



Clinical trial results:

A Randomized, Double-Blind, Parallel Group, International Study to Evaluate the Safety and Efficacy of Ocrelizumab Compared to Placebo in Patients with Active Rheumatoid Arthritis Who Have an Inadequate Response to at Least One Anti-TNF- Therapy

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2006-005330-20 |
| Trial protocol | BE DE FR HU ES CZ NL SI SE IT SK |
| Global end of trial date | 14 May 2018 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v3 (current) |
| This version publication date | 25 May 2019 |
| First version publication date | 15 July 2015 |
| Version creation reason | |
| Summary attachment (see zip file) | WA20495 Redacted CSR Synopsis (WA20495_Redacted_CSRSynopsis.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | WA20495 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|--------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00476996 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | ACT3986g: ACT3986g |

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, globa.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 | 17 May 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 May 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial to investigate the efficacy and safety of Ocrelizumab in combination with Methotrexate (MTX) or Leflunomide given either alone or in combination with other non-biologic DMARDs in patients with active Rheumatoid arthritis (RA) who had an inadequate response to anti-TNF- α therapy.

Protection of trial subjects:

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

Background therapy:

Subjects received either leflunomide or methotrexate for ≥ 12 weeks, with a stable dose for the last 4 weeks.

Evidence for comparator: -

| | |
|---|---------------------------|
| Actual start date of recruitment | 15 May 2007 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Regulatory reason |
| Long term follow-up duration | 8 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | Belgium: 12 |
| Country: Number of subjects enrolled | Brazil: 31 |
| Country: Number of subjects enrolled | Canada: 36 |
| Country: Number of subjects enrolled | Switzerland: 4 |
| Country: Number of subjects enrolled | Czech Republic: 16 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Spain: 19 |
| Country: Number of subjects enrolled | France: 20 |
| Country: Number of subjects enrolled | Hungary: 18 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Israel: 20 |
| Country: Number of subjects enrolled | Japan: 106 |
| Country: Number of subjects enrolled | Mexico: 30 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 3 |
| Country: Number of subjects enrolled | New Zealand: 4 |
| Country: Number of subjects enrolled | Panama: 1 |
| Country: Number of subjects enrolled | Peru: 17 |
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Argentina: 14 |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | Slovakia: 4 |
| Country: Number of subjects enrolled | Slovenia: 10 |
| Country: Number of subjects enrolled | United States: 416 |
| Worldwide total number of subjects | 836 |
| EEA total number of subjects | 145 |

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) | 681 |
| From 65 to 84 years | 155 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited across 25 countries.

Pre-assignment

Screening details:

Study population comprised adult subjects with active RA of ≥ 3 months duration who had an inadequate clinical response due to toxicity or inadequate efficacy, to previous or current treatment with one or more anti-TNF- α therapies.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo \times 2 IV + non-biologic DMARD therapy |

Arm description:

Subjects received Ocrelizumab matching Placebo Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs.

| | |
|--|------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Ocrelizumab matching Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Matching placebo, administered IV, separated by 14 day intervals (day 1 and day 15).

| | |
|--|--------------|
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | MTX |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

7.5-25 mg/week (oral or parenteral) for at least 12 weeks, with the last 4 weeks prior to baseline at stable dose.

| | |
|--|-------------|
| Investigational medicinal product name | Leflunomide |
| Investigational medicinal product code | |
| Other name | LFL |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Leflunomide was administered once daily, 10-20 mg for at least 12 weeks, with the last 4 weeks, prior to baseline at a stable dose.

| | |
|--|--------------------|
| Investigational medicinal product name | Methylprednisolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |

| | |
|---|--|
| Routes of administration | Not mentioned |
| Dosage and administration details: | |
| Methylprednisolone was administered by IV, slow infusion of 100 mg, completed at least 30 minutes prior to each infusion of study treatment. | |
| Investigational medicinal product name | Acetaminophen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 gram of acetaminophen taken by mouth 30 to 60 minutes prior to the start of the placebo infusion. | |
| Investigational medicinal product name | Diphenhydramine HCl |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 50 mg of Diphenhydramine HCl taken by mouth 30 to 60 minutes prior to the start of the placebo infusion | |
| Arm title | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy |
| Arm description: | |
| Subjects received 200 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs. | |
| Arm type | Experimental |
| Investigational medicinal product name | Ocrelizumab |
| Investigational medicinal product code | |
| Other name | Ocrevus |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 200 mg x2 administered by IV, separated by 14 day intervals (day 1 and day 15). | |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | MTX |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 7.5-25 mg/week (oral or parenteral) for at least 12 weeks, with the last 4 weeks prior to baseline at stable dose. | |
| Investigational medicinal product name | Leflunomide |
| Investigational medicinal product code | |
| Other name | LFL |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Leflunomide was administered once daily, 10-20 mg for at least 12 weeks, with the last 4 weeks, prior to baseline at a stable dose. | |
| Investigational medicinal product name | Methylprednisolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Parenteral use |

| | |
|---|--|
| Dosage and administration details: | |
| Methylprednisolone was administered by IV, slow infusion of 100 mg, completed at least 30 minutes prior to each infusion of study treatment. | |
| Investigational medicinal product name | Acetaminophen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 1 gram of acetaminophen taken by mouth 30 to 60 minutes prior to the start of the Ocrelizumab infusion. | |
| Investigational medicinal product name | Diphenhydramine HCl |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 50 mg taken by mouth 30 to 60 minutes prior to the start of the Ocrelizumab infusion. | |
| Arm title | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy |
| Arm description: | |
| Subjects received 500 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs. | |
| Arm type | Experimental |
| Investigational medicinal product name | Ocrelizumab |
| Investigational medicinal product code | |
| Other name | Ocrevus |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 500mg x2 administered by IV, separated by 14 day intervals (day 1 and day 15). | |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | MTX |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 7.5-25 mg/week (oral or parenteral) for at least 12 weeks, with the last 4 weeks prior to baseline at stable dose. | |
| Investigational medicinal product name | Leflunomide |
| Investigational medicinal product code | |
| Other name | LFL |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Leflunomide was administered once daily, 10-20 mg for at least 12 weeks, with the last 4 weeks, prior to baseline at a stable dose. | |
| Investigational medicinal product name | Methylprednisolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Parenteral use |
| Dosage and administration details: | |
| Methylprednisolone was administered by IV, slow infusion of 100 mg, completed at least 30 minutes | |

prior to each infusion of study treatment.

| | |
|--|---------------|
| Investigational medicinal product name | Acetaminophen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 gram of acetaminophen taken by mouth 30 to 60 minutes prior to the start of the Ocrelizumab infusion.

| | |
|--|---------------------|
| Investigational medicinal product name | Diphenhydramine HCl |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg taken by mouth 30 to 60 minutes prior to the start of the Ocrelizumab infusion.

| Number of subjects in period 1 | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non- biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non- biologic DMARD therapy |
|--------------------------------|---|--|--|
| | | | |
| Started | 277 | 277 | 282 |
| Completed | 205 | 222 | 237 |
| Not completed | 72 | 55 | 45 |
| Consent withdrawn by subject | 12 | 7 | 7 |
| Adverse event, non-fatal | 11 | 13 | 7 |
| Death | 2 | 1 | 1 |
| Non-compliance with study drug | - | 2 | - |
| Lost to follow-up | - | 4 | 3 |
| Early termination of study | 24 | 20 | 21 |
| Protocol deviation | 1 | 3 | - |
| Lack of efficacy | 22 | 5 | 6 |

Period 2

| | |
|------------------------------|------------------------|
| Period 2 title | Study extension period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Eligible subjects received open-label treatment with Ocrelizumab 500 mg x 2, separated by at least 3 months from the last infusion, at the discretion of the investigator

Arms

| | |
|------------------|--|
| Arm title | Ocrelizumab 500 mg × 2 IV + Non-biologic DMARD (OLE) |
|------------------|--|

Arm description:

Subjects received 500 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15)

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ocrelizumab |
| Investigational medicinal product code | |
| Other name | Ocrevus |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

500mg x2 administered by IV, separated by 14 day intervals (day 1 and day 15).

| | |
|---------------------------------------|--|
| Number of subjects in period 2 | Ocrelizumab 500 mg × 2 IV + Non- biologic DMARD (OLE) |
| Started | 664 |
| Completed | 0 |
| Not completed | 664 |
| Consent withdrawn by subject | 50 |
| Adverse event, non-fatal | 8 |
| Death | 7 |
| Non-compliance with study drug | 4 |
| Lost to follow-up | 4 |
| Early termination of study | 578 |
| Lack of efficacy | 13 |

Baseline characteristics

Reporting groups

| | |
|---|--|
| Reporting group title | Placebo × 2 IV + non-biologic DMARD therapy |
| Reporting group description: Subjects received Ocrelizumab matching Placebo Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs. | |
| Reporting group title | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy |
| Reporting group description: Subjects received 200 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs. | |
| Reporting group title | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy |
| Reporting group description: Subjects received 500 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs. | |

| Reporting group values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy |
|--|---|--|--|
| Number of subjects | 277 | 277 | 282 |
| Age Categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 222 | 222 | 237 |
| From 65-84 years | 55 | 55 | 45 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 54.2 | 54.5 | 53.8 |
| standard deviation | ± 11.3 | ± 11.2 | ± 11.6 |
| Gender Categorical Units: Subjects | | | |
| Female | 215 | 214 | 236 |
| Male | 62 | 63 | 46 |
| Ethnicity Units: Subjects | | | |
| Race Units: Subjects | | | |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 836 | | |

| | | | |
|---|-----|--|--|
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 681 | | |
| From 65-84 years | 155 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 665 | | |
| Male | 171 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Race | | | |
| Units: Subjects | | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Placebo × 2 IV + non-biologic DMARD therapy |
| Reporting group description: Subjects received Ocrelizumab matching Placebo Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs. | |
| Reporting group title | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy |
| Reporting group description: Subjects received 200 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs. | |
| Reporting group title | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy |
| Reporting group description: Subjects received 500 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs. | |
| Reporting group title | Ocrelizumab 500 mg × 2 IV + Non-biologic DMARD (OLE) |
| Reporting group description: Subjects received 500 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) | |
| Subject analysis set title | Intent to Treat (ITT) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All randomized subjects who received any part of an infusion of study medication were included in the ITT analysis | |
| Subject analysis set title | Modified Intent-to-Treat (mITT) |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: The Modified Intent-to-Treat (mITT) population included all subjects who were in the ITT analysis set and had both baseline radiograph and at least one post-baseline radiograph for campaign 1 | |
| Subject analysis set title | Per Protocol (PP) Population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per protocol analysis population included all subject in the ITT population who adhered to the protocol. Subjects could be excluded if they significantly violated the inclusion/exclusion criteria or deviated from the study protocol | |
| Subject analysis set title | Modified Per Protocol (mPP) Population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: A modified per protocol (mPP) population was also defined for radiographic analyses based on campaign 1 data. The mPP population included all subjects in the mITT population who adhered to the protocol. Subjects could be excluded if they significantly violated the inclusion/exclusion criteria or deviated from the study protocol | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety population included all subjects who were randomized and received any part of an infusion of study drug and provided at least one assessment of safety | |

Primary: Percentage of subjects with ACR20 responses

| | |
|--|---|
| End point title | Percentage of subjects with ACR20 responses |
| End point description: ACR20 response: greater than or equal to (\geq) 20% improvement in tender or swollen joint counts and 20% improvement in 3 of the following 5 criteria: 1) Physician's global assessment of disease activity, 2) participant assessment of disease activity, 3) Patient Assessment of Pain (visual analog scale [VAS]), 4) participant assessment of functional disability via a Health Assessment Questionnaire (HAQ), and 5) | |

erythrocyte sedimentation rate (ESR) at each visit.

Intent-to-Treat (ITT) All randomized participants who received any part of an infusion of study medication were included in the ITT analysis. Number of subjects for whom data was collected is indicated in each time point.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Weeks 24 and 48 | |

| End point values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy | |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 277 | 277 | 282 | |
| Units: Percentage | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Percentage of Responders at Week 24 | 22 (17.1 to 26.9) | 42.2 (36.4 to 48.1) | 47.9 (42.0 to 53.7) | |
| Percentage of Responders at Week 48 | 19.5 (14.8 to 24.2) | 48.7 (42.9 to 54.6) | 50.7 (44.9 to 56.5) | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Week 24 |
| Statistical analysis description: | |
| At Week 24, analysis was stratified by region and baseline DMARD therapy | |
| Comparison groups | Placebo × 2 IV + non-biologic DMARD therapy v Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy |
| Number of subjects included in analysis | 554 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Weighted difference |
| Point estimate | 20.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.8 |
| upper limit | 27.9 |

| | |
|--|---|
| Statistical analysis title | Week 24 |
| Statistical analysis description: | |
| At Week 24, analysis was stratified by region and baseline DMARD therapy | |
| Comparison groups | Placebo × 2 IV + non-biologic DMARD therapy v Ocrelizumab |

| | |
|---|--|
| | 500 mg × 2 IV + non-biologic DMARD therapy |
| Number of subjects included in analysis | 559 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Weighted Difference |
| Point estimate | 25.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17.7 |
| upper limit | 32.7 |

| | |
|--|--|
| Statistical analysis title | Week 48 |
| Statistical analysis description: | |
| At Week 48, analysis was stratified by region and baseline DMARD therapy | |
| Comparison groups | Placebo × 2 IV + non-biologic DMARD therapy v Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy |
| Number of subjects included in analysis | 554 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Weighted Difference |
| Point estimate | 29.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 21.6 |
| upper limit | 36.6 |

| | |
|--|--|
| Statistical analysis title | Week 48 |
| Statistical analysis description: | |
| At Week 48, analysis was stratified by region and baseline DMARD therapy | |
| Comparison groups | Placebo × 2 IV + non-biologic DMARD therapy v Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy |
| Number of subjects included in analysis | 559 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Weighted Difference |
| Point estimate | 30.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 22.8 |
| upper limit | 37.7 |

Secondary: Percentage of subjects with a major clinical response

| | |
|---|---|
| End point title | Percentage of subjects with a major clinical response |
| End point description: | |
| Major clinical response was defined as achieving an ACR70 response and maintaining this response for a consecutive period of at least 6 months. | |
| Intent-to-Treat (ITT) All randomized participants who received any part of an infusion of study medication were included in the ITT analysis. Number of subjects for whom data was collected is indicated in each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 48 | |

| End point values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 277 | 277 | 282 | |
| Units: percentage | | | | |
| number (confidence interval 95%) | | | | |
| Week 48 | 1.8 (0.2 to 3.4) | 4.0 (1.7 to 6.3) | 5.7 (3.0 to 8.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Disease Activity Score (DAS28) remission

| | |
|--|---|
| End point title | Percentage of subjects achieving Disease Activity Score (DAS28) remission |
| End point description: | |
| The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6. | |
| Intent-to-Treat (ITT) All randomized participants who received any part of an infusion of study medication were included in the ITT analysis. Number of subjects for whom data was collected is indicated in each time point. | |
| End point type | Secondary |

End point timeframe:

Weeks 24 and 48

| End point values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy | |
|---------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 277 | 277 | 282 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of Participants at Week 24 | 1.8 (0.2 to 3.4) | 5.8 (3.0 to 8.5) | 6.0 (3.3 to 8.8) | |
| Percentage of Participants at Week 48 | 1.4 (0.0 to 2.8) | 11.9 (8.1 to 15.7) | 12.1 (8.3 to 15.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DAS28 from baseline

| | |
|-----------------|-------------------------------|
| End point title | Change in DAS28 from baseline |
|-----------------|-------------------------------|

End point description:

The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10.

Intent-to-Treat (ITT) All randomized participants who received any part of an infusion of study medication were included in the ITT analysis. Number of subjects for whom data was collected is indicated in each time point.

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

End point timeframe:

Weeks 24 and 48

| End point values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 277 | 277 | 282 | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 6.50 (± 1.014) | 6.47 (± 1.217) | 6.44 (± 1.039) | |
| 24 weeks | -0.99 (± 1.16) | -1.60 (± 1.30) | -1.91 (± 1.34) | |
| 48 weeks | -1.13 (± 1.40) | -2.11 (± 1.34) | -2.38 (± 1.49) | |

Statistical analyses

No statistical analyses for this end point

Secondary: EULAR response rates

| | |
|-----------------|----------------------|
| End point title | EULAR response rates |
|-----------------|----------------------|

End point description:

The EULAR response rate was based on the assessment of disease activity using the DAS28. The EULAR response criteria included not only change in disease activity but current disease activity. To be classified as responders, participants had to have a significant change in DAS28 and a low current disease activity. There were 4 categories of EULAR response rates: good, moderate, good/moderate, and none.

Intent-to-Treat (ITT) All randomized participants who received any part of an infusion of study medication were included in the ITT analysis. Number of subjects for whom data were collected is indicated for each time point.

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

End point timeframe:

Weeks 24 and 48

| End point values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 277 | 277 | 282 | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| Week 24 | 31.4 | 54.2 | 61.0 | |
| Week 48 | 24.9 | 58.8 | 60.3 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving an ACR50 response

| | |
|-----------------|--|
| End point title | Percentage of subjects achieving an ACR50 response |
|-----------------|--|

End point description:

ACR50 response is defined as a $\geq 50\%$ improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: physician's global assessment of disease activity (MDG), patient's global assessment of disease activity (PGA), patient's assessment of pain, Health Assessment Questionnaire with Disability Index (HAQ-DI), and C-Reactive Protein (CRP).

Intent-to-Treat (ITT) All randomized participants who received any part of an infusion of study

medication were included in the ITT analysis. Number of subjects for whom data were collected is indicated for each time point.

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

| End point values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy | |
|---------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 277 | 277 | 282 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of Participants at Week 24 | 7.9 (4.8 to 11.1) | 21.3 (16.5 to 26.1) | 24.8 (19.8 to 29.9) | |
| Percentage of Participants at Week 48 | 9.0 (5.7 to 12.4) | 28.5 (23.2 to 33.8) | 30.9 (25.5 to 36.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving an ACR70 response

| | |
|---|--|
| End point title | Percentage of subjects achieving an ACR70 response |
| End point description: | |
| ACR70 response is defined as a $\geq 70\%$ improvement (reduction) compared with Baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: physician's global assessment of disease activity (MDG), patient's global assessment of disease activity (PGA), patient's assessment of pain, HAQ-DI and CRP. | |
| Intent-to-Treat (ITT) All randomized participants who received any part of an infusion of study medication were included in the ITT analysis. Number of subjects for whom data were collected is indicated for each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 24 and 48 | |

| End point values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 277 | 277 | 282 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |

| | | | | |
|---------------------------------------|------------------|--------------------|---------------------|--|
| Percentage of Participants at Week 24 | 2.9 (0.9 to 4.9) | 7.6 (4.5 to 10.7) | 9.9 (6.4 to 13.4) | |
| Percentage of Participants at Week 48 | 4.3 (1.9 to 6.7) | 11.2 (7.5 to 14.9) | 18.1 (13.6 to 22.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with a reduction in the HAQ-DI score

| | |
|-----------------|---|
| End point title | Percentage of subjects with a reduction in the HAQ-DI score |
|-----------------|---|

End point description:

Health Assessment Questionnaire – Disability Index (HAQ-DI): The Stanford Health Assessment Questionnaire disability index is a patient reported questionnaire specific for RA. It consists of 20 questions referring to eight component. Reduction in the HAQ-DI score of 0.25 units from baseline to weeks 24 and 48 represented a minimal clinically relevant improvement.

Intent-to-Treat (ITT) All randomized participants who received any part of an infusion of study medication were included in the ITT analysis. Number of subjects for whom data were collected is indicated for each time point.

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

End point timeframe:

Weeks 24 and 48

| End point values | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy | |
|---------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 277 | 277 | 282 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of Participants at Week 24 | 32.9 (27.3 to 38.4) | 52.3 (46.5 to 58.2) | 58.5 (52.8 to 64.3) | |
| Percentage of Participants at Week 48 | 23.1 (18.1 to 28.1) | 50.5 (44.7 to 56.4) | 51.8 (45.9 to 57.6) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to week 48 and week 96

Adverse event reporting additional description:

The safety population included all subjects who received at least one treatment with study medication

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Placebo × 2 IV + non-biologic DMARD therapy |
|-----------------------|---|

Reporting group description:

Subjects received Ocrelizumab matching Placebo Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs.

| | |
|-----------------------|--|
| Reporting group title | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy |
|-----------------------|--|

Reporting group description:

Subjects received 200 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs.

| | |
|-----------------------|--|
| Reporting group title | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy |
|-----------------------|--|

Reporting group description:

Subjects received 500 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15) in combination with any non-biologic DMARDs.

| | |
|-----------------------|--|
| Reporting group title | Ocrelizumab 500 mg × 2 IV (Open Label Extension) |
|-----------------------|--|

Reporting group description:

Subjects received 500 mg Ocrelizumab administered Intravenously (IV) in two infusions, separated by 14 days (day 1 and day 15)

| Serious adverse events | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non-biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non-biologic DMARD therapy |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 41 / 276 (14.86%) | 46 / 276 (16.67%) | 40 / 284 (14.08%) |
| number of deaths (all causes) | 2 | 1 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Benign ovarian tumour | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Lung adenocarcinoma metastatic | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Meningioma | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 2 / 284 (0.70%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Hypotension | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Arteritis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Peripheral venous disease | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 | | | |
| Hernia repair | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Hip arthroplasty | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Death | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Surgical failure | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Lead dislodgement | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Pyrexia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Social circumstances | | | |
| Physical assault | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Female genital tract fistula | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Pneumonitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 haemorrhage | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 failure | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Sinus polyp | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Upper respiratory tract inflammation | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Bipolar I disorder | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Dislocation of vertebra | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 / 276 (0.36%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Tendon rupture | | | |
| subjects affected / exposed | 2 / 276 (0.72%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Limb crushing injury | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Foreign body | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acetabulum fracture | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Comminuted fracture | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Coronary artery restenosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Fall | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Overdose | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Postoperative fever | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Wrist fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Congenital, familial and genetic disorders | | | |
| Hydrocele | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Cardiac disorders | | | |
| Angina Pectoris | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 2 / 276 (0.72%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 276 (0.36%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 2 / 276 (0.72%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 failure congestive | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Pericardial effusion | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Radiculitis lumbosacral | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Dementia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 myelopathy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorder | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 | 2 / 276 (0.72%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Granulocytopenia | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 276 (0.36%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Uveitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastric ulcer perforation | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Peptic ulcer haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Diverticular perforation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Enterovesical fistula | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Gastroduodenal ulcer | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Hepatitis toxic | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Focal segmental glomerulosclerosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Basedow's disease | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 276 (0.36%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Arthropathy | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 276 (0.72%) | 2 / 276 (0.72%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 7 / 276 (2.54%) | 4 / 276 (1.45%) | 4 / 284 (1.41%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint destruction | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 protrusion | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteochondritis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylolisthesis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist deformity | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 disc degeneration | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Tenosynovitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 276 (0.36%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 276 (0.72%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 276 (1.09%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Enteritis infectious | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Implant site infection | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 276 (1.81%) | 5 / 276 (1.81%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 3 / 5 | 3 / 5 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Serratia infection | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Enterocolitis viral | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis B | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Kidney infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 2 / 276 (0.72%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis pneumococcal | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis infective | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 2 / 284 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sycosis barbae | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Extradural abscess | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Genitourinary tract infection | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Incision site cellulitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Parotitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 sepsis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Urethritis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Hypoglycaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 276 (0.36%) | 0 / 284 (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 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 276 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|--|--|--|
| Serious adverse events | Ocrelizumab 500 mg × 2 IV (Open Label Extension) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 138 / 664 (20.78%) | | |
| number of deaths (all causes) | 7 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diffuse large B-cell lymphoma | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung neoplasm malignant | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Gastric cancer | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal cancer | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Uterine leiomyoma | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Benign ovarian tumour | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma of lung | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colon cancer | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung adenocarcinoma metastatic | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Lymphoma | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 3 / 664 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arteritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral venous disease | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vasculitis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Hernia repair | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Pregnancy | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 4 / 664 (0.60%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Surgical failure | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lead dislodgement | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Sudden death | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Social circumstances | | | |
| Physical assault | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Female genital tract fistula | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 664 (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 | 3 / 664 (0.45%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sinus polyp | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract inflammation | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bipolar I disorder | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dislocation of vertebra | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Limb crushing injury | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thermal burn | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Foreign body | | | | |
| subjects affected / exposed | 0 / 664 (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 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acetabulum fracture | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Comminuted fracture | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery restenosis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femur fracture | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple fractures | | | |
| subjects affected / exposed | 3 / 664 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative fever | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Hydrocele | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina Pectoris | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 6 / 664 (0.90%) | | |
| occurrences causally related to treatment / all | 1 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block complete | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular extrasystoles | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Radiculitis lumbosacral | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dementia | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 664 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical myelopathy | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| 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 | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Iron deficiency anaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Granulocytopenia | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uveitis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | | |
|---|-----------------|--|--|--|
| Gastric ulcer perforation | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mesenteric vein thrombosis | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrooesophageal reflux disease | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hiatus hernia | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestine perforation | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peptic ulcer haemorrhage | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinus bradycardia | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 664 (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 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inguinal hernia | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis ischaemic | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticular perforation | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Duodenal ulcer | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterovesical fistula | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroduodenal ulcer | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Focal segmental glomerulosclerosis | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Basedow's disease | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Osteonecrosis | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rheumatoid arthritis | | | | |
| subjects affected / exposed | 7 / 664 (1.05%) | | | |
| occurrences causally related to treatment / all | 1 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Joint destruction | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal column stenosis | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral disc protrusion | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteochondritis | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteoporotic fracture | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spondylolisthesis | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Wrist deformity | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot deformity | | | |
| subjects affected / exposed | 3 / 664 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tenosynovitis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis bacterial | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchitis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enteritis infectious | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Implant site infection | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Paronychia | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 11 / 664 (1.66%) | | | |
| occurrences causally related to treatment / all | 5 / 11 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pneumonia pneumococcal | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Serratia infection | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacterial infection | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Conjunctivitis | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis viral | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatitis B | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Kidney infection | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis pneumococcal | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchopneumonia | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bursitis infective | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis salmonella | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious colitis | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pilonidal cyst | | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia bacterial | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis acute | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sycosis barbae | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Candida infection | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Extradural abscess | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Genitourinary tract infection | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incision site cellulitis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteomyelitis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Parotitis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia streptococcal | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary sepsis | | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethritis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 664 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 664 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 664 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Placebo × 2 IV + non-biologic DMARD therapy | Ocrelizumab 200 mg × 2 IV + non- biologic DMARD therapy | Ocrelizumab 500 mg × 2 IV + non- biologic DMARD therapy |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 152 / 276 (55.07%) | 153 / 276 (55.43%) | 158 / 284 (55.63%) |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 25 / 276 (9.06%) | 41 / 276 (14.86%) | 41 / 284 (14.44%) |
| occurrences (all) | 34 | 62 | 47 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 21 / 276 (7.61%) | 18 / 276 (6.52%) | 20 / 284 (7.04%) |
| occurrences (all) | 21 | 19 | 20 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 15 / 276 (5.43%) | 12 / 276 (4.35%) | 15 / 284 (5.28%) |
| occurrences (all) | 16 | 13 | 20 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 276 (3.62%) | 15 / 276 (5.43%) | 15 / 284 (5.28%) |
| occurrences (all) | 11 | 15 | 18 |
| Nausea | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 15 / 276 (5.43%) 16 | 11 / 276 (3.99%) 11 | 10 / 284 (3.52%) 10 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 12 / 276 (4.35%) | 9 / 276 (3.26%) | 16 / 284 (5.63%) |
| occurrences (all) | 13 | 9 | 16 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 19 / 276 (6.88%) | 28 / 276 (10.14%) | 22 / 284 (7.75%) |
| occurrences (all) | 22 | 35 | 29 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 31 / 276 (11.23%) | 28 / 276 (10.14%) | 22 / 284 (7.75%) |
| occurrences (all) | 45 | 36 | 42 |
| Sinusitis | | | |
| subjects affected / exposed | 14 / 276 (5.07%) | 13 / 276 (4.71%) | 13 / 284 (4.58%) |
| occurrences (all) | 14 | 17 | 16 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 36 / 276 (13.04%) | 37 / 276 (13.41%) | 45 / 284 (15.85%) |
| occurrences (all) | 40 | 43 | 67 |
| Urinary tract infection | | | |
| subjects affected / exposed | 23 / 276 (8.33%) | 19 / 276 (6.88%) | 24 / 284 (8.45%) |
| occurrences (all) | 30 | 22 | 32 |
| Influenza | | | |
| subjects affected / exposed | 9 / 276 (3.26%) | 7 / 276 (2.54%) | 15 / 284 (5.28%) |
| occurrences (all) | 9 | 7 | 17 |

| | | | |
|--|--|--|--|
| Non-serious adverse events | Ocrelizumab 500 mg × 2 IV (Open Label Extension) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 361 / 664 (54.37%) | | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 128 / 664 (19.28%) | | |
| occurrences (all) | 203 | | |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|---|--|--|
| subjects affected / exposed occurrences (all) | 44 / 664 (6.63%) 48 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 664 (0.00%) 0 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 0 / 664 (0.00%) 0 0 / 664 (0.00%) 0 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 664 (0.00%) 0 | | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) | 64 / 664 (9.64%) 75 69 / 664 (10.39%) 96 53 / 664 (7.98%) 74 96 / 664 (14.46%) 132 78 / 664 (11.75%) 101 0 / 664 (0.00%) 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 27 August 2008 | The sample size for this study was based on the need to obtain sufficient safety data across the RA phase III program. The recent introduction of the phase III study WA29496 (FEATURE) has resulted in an additional 300 patients being included in the development program. At least 240 of the subjects randomized into WA20496 will receive exposure to ocrelizumab. As such it was decided to reduce the sample size in WA20495 (SCRIPT) by 200 patients, to a total sample size of 800. |
| 26 April 2010 | All patients have finished the 48 Week double blind period of the study. Those who are in the open label extension should continue with their study visits as usual, but will not receive ocrelizumab treatment. Patients in safety follow-up (SFU) should continue with scheduled visits as normal. |
| 15 July 2010 | Open label treatment with ocrelizumab is discontinued and the RA program has been terminated by the Sponsor. Patients will not receive any further treatments with ocrelizumab. Patients who were on placebo and did not receive any ocrelizumab in open label study extension period should return for their next scheduled visit, which will be their final study visit. These patients will not be required to enter safety follow-up. Patients who have received at least one dose of ocrelizumab in the study should complete the withdrawal visit on their next scheduled visit and enter the Safety Follow Up (SFU) period. Patients should remain in SFU for at least 48 weeks from the first infusion of their last course; if at this time the peripheral blood B cell count is still low, patients should continue visits every 12 weeks until the B cell count has returned to the baseline value or into the lower limit of the normal range. Patients who are subsequently treated with an alternative B cell depleting therapy such as commercial rituximab will only be followed for 48 weeks from the date of the first infusion of their last course of ocrelizumab, regardless of peripheral blood. B cell count. During SFU, patients should be clinically managed according to the local standard of care and clinical judgement of the investigator. Study extension period (treatment with ocrelizumab is discontinued, patients remaining on the study extension period should enter Safety Follow Up (SFU) on their next scheduled visit) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported