra |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Tocilizumab supplied in vials as a sterile solution for 8 mg/kg intravenous infusion every 4 weeks. | |
| Arm title | Tocilizumab IV Then Tocilizumab SC |
| Arm description: Subjects who received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC once a week in double blind treatment period switched to tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose will be continued throughout the study. | |
| Arm type | Experimental |

| | |
|--|--|
| Investigational medicinal product name | tocilizumab SC |
| 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 supplied in a single-use pre-filled syringe, with a needle safety device, delivering 162 mg/0.9 mL solution for subcutaneous injection once a week.

| Number of subjects in period 2^[1] | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV |
|---|----------------|----------------|------------------------------------|
| Started | 524 | 377 | 48 |
| Completed | 445 | 311 | 40 |
| Not completed | 79 | 66 | 8 |
| Adverse event, serious fatal | 1 | 2 | - |
| Physician decision | 3 | 5 | - |
| Subject/legal Guardian Decision | 20 | 14 | 1 |
| Adverse event, non-fatal | 35 | 21 | 2 |
| Other | 2 | 1 | - |
| Pregnancy | 1 | 3 | 1 |
| Anaphylaxis or Hypersensitivity Reaction | 1 | 1 | - |
| Protocol Violation | - | - | - |
| Lost to follow-up | 4 | 3 | 2 |
| Insufficient Therapeutic Response | 9 | 11 | 2 |
| Randomised but not Treated | 3 | 5 | - |

| Number of subjects in period 2^[1] | Tocilizumab IV Then Tocilizumab SC |
|---|------------------------------------|
| Started | 186 |
| Completed | 160 |
| Not completed | 26 |
| Adverse event, serious fatal | 2 |
| Physician decision | - |
| Subject/legal Guardian Decision | 6 |
| Adverse event, non-fatal | 12 |
| Other | - |
| Pregnancy | 1 |
| Anaphylaxis or Hypersensitivity Reaction | - |
| Protocol Violation | 1 |
| Lost to follow-up | 1 |
| Insufficient Therapeutic Response | 3 |

| | |
|----------------------------|---|
| Randomised but not Treated | - |
|----------------------------|---|

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: Out of 1136 subjects who completed the 24 weeks double blind period, 234 were switched to either tocilizumab IV infusion (48 subjects) or tocilizumab SC (186 subjects) in 72 weeks open label extension period.

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | 24 Weeks Double Blind Period |
|-----------------------|------------------------------|

Reporting group description: -

| Reporting group values | 24 Weeks Double Blind Period | Total | |
|--|------------------------------|-------|--|
| Number of subjects | 1262 | 1262 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 1041 | 1041 | |
| From 65-84 years | 219 | 219 | |
| 85 years and over | 2 | 2 | |
| Age continuous Units: years | | | |
| arithmetic mean | 52.7 | | |
| standard deviation | ± 12.44 | - | |
| Gender, Male/Female Units: participants | | | |
| Female | 1041 | 1041 | |
| Male | 221 | 221 | |

End points

End points reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Tocilizumab SC |
| Reporting group description: Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study. | |
| Reporting group title | Tocilizumab IV |
| Reporting group description: Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study. | |
| Reporting group title | Tocilizumab SC |
| Reporting group description: Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study. | |
| Reporting group title | Tocilizumab IV |
| Reporting group description: Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study. | |
| Reporting group title | Tocilizumab SC Then Tocilizumab IV |
| Reporting group description: Subjects who received tocilizumab 162 mg subcutaneous (SC) injection weekly and placebo to tocilizumab IV every 4 weeks for 24 weeks in double blind treatment period switched to tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study. | |
| Reporting group title | Tocilizumab IV Then Tocilizumab SC |
| Reporting group description: Subjects who received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC once a week in double blind treatment period switched to tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose will be continued throughout the study. | |

Primary: Percentage of Subject Achieving an American College of Rheumatology Criteria (ACR20) Response at Week 24

| | |
|---|---|
| End point title | Percentage of Subject Achieving an American College of Rheumatology Criteria (ACR20) Response at Week 24 ^[1] |
| End point description: ACR20 response: ≥20% reduction from baseline for both TJC68 and SJC66, as well as for 3 of 5 additional ACR variables: Patient's Assessment of Pain in last 24 hours using a Visual Analog Scale (VAS) (0=no pain and 100=unbearable pain); Patient's and Physician's Global Assessment of Disease Activity in last 24 hours using a VAS (0=no disease activity and 100=maximum disease activity); Health Assessment Questionnaire: 20 questions in 8 areas (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities) answered on a scale of 0=without difficulty to 3=unable to do; and | |

acute-phase reactant (either C-reactive protein [CRP] or Erythrocyte Sedimentation Rate [ESR]). Per Protocol Population included all randomised subjects who received study drug and had no major protocol violations. Last Observation Carried Forward was used for missing joint counts, no imputation for other components. CRP will be used primarily for calculation of response. If missing, ESR will be used.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline, 24 weeks | |

Notes:

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

Justification: Inferential statistical analysis was not performed.

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 558 | 537 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 69.4 (65.5 to 73.2) | 73.4 (69.6 to 77.1) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Adverse Events, Serious Adverse Events and Clinically Significant Laboratory Assessments

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Adverse Events, Serious Adverse Events and Clinically Significant Laboratory Assessments ^[2] |
|-----------------|---|

End point description:

The safety population includes all subjects who received at least one dose of study drug, whether re-randomised or not, and who had at least one post-dose safety assessment. Data are included from double blind and open label (OL) periods in the SC and IV arms but only from the OL period in IV-SC and SC-IV switch arms.

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline to up to 3 months after last dose of study drug (approximately up to 2 years) | |

Notes:

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

Justification: Inferential statistical analysis was not performed.

| End point values | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV | Tocilizumab IV Then Tocilizumab SC |
|---|-----------------|-----------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 631 | 631 | 48 | 186 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Adverse Events (AEs) | 91.6 | 87.8 | 81.3 | 86.6 |
| Serious Adverse Events (SAEs) | 13.9 | 12.7 | 12.5 | 11.3 |
| Clinically Significant Laboratory Assessments | 37.7 | 28.2 | 25 | 19.4 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving an American College of Rheumatology Criteria (ACR50) Response at Week 24

| | |
|-----------------|---|
| End point title | Percentage of Subjects Achieving an American College of Rheumatology Criteria (ACR50) Response at Week 24 |
|-----------------|---|

End point description:

ACR50 response is defined as $\geq 50\%$ reduction from baseline for both TJC68 and SJC66, as well as for 3 of 5 additional ACR variables: Patient's Assessment of Pain in last 24 hours using a Visual Analog Scale (VAS) (0=no pain and 100=unbearable pain); Patient's and Physician's Global Assessment of Disease Activity in last 24 hours using a VAS (0=no disease activity and 100=maximum disease activity); Health Assessment Questionnaire: 20 questions in 8 areas (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities) answered on a scale of 0=without difficulty to 3=unable to do; and acute-phase reactant (either CRP or ESR). Per Protocol Population included all randomised subjects who received study drug and had no major protocol violations. Last Observation Carried Forward was used for missing joint counts, no imputation for other ACR components. CRP will be used primarily for the calculation of the ACR response. If missing, the ESR will be used for that subject.

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

End point timeframe:

Baseline, 24 weeks

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 558 | 537 | | |
| Units: percentage of subject | | | | |
| number (not applicable) | 47 | 48.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving an American College of Rheumatology Criteria (ACR70) Response at Week 24

| | |
|-----------------|---|
| End point title | Percentage of Subjects Achieving an American College of Rheumatology Criteria (ACR70) Response at Week 24 |
|-----------------|---|

End point description:

ACR70 response is defined as $\geq 70\%$ reduction from baseline for both TJC68 and SJC66, as well as for 3 of 5 additional ACR variables: Patient's Assessment of Pain in last 24 hours using a Visual Analog Scale (VAS) (0=no pain and 100=unbearable pain); Patient's and Physician's Global Assessment of Disease Activity in last 24 hours using a VAS (0=no disease activity and 100=maximum disease activity); Health Assessment Questionnaire: 20 questions in 8 areas (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities) answered on a scale of 0=without difficulty to 3=unable to do; and

acute-phase reactant (either CRP or ESR). Per Protocol Population included all randomised subjects who received study drug and had no major protocol violations. LOCF was used for missing joint counts, no imputation for other ACR components. CRP will be used primarily for the calculation of the ACR response. If missing, the ESR will be used for that subject.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 24 weeks | |

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 558 | 537 | | |
| Units: percentage of subject | | | | |
| number (not applicable) | 24 | 27.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Activity Score 28 (DAS28) Remission at Week 24

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Disease Activity Score 28 (DAS28) Remission at Week 24 |
|-----------------|--|

End point description:

The DAS28 (ESR) score is a measure of the subject's disease activity. It is calculated using the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity VAS where left side of the line 0=no disease activity to right side of the line 100=extreme disease activity and ESR. DAS28-(ESR) total scores range from 0 - 10. Remission is defined as achieving a DAS28-ESR score of less than 2.6. Subjects from the Per Protocol Population (randomised subjects who received study drug and had no major protocol violations) with data available for analysis. Missing SJC and TJC will be imputed using the last post-baseline value for the subject(LOCF). No imputation for missing ESR or patient's global assessment of disease activity.

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

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 516 | 498 | | |
| Units: percentage of subject | | | | |
| number (not applicable) | 38.4 | 36.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving a Decrease of ≥ 0.3 in the Health Assessment Questionnaire-Disability Index (HAQ-DI) From Baseline to Week 24

| | |
|-----------------|---|
| End point title | Percentage of Subjects Achieving a Decrease of ≥ 0.3 in the Health Assessment Questionnaire-Disability Index (HAQ-DI) From Baseline to Week 24 |
|-----------------|---|

End point description:

The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a subject completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 4 (unable to do). HAQ-DI = sum of worst scores in each domain divided by the number of domains answered. A decrease indicates improvement. Subjects from the Per Protocol Population (all randomised subjects who received study drug and had no major protocol violations) with data available for analysis. No imputation of missing scores will be made other than for missing baseline scores, for which last score prior to defined protocol baseline time window will be carried forward.

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

End point timeframe:

Baseline, 24 Weeks

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 515 | 500 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 65.2 | 67.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Withdrew Because of Lack of Therapeutic Response at Week 24

| | |
|-----------------|--|
| End point title | Percentage of Subjects Who Withdrew Because of Lack of Therapeutic Response at Week 24 |
|-----------------|--|

End point description:

The percentage of subjects who withdrew from the study because they were not responding to treatment with the study drug. Per Protocol Population included all randomised subjects who received study drug and had no major protocol violations.

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

End point timeframe:

24 Weeks

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 558 | 537 | | |
| Units: percentage of subject | | | | |
| number (not applicable) | 1.8 | 0.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With American College of Rheumatology Criteria (ACR20, ACR50, ACR70) at Week 97

| | |
|-----------------|--|
| End point title | Percentage of Subjects With American College of Rheumatology Criteria (ACR20, ACR50, ACR70) at Week 97 |
|-----------------|--|

End point description:

ACR20, ACR50 and ACR70: $\geq 20\%$, $\geq 50\%$ and $\geq 70\%$ reduction from baseline for both TJC68 and SJC66, as well as for 3 of 5 additional ACR variables: Patient's Assessment of Pain in last 24 hours using a Visual Analog Scale (VAS) (0=no pain and 100=unbearable pain); Patient's and Physician's Global Assessment of Disease Activity in last 24 hours using a VAS (0=no disease activity and 100=maximum disease activity); Health Assessment Questionnaire: 20 questions in 8 areas (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities) answered on a scale of 0=without difficulty to 3=unable to do; and acute-phase reactant (either CRP or ESR). Re-Randomized Intent-to-Treat Population (ITT Population) included all subject who completed double blind period and were re-randomised at Week 24, received at least 1 dose of study drug. CRP was used for calculation of ACR. If missing, ESR was used. Here, number of subject analysed is subjects for whom parameter was collected.

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

End point timeframe:

Week 97

| End point values | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV | Tocilizumab IV Then Tocilizumab SC |
|------------------------------|-----------------|-----------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 451 | 317 | 40 | 165 |
| Units: percentage of subject | | | | |
| number (not applicable) | | | | |
| ACR20 | 83.6 | 83.3 | 82.5 | 88.5 |
| ACR50 | 65.4 | 62.5 | 57.5 | 67.3 |
| ACR70 | 44.8 | 42 | 37.5 | 47.3 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Activity Score 28 (DAS28) Remission at Week 97

| | |
|---|--|
| End point title | Percentage of Subjects With Disease Activity Score 28 (DAS28) Remission at Week 97 |
| End point description: The DAS28 (ESR) score is a measure of the subject's disease activity. It is calculated using the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity VAS where left side of the line 0=no disease activity to right side of the line 100=extreme disease activity and ESR. DAS28-(ESR) total scores range from 0 - 10. Remission is defined as achieving a DAS28-ESR score of less than 2.6. LOCF used for tender and swollen joint counts, no imputation used for ESR and Patient's Global Assessment of Disease Activity VAS. ITT Population included all subject who completed double blind period and were re-randomised at Week 24 and received at least one dose of study drug. If ESR=0 then ESR=1 is substituted into the DAS28 calculation to enable a non-missing DAS28 score. Here, number of subjects analysed is the subjects for whom parameter was collected. | |
| End point type | Secondary |
| End point timeframe: Week 97 | |

| End point values | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV | Tocilizumab IV Then Tocilizumab SC |
|------------------------------|-----------------|-----------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 446 | 306 | 40 | 162 |
| Units: percentage of subject | | | | |
| number (not applicable) | 53.4 | 46.4 | 50 | 55.6 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving a Decrease of ≥ 0.3 in the Health Assessment Questionnaire-Disability Index (HAQ-DI) From Baseline to Week 97

| | |
|---|---|
| End point title | Percentage of Subjects Achieving a Decrease of ≥ 0.3 in the Health Assessment Questionnaire-Disability Index (HAQ-DI) From Baseline to Week 97 |
| End point description: The HAQ-DI is a subject completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component ranging from 0(without any difficulty) to 4 (unable to do). HAQ-DI=sum of worst scores in each domain divided by number of domains answered. A decrease indicates improvement. No imputation of missing scores was made other than for missing baseline scores, for which last score prior to baseline will be carried forward. For subjects who prematurely withdrew, data collected at withdrawal visit was used and data thereafter is missing. ITT Population included all subjects who completed double blind period and were re-randomised at Week 24 and received at least one dose of study drug. Here, number of subjects analysed is the subjects for whom parameter was collected. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 97 | |

| End point values | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV | Tocilizumab IV Then Tocilizumab SC |
|-------------------------------|-----------------|-----------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 445 | 317 | 39 | 162 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 72.4 | 69.1 | 56.4 | 71 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Withdrew Because of Lack of Therapeutic Response at Week 97

| | |
|--|--|
| End point title | Percentage of Subjects Who Withdrew Because of Lack of Therapeutic Response at Week 97 |
| End point description: The percentage of subjects who withdrew from the study because they were not responding to treatment with the study drug. ITT Population included all subjects who completed double blind period and were re-randomised at Week 24 and received at least one dose of study drug. | |
| End point type | Secondary |
| End point timeframe: Week 97 | |

| End point values | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV | Tocilizumab IV Then Tocilizumab SC |
|-------------------------------|-----------------|-----------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 521 | 372 | 48 | 186 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 1.7 | 3 | 4.2 | 1.6 |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration Curve of Tocilizumab After First SC Injection or IV Infusion

| | |
|--|---|
| End point title | Area Under the Serum Concentration Curve of Tocilizumab After First SC Injection or IV Infusion |
| End point description: Pharmacokinetic-Evaluable Population included all subject who provided at least one evaluable PK sample were included in the pharmacokinetic analysis (PK) analysis. Here, number of subject analysed who were evaluable for this outcome measure. | |
| End point type | Secondary |
| End point timeframe: Week 0: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after first dose. | |

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 16 | | |
| Units: microgram*hour/milliliter (mcg*hr/mL) | | | | |
| arithmetic mean (standard deviation) | 1444 (± 839) | 30988 (± 9114) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration Curve of Tocilizumab at Steady State for SC and IV Treatment

| | |
|-----------------|---|
| End point title | Area Under the Serum Concentration Curve of Tocilizumab at Steady State for SC and IV Treatment |
|-----------------|---|

End point description:

Pharmacokinetic-Evaluable Population included all subjects who provided at least one evaluable PK sample were included in the pharmacokinetic analysis (PK) analysis. Here, number of subjects analysed who were evaluable for this outcome measure.

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

End point timeframe:

Week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose.

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 13 | | |
| Units: µg*hr/mL | | | | |
| arithmetic mean (standard deviation) | 7542 (± 3989) | 41304 (± 15104) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Serum Concentration (Cmin) of Tocilizumab

| | |
|-----------------|---|
| End point title | Minimum Serum Concentration (Cmin) of Tocilizumab |
|-----------------|---|

End point description:

Pharmacokinetic-Evaluable Population included all subjects who provided at least one evaluable PK sample were included in the PK analysis. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

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

End point timeframe:

Week 0, Week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 16 | | |
| Units: microgram/milliliter (mcg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0 (after first dose) (n=17, 16) | 7.48 (± 4.91) | 6.65 (± 6.05) | | |
| Week 20 (n=13, 13) | 35.7 (± 16.2) | 16 (± 10.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of Tocilizumab

End point title Maximum Serum Concentration (Cmax) of Tocilizumab

End point description:

Pharmacokinetic-Evaluable Population included all subjects who provided at least one evaluable PK sample were included in the PK analysis. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

End point type Secondary

End point timeframe:

Week 0, Week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 16 | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0 (after first dose) (n=17, 16) | 14.7 (± 8.74) | 180 (± 40.1) | | |
| Week 20 (n=13, 13) | 52.7 (± 27.3) | 233 (± 117) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Serum Concentration (Tmax) of Tocilizumab

End point title Time to Maximum Serum Concentration (Tmax) of Tocilizumab

End point description:

Pharmacokinetic-Evaluable Population included all subjects who provided at least one evaluable PK

sample were included in the PK analysis. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

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

End point timeframe:

Week 0, Week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose

| End point values | Tocilizumab SC | Tocilizumab IV | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 16 | | |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | | | | |
| Week 0 (after first dose) (n=17, 16) | 74 (24 to 121) | 6 (3 to 7) | | |
| Week 20 (n=13, 13) | 70 (0 to 122) | 6 (4 to 46) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Interleukin-6 (IL-6) Concentration at Week 25

| | |
|-----------------|---|
| End point title | Change From Baseline in Serum Interleukin-6 (IL-6) Concentration at Week 25 |
|-----------------|---|

End point description:

The ITT-PK population includes all subjects who were eligible for the ITT population and provided at least 1 evaluable PK sample in the double blind or open label periods. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

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

End point timeframe:

Baseline, Week 25

| End point values | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV | Tocilizumab IV Then Tocilizumab SC |
|---|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 493 | 359 | 46 | 186 |
| Units: picogram/milliliter (pg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=493, 359, 46, 186) | 39.04 (± 55.456) | 52.48 (± 240.964) | 62.18 (± 125.081) | 50.07 (± 161.045) |
| Change at Week 25 (n=385, 280, 33, 149) | 34.42 (± 110.842) | 52.61 (± 507.157) | 37.54 (± 93.464) | 44.12 (± 136.955) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Soluble Interleukin-6 Receptor (sIL-6R) Concentration at Week 97

| | |
|-----------------|--|
| End point title | Change From Baseline in Serum Soluble Interleukin-6 Receptor (sIL-6R) Concentration at Week 97 |
|-----------------|--|

End point description:

The ITT-PK population includes all subjects who were eligible for the ITT population and provided at least 1 evaluable PK sample in the double blind or open label periods. Here, number of subjects analysed who were evaluable for this outcome measure and 'n' indicates number of subjects who were evaluated at specified time point.

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

End point timeframe:

Baseline, Week 97

| End point values | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV | Tocilizumab IV Then Tocilizumab SC |
|---|--------------------|--------------------|---------------------------------------|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 504 | 366 | 46 | 186 |
| Units: nanogram/milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=504, 366, 46, 186) | 44.53 (± 35.47) | 45.72 (± 40.219) | 44.71 (± 13.068) | 43.28 (± 16.197) |
| Change at Week 25 (n=416, 296, 37, 157) | 601.52 (± 222.141) | 575.75 (± 244.398) | 569.6 (± 213.588) | 586.5 (± 226.915) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Developed Antibodies To Tocilizumab at Week 97

| | |
|-----------------|---|
| End point title | Percentage of Subjects Who Developed Antibodies To Tocilizumab at Week 97 |
|-----------------|---|

End point description:

The safety population includes all subjects who received at least one dose of study drug, whether re-randomised or not, and who had at least one post-dose safety assessment. Here, 'n' indicates number of subjects in the safety population tested by screening assay at any time point.

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

End point timeframe:

Week 97

| End point values | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV | Tocilizumab IV Then Tocilizumab SC |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 629 | 629 | 46 | 184 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 1.3 | 1 | 0 | 0.5 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to up to 3 months after last dose of study drug (approximately up to 2 years)

Adverse event reporting additional description:

The safety population includes all subjects who received at least one dose of study drug, whether re-randomized or not, and who had at least one post-dose safety assessment. Data are included from double blind and open label (OL) periods in the SC and IV arms but only from the OL period in IV-SC and SC-IV switch arms.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Tocilizumab SC |
|-----------------------|----------------|

Reporting group description:

Subjects received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for a total of 24 weeks in the double-blind period. Participants continued to receive tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

| | |
|-----------------------|----------------|
| Reporting group title | Tocilizumab IV |
|-----------------------|----------------|

Reporting group description:

Subjects received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly for a total of 24 weeks in the double-blind period. Subjects continued to receive tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Tocilizumab SC Then Tocilizumab IV |
|-----------------------|------------------------------------|

Reporting group description:

Subjects who received tocilizumab 162 mg subcutaneous (SC) injection weekly plus placebo to tocilizumab intravenous (IV) infusion every 4 weeks for 24 weeks in double blind treatment period switched to tocilizumab 8 mg/kg IV infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose continued throughout the study.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Tocilizumab IV Then Tocilizumab SC |
|-----------------------|------------------------------------|

Reporting group description:

Subjects who received tocilizumab 8 mg/kg infusion (IV) every 4 weeks plus placebo to tocilizumab SC injection weekly in double blind treatment period switched to tocilizumab 162 mg SC injection weekly for a total of 72 weeks in open label extension period. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at a stable dose will be continued throughout the study.

| Serious adverse events | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV |
|---|-------------------|-------------------|------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 88 / 631 (13.95%) | 80 / 631 (12.68%) | 6 / 48 (12.50%) |
| number of deaths (all causes) | 4 | 4 | 0 |
| number of deaths resulting from adverse events | 2 | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Breast Cancer | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Brain neoplasm malignant | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Cervix carcinoma stage 0 | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Endometrial adenoma | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Fibroadenoma of breast | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Gastrointestinal tract adenoma | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Leiomyoma | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Lentigo maligna | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Morton's neuroma | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Schwannoma | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Shock | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Venous thrombosis limb | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Imminent abortion | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Death | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Ischaemic ulcer | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Non-cardiac chest pain | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 3 / 631 (0.48%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amyloidosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic floor muscle weakness | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Idiopathic pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Pleurisy | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 | | | |
| Fall | | | |
| subjects affected / exposed | 3 / 631 (0.48%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Adrenal gland injury | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Anastomotic ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Chillblains | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Comminuted fracture | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Hepatic haematoma | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Jaw fracture | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Laceration | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Pulmonary contusion | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Synovial rupture | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Congenital, familial and genetic disorders | | | |
| Hydrocele | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Angina unstable | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Atrioventricular block first degree | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac valve disease | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Nervous system disorders | | | |
| Sciatica | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 2 / 631 (0.32%) | 0 / 48 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 3 / 631 (0.48%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 631 (0.32%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery thrombosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Cerebellar ischaemia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Grand mal convulsion | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Migraine | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 global amnesia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Eye disorders | | | |
| Amaurosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Ileus | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Lumbar hernia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Megacolon | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Oesophageal ulcer | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 haemorrhage | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Small intestinal perforation | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 | 3 / 631 (0.48%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Cholecystitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Sphincter of oddi dysfunction | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 3 / 631 (0.48%) | 5 / 631 (0.79%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Compartment syndrome | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Costochondritis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Intervertebral disc disorder | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 | 4 / 631 (0.63%) | 6 / 631 (0.95%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 5 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 8 / 631 (1.27%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 6 / 8 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic Shock | | | |
| subjects affected / exposed | 3 / 631 (0.48%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 3 / 631 (0.48%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 2 / 631 (0.32%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 3 / 631 (0.48%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis infective | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 2 / 631 (0.32%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Subcutaneous abscess | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Bone tuberculosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Burkholderia pseudomallei infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Dacryocystitis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Groin abscess | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Intervertebral discitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Muscle abscess | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Pericolic abscess | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Pharyngeal abscess | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Post procedural infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 abscess | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal abscess | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 631 (0.00%) | 1 / 631 (0.16%) | 0 / 48 (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 |
| Tracheobronchitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Whipple's disease | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (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 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 631 (0.16%) | 0 / 631 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------------------------------|--|--|
| Serious adverse events | Tocilizumab IV Then Tocilizumab SC | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 186 (11.29%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast Cancer | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain neoplasm malignant | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervix carcinoma stage 0 | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial adenoma | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fibroadenoma of breast | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal tract adenoma | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intraductal proliferative breast lesion | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Invasive ductal breast carcinoma | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leiomyoma | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lentigo maligna | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Morton's neuroma | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Parathyroid tumour benign | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal cell carcinoma | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Schwannoma | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Shock | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis limb | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Imminent abortion | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic ulcer | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Amyloidosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic floor muscle weakness | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Uterine polyp | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumothorax | | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute respiratory failure | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute respiratory distress syndrome | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Idiopathic pulmonary fibrosis | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|-----------------|--|--|
| Pleurisy | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Adrenal gland injury | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anastomotic ulcer haemorrhage | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arthropod sting | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cervical vertebral fracture | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chillblains | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Comminuted fracture | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Facial bones fracture | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral neck fracture | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic haematoma | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary contusion | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sternal fracture | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Synovial rupture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Hydrocele | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |

| | | | | |
|---|-----------------|--|--|--|
| Angina unstable | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure congestive | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery disease | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angina pectoris | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial tachycardia | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrioventricular block first degree | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac valve disease | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery thrombosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebellar ischaemia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Grand mal convulsion | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Migraine | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient global amnesia | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Amaurosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar hernia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Megacolon | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal ulcer | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sphincter of oddi dysfunction | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Rheumatoid arthritis | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bursitis | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal chest pain | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteonecrosis | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal osteoarthritis | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Compartment syndrome | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Costochondritis | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral disc degeneration | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral disc disorder | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 186 (2.15%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic Shock | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bursitis infective | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Subcutaneous abscess | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone tuberculosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Burkholderia pseudomallei infection | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dacryocystitis | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related infection | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Empyema | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocarditis | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Groin abscess | | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious pleural effusion | | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral discitis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscle abscess | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericolic abscess | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pharyngeal abscess | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal abscess | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retroperitoneal abscess | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tracheobronchitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Whipple's disease | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Tocilizumab SC | Tocilizumab IV | Tocilizumab SC Then Tocilizumab IV |
|---|--------------------|--------------------|---------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 488 / 631 (77.34%) | 430 / 631 (68.15%) | 29 / 48 (60.42%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 188 / 631 (29.79%) | 140 / 631 (22.19%) | 7 / 48 (14.58%) |
| occurrences (all) | 247 | 184 | 10 |

| | | | |
|---|--|--|--|
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 135 / 631 (21.39%) 171 | 96 / 631 (15.21%) 115 | 3 / 48 (6.25%) 5 |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 33 / 631 (5.23%) 39 | 25 / 631 (3.96%) 28 | 1 / 48 (2.08%) 1 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 49 / 631 (7.77%) 56 | 65 / 631 (10.30%) 77 | 4 / 48 (8.33%) 4 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 46 / 631 (7.29%) 62 | 41 / 631 (6.50%) 55 | 3 / 48 (6.25%) 3 |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 62 / 631 (9.83%) 85 | 50 / 631 (7.92%) 74 | 2 / 48 (4.17%) 4 |
| General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all) | 33 / 631 (5.23%) 188 | 5 / 631 (0.79%) 53 | 1 / 48 (2.08%) 1 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 55 / 631 (8.72%) 67 35 / 631 (5.55%) 42 | 39 / 631 (6.18%) 44 40 / 631 (6.34%) 54 | 1 / 48 (2.08%) 1 2 / 48 (4.17%) 2 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 32 / 631 (5.07%) 35 | 27 / 631 (4.28%) 34 | 1 / 48 (2.08%) 1 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---------------------------|---------------------------|-----------------------|
| Back pain subjects affected / exposed occurrences (all) | 33 / 631 (5.23%) 36 | 34 / 631 (5.39%) 37 | 2 / 48 (4.17%) 2 |
| Osteoarthritis subjects affected / exposed occurrences (all) | 21 / 631 (3.33%) 26 | 11 / 631 (1.74%) 12 | 3 / 48 (6.25%) 3 |
| Arthralgia subjects affected / exposed occurrences (all) | 24 / 631 (3.80%) 26 | 28 / 631 (4.44%) 31 | 3 / 48 (6.25%) 3 |
| Rheumatoid arthritis subjects affected / exposed occurrences (all) | 29 / 631 (4.60%) 36 | 26 / 631 (4.12%) 37 | 3 / 48 (6.25%) 3 |
| Infections and infestations | | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 122 / 631 (19.33%) 192 | 130 / 631 (20.60%) 182 | 8 / 48 (16.67%) 12 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 67 / 631 (10.62%) 100 | 53 / 631 (8.40%) 73 | 4 / 48 (8.33%) 5 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 88 / 631 (13.95%) 146 | 68 / 631 (10.78%) 86 | 7 / 48 (14.58%) 13 |
| Bronchitis subjects affected / exposed occurrences (all) | 44 / 631 (6.97%) 51 | 35 / 631 (5.55%) 38 | 2 / 48 (4.17%) 2 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 41 / 631 (6.50%) 45 | 26 / 631 (4.12%) 28 | 3 / 48 (6.25%) 3 |
| Pharyngitis subjects affected / exposed occurrences (all) | 23 / 631 (3.65%) 25 | 39 / 631 (6.18%) 51 | 2 / 48 (4.17%) 2 |
| Sinusitis subjects affected / exposed occurrences (all) | 33 / 631 (5.23%) 38 | 19 / 631 (3.01%) 27 | 0 / 48 (0.00%) 0 |

| | | | |
|-----------------------------------|---------------------------------------|--|--|
| Non-serious adverse events | Tocilizumab IV Then Tocilizumab SC | | |
|-----------------------------------|---------------------------------------|--|--|

| | | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 118 / 186 (63.44%) | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 29 / 186 (15.59%) 36 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 14 / 186 (7.53%) 17 | | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 7 / 186 (3.76%) 7 | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 8 / 186 (4.30%) 8 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 9 / 186 (4.84%) 9 | | |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 13 / 186 (6.99%) 19 | | |
| General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all) | 9 / 186 (4.84%) 122 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 14 / 186 (7.53%) 16 4 / 186 (2.15%) 4 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-------------------|--|--|
| Rash | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | | |
| occurrences (all) | 3 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 9 / 186 (4.84%) | | |
| occurrences (all) | 10 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | | |
| occurrences (all) | 1 | | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 186 (3.23%) | | |
| occurrences (all) | 7 | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 11 / 186 (5.91%) | | |
| occurrences (all) | 12 | | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 33 / 186 (17.74%) | | |
| occurrences (all) | 41 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 15 / 186 (8.06%) | | |
| occurrences (all) | 17 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 26 / 186 (13.98%) | | |
| occurrences (all) | 42 | | |
| Bronchitis | | | |
| subjects affected / exposed | 6 / 186 (3.23%) | | |
| occurrences (all) | 7 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 6 / 186 (3.23%) | | |
| occurrences (all) | 7 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 4 / 186 (2.15%) | | |
| occurrences (all) | 4 | | |
| Sinusitis | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 6 / 186 (3.23%) | | |
| occurrences (all) | 7 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 November 2010 | 1) Given the course of treatment and fatal outcome of the anaphylaxis case reported, continued treatment with TCZ was no longer acceptable for subjects who experience serious hypersensitivity reactions. Subjects who experience serious hypersensitivity reactions that led to a disruption were to be permanently discontinued from TCZ treatment and withdrawn from the study. Treatment recommendations were removed from the protocol to allow health care providers to include all therapies available, according to the standard of care appropriate for the subject's reaction. Addition of event-driven sampling to detect anti-TCZ antibodies in subjects who withdraw due to anaphylaxis or serious hypersensitivity. 2) To aid recruitment, the inclusion criteria were revised to include subjects with either elevated CRP and/or ESR. 3) Clarification that subjects who have received previous treatment with any cell-depleting therapy were excluded from participating in this trial. 4) No tocilizumab to be given at the Week 97 visit. 5) Clarification of the minimum and maximum interval required between each subcutaneous injection and that the first 2 injections must be administered by site staff, but the following injections can be administered by the subject or her/his caregiver with specific recommendation regarding the injection sites. 6) The PK/PD sub-study and Roche clinical repository sampling has been removed from the open-label period. 7) To allow a window around the baseline visit of +/- 3 days, clarify the +/-3 day visit window and the minimum period between IV infusions. 8) Extension of DMARD wash out, clarify that subjects are eligible for this study if they have had previous inadequate response to DMARDs and clarify concomitant DMARDs during the study. 9) As the study has a safety follow-up period of 8 weeks, all adverse events will be collected through the follow-up Week 8 visit. |
| 02 December 2011 | A drug-free serum sample should be obtained after an appropriate washout period for TCZ to optimize anti-TCZ antibody detection. TCZ is predicted to be cleared from serum at 6 weeks after the last 8 mg/kg IV infusion and 4 weeks after the last 162 mg SC weekly injection. In order not to interrupt subject treatment during the study, protocol version C is amended to allow for this additional sample collection from subjects who have terminated from the study early, completed the study or missed TCZ treatment during the study, when the TCZ concentration is expected to be cleared from the serum. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported