# Clinical trial results:
# A Multinational, Multicenter, Open-Label, Single-Assignment Extension of the MS-LAQ-301 (ALLEGRO) Study, to Evaluate the Long-Term Safety, Tolerability and Effect on Disease Course of Daily Oral Laquinimod 0.6 mg in Subjects with Relapsing Multiple Sclerosis

## Summary

| | |
|---|---|
| EudraCT number | 2009-012989-30 |
| Trial protocol | GB NL EE ES HU DE CZ IT FR LT AT SE BG |
| Global end of trial date | 01 July 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 23 January 2019 |
| First version publication date | 23 January 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | MS-LAQ-301E |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00988052 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Teva Pharmaceutical Industries, Ltd |
| Sponsor organisation address | 5 Bael Street, Petach-Tikva, Israel, 49131 |
| Public contact | Director, Clinical Research, Teva Pharmaceutical Industries, Ltd, 001 888-483-8279, info.era-clinical@teva.de |
| Scientific contact | Director, Clinical Research, Teva Pharmaceutical Industries, Ltd, 001 888-483-8279, info.era-clinical@teva.de |

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 | 14 March 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 01 July 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The objectives of the study were as follows:
- to make treatment with oral laquinimod 0.6 mg available to all subjects who participated in the double-blind, placebo-controlled MS-LAQ-301 study and who completed the termination visit of this study according to the MS-LAQ-301 protocol, as long as the Sponsor continued the development of laquinimod 0.6 mg for RRMS
- to assess the long-term safety and tolerability of laquinimod 0.6 mg once daily in patients with RRMS
to assess the long-term effects of laquinimod 0.6 mg on the disease course, as measured by clinical efficacy outcomes, which were evaluated in the double-blind treatment phase in this subject population

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations.

Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each patient’s willingness to participate in the study was documented in writing in a consent form that was signed by the patient with the date of that signature indicated. Each Investigator kept the original consent forms, and copies were given to the patient.

This study included the following separate informed consent forms:
- a single informed consent form at the baseline visit
- an informed consent for patients who were permitted by the Sponsor to re-enroll in the study after study discontinuation due to a planned pregnancy (introduced by Global Protocol Amendment 2)
- additional informed consent forms for ancillary studies at the baseline visit (in selected countries/sites)
- magnetic resonance imaging (MRI) ancillary study
- magnetization transfer (MT) ancillary study
- magnetic resonance spectroscopy (MRS) ancillary study
- As of 25 February 2016, a separate reconsent form that described the cardiovascular risk findings at higher doses of laquinimod (1.2 and 1.5 mg/day) was required to be signed by all patients, as introduced by Global Protocol Amendment 3.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 10 November 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Bulgaria: 81 |
| Country: Number of subjects enrolled | Canada: 33 |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | Germany: 99 |
| Country: Number of subjects enrolled | Spain: 39 |
| Country: Number of subjects enrolled | Estonia: 15 |
| Country: Number of subjects enrolled | France: 24 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | Georgia: 22 |
| Country: Number of subjects enrolled | Hungary: 25 |
| Country: Number of subjects enrolled | Israel: 12 |
| Country: Number of subjects enrolled | Italy: 35 |
| Country: Number of subjects enrolled | Lithuania: 12 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Poland: 100 |
| Country: Number of subjects enrolled | Romania: 23 |
| Country: Number of subjects enrolled | Russian Federation: 86 |
| Country: Number of subjects enrolled | Serbia: 20 |
| Country: Number of subjects enrolled | Sweden: 11 |
| Country: Number of subjects enrolled | Turkey: 1 |
| Country: Number of subjects enrolled | Ukraine: 62 |
| Country: Number of subjects enrolled | United States: 95 |
| Worldwide total number of subjects | 839 |
| EEA total number of subjects | 508 |

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) | 839 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

In the preceding double-blind, placebo-controlled ALLEGRO study (study MS-LAQ-301), 1106 subjects with RRMS
were randomized to treatment, and 864 subjects completed the study according to the protocol (ie, by completing the ALLEGRO study termination visit procedures).

### Pre-assignment

Screening details:

In this open-label extension study, 839 subjects with RRMS were enrolled to receive laquinimod 0.6 mg at 135 study sites in 22 countries by 135 investigators.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Early laquinimod |

Arm description:

All participants in MS-LAQ-301E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Early laquinimod subgroup included participants in MS-LAQ-301 double-blind study who were administered laquinimod 0.6 mg daily for 24 months.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | laquinimod |
| Investigational medicinal product code | |
| Other name | TV-5600 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One capsule containing laquinimod 0.6 mg was taken orally at the same hour every day.

| | |
|---|---|
| **Arm title** | Switch from placebo |

Arm description:

All participants in MS-LAQ-301E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from placebo subgroup included participants in MS-LAQ-301 double-blind study who were administered placebo daily for 24 months.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | laquinimod |
| Investigational medicinal product code | |
| Other name | TV-5600 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One capsule containing laquinimod 0.6 mg was taken orally at the same hour every day.

| **Number of subjects in period 1** | Early laquinimod | Switch from placebo |
|---|---|---|
| Started | 423 | 416 |
| Completed | 0 | 0 |
| Not completed | 423 | 416 |
| Adverse event, serious fatal | 1 | 3 |
| Physician decision | 27 | 28 |
| Consent withdrawn by subject | 90 | 91 |
| Adverse event, non-fatal | 35 | 28 |
| Teva requested subject withdrawal | 3 | 1 |
| Pregnancy | 6 | 6 |
| Study terminated by sponsor | 240 | 236 |
| Lost to follow-up | 6 | 11 |
| Missing | 1 | - |
| Protocol deviation | 6 | 5 |
| Lack of efficacy | 8 | 7 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Early laquinimod |
| Reporting group description: | |
| All participants in MS-LAQ-301E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Early laquinimod subgroup included participants in MS-LAQ-301 double-blind study who were administered laquinimod 0.6 mg daily for 24 months. | |
| Reporting group title | Switch from placebo |
| Reporting group description: | |
| All participants in MS-LAQ-301E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from placebo subgroup included participants in MS-LAQ-301 double-blind study who were administered placebo daily for 24 months. | |

| Reporting group values | Early laquinimod | Switch from placebo | Total |
|---|---|---|---|
| Number of subjects | 423 | 416 | 839 |
| Age categorical<br>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) | 423 | 416 | 839 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 41.1 | 40.5 | |
| standard deviation | ± 9.10 | ± 9.14 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 298 | 271 | 569 |
| Male | 125 | 145 | 270 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Asian / Oriental | 2 | 0 | 2 |
| Black / African American | 1 | 5 | 6 |
| Caucasian | 414 | 401 | 815 |
| Unknown | 3 | 6 | 9 |
| Other | 2 | 2 | 4 |
| Missing | 1 | 2 | 3 |

## End points

### End points reporting groups

| Reporting group title | Early laquinimod |
|---|---|

Reporting group description:

All participants in MS-LAQ-301E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Early laquinimod subgroup included participants in MS-LAQ-301 double-blind study who were administered laquinimod 0.6 mg daily for 24 months.

| Reporting group title | Switch from placebo |
|---|---|

Reporting group description:

All participants in MS-LAQ-301E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from placebo subgroup included participants in MS-LAQ-301 double-blind study who were administered placebo daily for 24 months.

### Primary: Participants with Treatment-Emergent Adverse Events (TEAEs)

| End point title | Participants with Treatment-Emergent Adverse Events |
|---|---|

End point description:

A treatment-emergent adverse event was defined as any untoward medical occurrence that develops or worsens in severity following start of treatment and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents normal daily activities. Relation of AE to treatment was determined by the investigator. Serious AEs (SAE) include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes. TEAEs associated with cancer, ischemic heart disease, cerebrovascular events, and arthritis were considered to be of special interest.

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

End point timeframe:

Day 1 up to 7.64 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgment.

| End point values | Early laquinimod | Switch from placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 423 | 416 | | |
| Units: participants | | | | |
| =>1 TEAE\| | 375 | 374 | | |
| =>1 Severe TEAE\| | 76 | 69 | | |
| =>1 TEAE of special interest\| | 109 | 105 | | |
| =>1 treatment-related TEAE\| | 139 | 153 | | |
| =>1 TEAE leading to death\| | 3 | 3 | | |
| =>1 Serious TEAE\| | 108 | 92 | | |
| =>1 TEAE causing discontinuation\| | 35 | 32 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Participants with Potentially Clinically Significant Abnormal Vital Signs

| End point title | Participants with Potentially Clinically Significant Abnormal Vital Signs |
|---|---|

End point description:

Vital signs with potentially clinically significant abnormal results were evaluated using the following significance criteria: - Pulse rate low: <=45 and decrease >=30 beats/minute - Pulse rate high: >=120 and increase >=30 beats/minute - Systolic blood pressure low: <=90 and decrease >=30 mmHg - Systolic blood pressure high: >=180 and increase >=30 mmHg - Diastolic blood pressure low: <=50 and decrease >=20 mmHg - Diastolic blood pressure high: >=100 and increase >=20 mmHg

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

End point timeframe:

Day 1 up to 7.64 years

| End point values | Early laquinimod | Switch from placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 423 | 416 | | |
| Units: participants | | | | |
| Participants with at least one abnormality\| | 36 | 34 | | |
| Pulse rate - low\| | 1 | 1 | | |
| Pulse rate - high\| | 2 | 1 | | |
| Systolic blood pressure - low\| | 20 | 10 | | |
| Systolic blood pressure - high\| | 1 | 2 | | |
| Diastolic blood pressure - low\| | 7 | 7 | | |
| Diastolic blood pressure - high\| | 8 | 14 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Participants with Serum Chemistry Laboratory Tests That Were Potentially Clinically Significant (PCS) Abnormal Comparing Baseline to Any Time During the Study

| End point title | Participants with Serum Chemistry Laboratory Tests That Were Potentially Clinically Significant (PCS) Abnormal Comparing Baseline to Any Time During the Study |
|---|---|

End point description:

Counts include two conditions: - a change from High / Non-PCS at baseline to Low PCS at any point during the study - a change from Low / Non-PCS at baseline to High PCS at any point during the study Participants whose condition was not changed from baseline or was changed to a non- PCS value are included in the population count. ALT=alanine aminotransferase ALP=alkaline phosphatase P-amylase=amylase, pancreatic AST=aspartate aminotransferase CRP=C reactive protein CK=creatine kinase CTN=creatinine FIB=fibrinogen GGT=gamma glutamyl transferase K=potassium

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

End point timeframe:

Day 1 up to 7.64 years

| End point values | Early laquinimod | Switch from placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 422 | 415 | | |
| Units: participants | | | | |
| ALT - change from Low / Non- PCS to High PCS\| | 8 | 14 | | |
| Albumen - change from High / Non-PCS to Low PCS\| | 1 | 0 | | |
| ALP - change from Low / Non- PCS to High PCS\| | 3 | 0 | | |
| p-Amylase - change from Low / Non-PCS to High PCS\| | 2 | 6 | | |
| AST - change from Low / Non- PCS to High PCS\| | 4 | 5 | | |
| CRP - change from Low / Non- PCS to High PCS\| | 41 | 51 | | |
| Calcium - change from High / Non-PCS to Low PCS\| | 1 | 4 | | |
| Calcium - change from Low / Non-PCS to High PCS\| | 1 | 2 | | |
| CK - change from Low / Non- PCS to High PCS\| | 16 | 17 | | |
| CTN - change from Low / Non- PCS to High PCS\| | 2 | 2 | | |
| FIB - change from Low / Non- PCS to High PCS\| | 37 | 38 | | |
| GGT - change from Low / Non- PCS to High PCS\| | 33 | 24 | | |
| Glucose - change from High / Non-PCS to Low PCS\| | 23 | 27 | | |
| Glucose - change from Low / Non-PCS to High PCS\| | 9 | 5 | | |
| Phosphate-change from High / Non-PCS to Low PCS\| | 14 | 15 | | |
| Phosphate-change from Low / Non-PCS to High PCS\| | 19 | 16 | | |
| K - change from High / Non- PCS to Low PCS\| | 4 | 3 | | |
| K - change from Low / Non- PCS to High PCS\| | 46 | 55 | | |
| Sodium - change from High / Non-PCS to Low PCS\| | 8 | 3 | | |
| Sodium - change from Low / Non-PCS to High PCS\| | 13 | 17 | | |
| Urea - change from Low / Non- PCS to High PCS\| | 3 | 4 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Participants with Serum Hematology Laboratory Tests That Were

## Potentially Clinically Significant (PCS) Abnormal Comparing Baseline to Any Time During the Study

| End point title | Participants with Serum Hematology Laboratory Tests That Were Potentially Clinically Significant (PCS) Abnormal Comparing Baseline to Any Time During the Study |
|---|---|

End point description:

Counts include two conditions: - a change from High / Non-PCS at baseline to Low PCS at any point during the study - a change from Low / Non-PCS at baseline to High PCS at any point during the study Participants whose condition was not changed from baseline or was changed to a non- PCS value are included in the population count.

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

End point timeframe:

Day 1 up to 7.64 years

| End point values | Early laquinimod | Switch from placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 422 | 415 | | |
| Units: participants | | | | |
| Hematocrit-change from High/Non-PCS to Low PCS\| | 36 | 29 | | |
| Hemoglobin-change from High/Non-PCS to Low PCS\| | 27 | 22 | | |
| Hemoglobin-change from Low/Non-PCS to High PCS\| | 0 | 1 | | |
| Leukocytes- change from High/Non-PCS to Low PCS\| | 1 | 1 | | |
| Leukocytes- change from Low/Non-PCS to High PCS\| | 4 | 3 | | |
| Neutrophils-change from High/Non-PCS to Low PCS\| | 15 | 12 | | |
| Platelets-change from High/Non-PCS to Low PCS\| | 4 | 7 | | |
| Platelets-change from Low/Non-PCS to High PCS\| | 2 | 6 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Participants with Electrocardiogram (ECG) Fiindings That Shifted from Baseline to Any Time During the Study

| End point title | Participants with Electrocardiogram (ECG) Fiindings That Shifted from Baseline to Any Time During the Study |
|---|---|

End point description:

Shifts are presented as Baseline finding / Worse finding at anytime during the study. Categories for findings are: - normal - abnormal, not clinically significant (Not CS) - abnormal, clinically significant (CS)

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

End point timeframe:

Day 1 up to 7.64 years

| End point values | Early laquinimod | Switch from placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 420 | 412 | | |
| Units: participants | | | | |
| Normal / Normal\| | 189 | 198 | | |
| Normal / Abnormal, Not CS\| | 145 | 126 | | |
| Normal / Abnormal, CS\| | 2 | 3 | | |
| Abnormal, Not CS / Normal\| | 12 | 14 | | |
| Abnormal, Not CS / Abnormal, Not CS\| | 70 | 67 | | |
| Abnormal, Not CS / Abnormal, CS\| | 2 | 4 | | |
| Abnormal, CS / Normal\| | 0 | 0 | | |
| Abnormal, CS / Abnormal, Not CS\| | 0 | 0 | | |
| Abnormal, CS / Abnormal, CS\| | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 7.64 years

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Switch from Placebo to Laquinimod 0.6 mg |

Reporting group description:

All participants in MS-LAQ-301E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from placebo subgroup included participants in MS-LAQ-301 double-blind study who were administered placebo daily for 24 months.

| | |
|---|---|
| Reporting group title | Early Laquinimod 0.6 mg |

Reporting group description:

All participants in MS-LAQ-301E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Early laquinimod subgroup included participants in MS-LAQ-301 double-blind study who were administered laquinimod 0.6 mg daily for 24 months.

| Serious adverse events | Switch from Placebo to Laquinimod 0.6 mg | Early Laquinimod 0.6 mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 92 / 416 (22.12%) | 108 / 423 (25.53%) | |
| number of deaths (all causes) | 3 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Anogenital warts | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign neoplasm of thyroid gland | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign ovarian tumour | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer stage II | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervix carcinoma stage 0 | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic lymphocytic leukaemia stage 1 | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibroadenoma of breast | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hodgkin's disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive breast carcinoma | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Keratoacanthoma | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Langerhans' cell histiocytosis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma metastatic | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to lung | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oncocytoma | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian adenoma | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cancer metastatic | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubular breast carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 4 / 416 (0.96%) | 3 / 423 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulval cancer | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |

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|---|---|---|---|
| Cholecystectomy | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hysterectomy | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc operation | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Knee arthroplasty | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrectomy | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fusion surgery | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Drowning | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inflammation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device pain | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Immune system disorders** | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Reproductive system and breast disorders** | | | |
| Acquired hydrocele | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometriosis | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibrocystic breast disease | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrosalpinx | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Menometrorrhagia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine prolapse | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal prolapse | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal polyps | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal septum deviation | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal polyp | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Psychiatric disorders** | | | |
| Agoraphobia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Depression | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Mood disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurosis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panic disorder | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Substance-induced psychotic disorder | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 4 / 423 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 1 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Comminuted fracture | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 6 / 423 (1.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Foot fracture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural complication | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seroma | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skull fracture | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Silent myocardial infarction | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Nervous system disorders** | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral artery occlusion | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 3 / 423 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar radiculopathy | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 3 / 423 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Optic neuritis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Simple partial seizures | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 3 / 423 (0.71%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigeminal neuralgia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow oedema | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Blindness unilateral | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Uveitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Omental infarction | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Volvulus | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary colic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocholecystis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Skin and subcutaneous tissue disorders** | | | |
| Hidradenitis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Renal and urinary disorders** | | | |

| | | | |
|---|---|---|---|
| Bladder dysfunction | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Calculus urinary | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ketonuria | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral meatus stenosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral stenosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperparathyroidism primary | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parathyroid gland enlargement | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Arthritis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc space narrowing | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint hyperextension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint instability | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Knee impingement syndrome | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 2 / 416 (0.48%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteochondrosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudarthrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon calcification | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute sinusitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 4 / 423 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bartholin's abscess | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast abscess | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Furuncle | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin abscess | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic echinococciasis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Latent syphilis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Latent tuberculosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis viral | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mycotoxicosis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media chronic | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian abscess | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 4 / 423 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periumbilical abscess | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pertussis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal abscess | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 416 (0.72%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salpingo-oophoritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubo-ovarian abscess | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 2 / 423 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vestibular neuronitis | | | |
| subjects affected / exposed | 1 / 416 (0.24%) | 0 / 423 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obesity | | | |
| subjects affected / exposed | 0 / 416 (0.00%) | 1 / 423 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Switch from Placebo to Laquinimod 0.6 mg | Early Laquinimod 0.6 mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 300 / 416 (72.12%) | 299 / 423 (70.69%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 22 / 416 (5.29%) | 13 / 423 (3.07%) | |
| occurrences (all) | 27 | 16 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 31 / 416 (7.45%) | 26 / 423 (6.15%) | |
| occurrences (all) | 37 | 31 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 16 / 416 (3.85%) | 22 / 423 (5.20%) | |
| occurrences (all) | 23 | 27 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Fall | | | |
| subjects affected / exposed | 23 / 416 (5.53%) | 20 / 423 (4.73%) | |
| occurrences (all) | 30 | 30 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 26 / 416 (6.25%) | 32 / 423 (7.57%) | |
| occurrences (all) | 26 | 32 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 86 / 416 (20.67%) | 57 / 423 (13.48%) | |
| occurrences (all) | 160 | 132 | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 29 / 416 (6.97%) | 17 / 423 (4.02%) | |
| occurrences (all) | 36 | 35 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 16 / 416 (3.85%) | 22 / 423 (5.20%) | |
| occurrences (all) | 17 | 25 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 31 / 416 (7.45%) | 25 / 423 (5.91%) | |
| occurrences (all) | 38 | 30 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 31 / 416 (7.45%) | 19 / 423 (4.49%) | |
| occurrences (all) | 39 | 23 | |
| Diarrhoea | | | |
| subjects affected / exposed | 21 / 416 (5.05%) | 24 / 423 (5.67%) | |
| occurrences (all) | 23 | 31 | |
| Nausea | | | |
| subjects affected / exposed | 26 / 416 (6.25%) | 24 / 423 (5.67%) | |
| occurrences (all) | 37 | 27 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 35 / 416 (8.41%) | 24 / 423 (5.67%) | |
| occurrences (all) | 40 | 26 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Depression | | | |
| subjects affected / exposed | 28 / 416 (6.73%) | 35 / 423 (8.27%) | |
| occurrences (all) | 35 | 41 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 47 / 416 (11.30%) | 41 / 423 (9.69%) | |
| occurrences (all) | 59 | 57 | |
| Back pain | | | |
| subjects affected / exposed | 77 / 416 (18.51%) | 78 / 423 (18.44%) | |
| occurrences (all) | 124 | 127 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 25 / 416 (6.01%) | 11 / 423 (2.60%) | |
| occurrences (all) | 29 | 15 | |
| Pain in extremity | | | |
| subjects affected / exposed | 33 / 416 (7.93%) | 28 / 423 (6.62%) | |
| occurrences (all) | 45 | 35 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 33 / 416 (7.93%) | 33 / 423 (7.80%) | |
| occurrences (all) | 46 | 44 | |
| Influenza | | | |
| subjects affected / exposed | 34 / 416 (8.17%) | 28 / 423 (6.62%) | |
| occurrences (all) | 46 | 41 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 112 / 416 (26.92%) | 106 / 423 (25.06%) | |
| occurrences (all) | 210 | 169 | |
| Sinusitis | | | |
| subjects affected / exposed | 28 / 416 (6.73%) | 27 / 423 (6.38%) | |
| occurrences (all) | 47 | 36 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 41 / 416 (9.86%) | 43 / 423 (10.17%) | |
| occurrences (all) | 65 | 69 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 39 / 416 (9.38%) | 55 / 423 (13.00%) | |
| occurrences (all) | 76 | 110 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 01 November 2009 | Amendment 1 (dated 01 November 2009) to the protocol was issued before any subjects were enrolled into the study. The amendment was aimed to modify the protocol according to the Food and Drug Administration (FDA) Guidance for Industry on the issue of Drug-Induced Liver Injury: Premarketing Clinical Evaluation.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br><br>- Modification of the "Guidance for Safety Monitoring" (Appendix 6) adopting the principles of the FDA Guideline titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (July, 2009)<br><br>- Clarification of the sequence of administration of questionnaires and the Multiple Sclerosis Functional Composite assessment at each visit<br><br>- Modification of the MRI outcome of brain volume change in light of technical capabilities of the equipment |
| 17 July 2014 | Amendment 2 (dated 17 July 2014) to the protocol was issued when 639 subjects were ongoing in this study. Changes to the protocol were considered to have no negative impact on the safety of subjects ongoing in this study. These changes did not alter the study population, study design, or endpoints.<br><br>The following major procedural changes (not all-inclusive) were made to the protocol:<br><br>- Updates were made to the introduction and safety sections based on accumulating data with laquinimod and more stringent pregnancy prevention measures.<br><br>- In addition to the major revisions, this amended protocol included updates, modifications, and clarifications in sections related to stopping rules, disallowed medication, and study duration. |

| | |
|---|---|
| 25 February 2016 | Amendment 3 (dated 25 February 2016) to the protocol was issued when 542 subjects were ongoing in this study. The primary purpose of this amendment was to introduce additional safety measures due to cardiovascular (CV) findings in other MS studies where higher doses of laquinimod (1.2 and 1.5 mg) were administered. The DMC recommended that study subjects continuing on laquinimod 0.6 mg be reconsented with information about the CV risk seen in higher doses.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>- All ongoing subjects were asked to re-consent to a revised form that includes information on the CV risk findings at higher doses of laquinimod (1.2 mg and 1.5 mg).<br><br>- Stopping rules were added for renal and hepatic impairment.<br><br>- Glomerular filtration rate and weight were to be performed at all visits to assess renal function.<br><br>- Extra emphasis was placed on moderate/strong inhibitors of cytochrome p450 (CYP)3A4 being disallowed.<br><br>- Unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analyses may have been collected at the discretion of the Investigator at any time to assist with further investigations of CV events or other clinical event of interest.<br><br>- A CV risk assessment and management procedure were added.<br><br>- Ischemic cardiac events and cerebrovascular events were classed as protocol-defined adverse events for expedited reporting and were to be reported to the Sponsor within 48 hours.<br><br>- Subjects who were discontinued from study drug were encouraged to continue all scheduled visits and procedures until completion of the study. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported