# Clinical trial results:
# Multicenter, Double-blind, Randomized, Parallel-group, Monotherapy, Active-control Study to Determine the Efficacy and Safety of Daclizumab High Yield Process (DAC HYP) Versus Avonex® (Interferon Beta-1a) in Patients With Relapsing-Remitting Multiple Sclerosis

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

| | |
|---|---|
| EudraCT number | 2009-012500-11 |
| Trial protocol | IE FR DE CZ HU FI SE ES GB GR IT DK SI |
| Global end of trial date | 28 July 2014 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 19 February 2016 |
| First version publication date | 12 August 2015 |
| Version creation reason | • Correction of full data set<br>Data correction due to a system error in EudraCT – Results |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 205MS301 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01064401 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Biogen |
| Sponsor organisation address | 225 Binney Street, Cambridge, United States, 02142 |
| Public contact | Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com |
| Scientific contact | Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 28 July 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary study objective is to test the superiority of Daclizumab High Yield Process (DAC HYP) compared with interferon β-1a (IFN β-1a) in preventing multiple sclerosis (MS) relapse in participants with relapsing remitting multiple sclerosis.

The secondary study objectives are to test the superiority of DAC HYP compared with IFN β-1a in slowing functional decline and disability progression and maintaining quality of life in this participant population.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 11 May 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 451 |
| Country: Number of subjects enrolled | United States: 217 |
| Country: Number of subjects enrolled | Russian Federation: 198 |
| Country: Number of subjects enrolled | Ukraine: 129 |
| Country: Number of subjects enrolled | Serbia: 111 |
| Country: Number of subjects enrolled | Italy: 97 |
| Country: Number of subjects enrolled | Czech Republic: 85 |
| Country: Number of subjects enrolled | United Kingdom: 70 |
| Country: Number of subjects enrolled | France: 54 |
| Country: Number of subjects enrolled | India: 50 |

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 46 |
| Country: Number of subjects enrolled | Germany: 40 |
| Country: Number of subjects enrolled | Hungary: 36 |
| Country: Number of subjects enrolled | Brazil: 34 |
| Country: Number of subjects enrolled | Romania: 33 |
| Country: Number of subjects enrolled | Sweden: 31 |
| Country: Number of subjects enrolled | Greece: 26 |
| Country: Number of subjects enrolled | Argentina: 24 |
| Country: Number of subjects enrolled | Canada: 19 |
| Country: Number of subjects enrolled | Moldova, Republic of: 17 |
| Country: Number of subjects enrolled | Mexico: 15 |
| Country: Number of subjects enrolled | Israel: 14 |
| Country: Number of subjects enrolled | Denmark: 12 |
| Country: Number of subjects enrolled | Ireland: 10 |
| Country: Number of subjects enrolled | Australia: 8 |
| Country: Number of subjects enrolled | Switzerland: 6 |
| Country: Number of subjects enrolled | Georgia: 5 |
| Country: Number of subjects enrolled | Finland: 3 |
| Worldwide total number of subjects | 1841 |
| EEA total number of subjects | 994 |

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) | 1841 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study included a 4-week screening period.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Interferon beta-1a |

Arm description:

Interferon beta-1a (IFN β-1a) 30 µg IM injection once weekly plus placebo to DAC HYP SC once every 4 weeks for 96 to 144 weeks

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Interferon beta-1A |
| Investigational medicinal product code | |
| Other name | Avonex |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Avonex was supplied in treatment kits that were dispensed to subjects at each visit and contained a sufficient supply of Avonex prefilled syringes and IM needles for each dosing interval. Subjects were instructed on how to perform injections at home.

| | |
|---|---|
| Investigational medicinal product name | Placebo to DAC HYP |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo to DAC HYP was prepared and administered in an identical manner to DAC HYP.

| | |
|---|---|
| **Arm title** | Daclizumab High Yield Process |

Arm description:

DAC HYP 150 mg subcutaneous (SC) injection once every 4 weeks plus placebo to IFN β-1a intramuscular (IM) injection once weekly for 96 to 144 weeks

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Daclizumab HYP |
| Investigational medicinal product code | BIIB019 |
| Other name | DAC HYP |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The individual preparing the DAC HYP carefully reviewed the instructions provided in the Directions for Handling and Administration, which superseded all other references (e.g., the DAC HYP Investigator Brochure), and DAC HYP was administered by staff in the clinic at the monthly visits. Subjects received SC injections of DAC HYP in one or more of the following locations: the back of the upper arm, the thigh,

or the abdomen.

| | |
|---|---|
| Investigational medicinal product name | Placebo to Avonex |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Placebo to Avonex was supplied in treatment kits, which was dispensed to subjects at each visit and contained a sufficient supply of Avonex placebo prefilled syringes and IM needles for each dosing interval. Subjects were instructed on how to perform injections at home.

| **Number of subjects in period 1** | Interferon beta-1a | Daclizumab High Yield Process |
|---|---|---|
| Started | 922 | 919 |
| Completed | 694 | 724 |
| Not completed | 228 | 195 |
| Consent withdrawn by subject | 98 | 80 |
| Physician decision | 4 | 6 |
| Death | 4 | - |
| Not specified | 2 | 1 |
| Pregnancy | 4 | 7 |
| Adverse event | 47 | 56 |
| Non-compliance | 7 | 8 |
| Lost to follow-up | 12 | 9 |
| Site closure | 4 | 5 |
| Lack of efficacy | 46 | 23 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Interferon beta-1a |
| Reporting group description: | |
| Interferon beta-1a (IFN β-1a) 30 µg IM injection once weekly plus placebo to DAC HYP SC once every 4 weeks for 96 to 144 weeks | |
| Reporting group title | Daclizumab High Yield Process |
| Reporting group description: | |
| DAC HYP 150 mg subcutaneous (SC) injection once every 4 weeks plus placebo to IFN β-1a intramuscular (IM) injection once weekly for 96 to 144 weeks | |

| Reporting group values | Interferon beta-1a | Daclizumab High Yield Process | Total |
|---|---|---|---|
| Number of subjects | 922 | 919 | 1841 |
| Age categorical<br>Units: Subjects | | | |
| 18 to 19 years | 25 | 14 | 39 |
| 20 to 29 years | 227 | 236 | 463 |
| 30 to 39 years | 327 | 322 | 649 |
| 40 to 49 years | 256 | 250 | 506 |
| 50 to 55 years | 86 | 96 | 182 |
| > 55 years | 1 | 1 | 2 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 36.2 | 36.4 | |
| standard deviation | ± 9.32 | ± 9.36 | - |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 627 | 625 | 1252 |
| Male | 295 | 294 | 589 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Interferon beta-1a |
| Reporting group description: | |
| Interferon beta-1a (IFN β-1a) 30 µg IM injection once weekly plus placebo to DAC HYP SC once every 4 weeks for 96 to 144 weeks | |
| Reporting group title | Daclizumab High Yield Process |
| Reporting group description: | |
| DAC HYP 150 mg subcutaneous (SC) injection once every 4 weeks plus placebo to IFN β-1a intramuscular (IM) injection once weekly for 96 to 144 weeks | |

### Primary: Adjusted Annualized Relapse Rate (ARR)

| | |
|---|---|
| End point title | Adjusted Annualized Relapse Rate (ARR) |
| End point description: | |
| Relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. Only relapses confirmed by Independent Neurology Evaluation Committee (INEC) are included in this analysis. Adjusted ARR was estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline Expanded Disability Status Scale (EDSS; ≤ 2.5 vs > 2.5) and baseline age (≤ 35 vs > 35). Data after subjects switched to alternative MS medications are excluded. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 144 weeks | |

| End point values | Interferon beta-1a | Daclizumab High Yield Process | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 392[1] | 260[2] | | |
| Units: relapses per person-years | | | | |
| number (confidence interval 95%) | 0.393 (0.353 to 0.438) | 0.216 (0.191 to 0.244) | | |

Notes:

[1] - subject with a relapse; number of relapses analyzed = 643

[2] - subject with a relapse; number of relapses analyzed = 402

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Daclizumab High Yield Process v Interferon beta-1a |
| Number of subjects included in analysis | 652 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [3] |
| Method | negative binomial regression |
| Parameter estimate | rate ratio |
| Point estimate | 0.55 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.469 |
| upper limit | 0.645 |

Notes:

[3] - Estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (≤ 2.5 vs > 2.5) and baseline age (≤ 35 vs > 35).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Interferon beta-1a v Daclizumab High Yield Process |
| Number of subjects included in analysis | 652 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | percent reduction |
| Point estimate | 45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 35.5 |
| upper limit | 53.1 |

## Secondary: Adjusted Mean Number of New or Newly Enlarging T2 Hyperintense Lesions up to Week 96

| End point title | Adjusted Mean Number of New or Newly Enlarging T2 Hyperintense Lesions up to Week 96 |
|---|---|

End point description:

Assessed by brain magnetic resonance imaging (MRI). Estimated from a negative binomial regression model, adjusted for baseline volume of T2 hyperintense lesions, history of prior IFN beta use and baseline age (≤ 35 vs > 35). To account for the timing of the MRI measurement, the logarithmic transformation of the scan number of the MRI assessment was included in the model as the 'offset' parameter. Observed data after subjects switched to alternative MS medications are excluded. Missing data are not imputed. Only observed new or newly enlarging T2 lesions at the last visit of the subject up to Week 96 visit are used in this analysis.

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

End point timeframe:

up to 96 weeks

| **End point values** | Interferon beta-1a | Daclizumab High Yield Process | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 841[4] | 864[5] | | |
| Units: lesions | | | | |
| arithmetic mean (confidence interval 95%) | 9.44 (8.46 to 10.54) | 4.31 (3.85 to 4.81) | | |

Notes:

[4] - subjects with baseline and at least 1 post-baseline MRI measurement

[5] - subjects with baseline and at least 1 post-baseline MRI measurement

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects With Sustained Disability Progression at 144 Weeks

| End point title | Proportion of Subjects With Sustained Disability Progression at 144 Weeks |
|---|---|

End point description:

Sustained disability progression is defined as: at least a 1.0-point increase on the Expanded Disability Status Scale (EDSS) from Baseline EDSS ≥1.0 that is sustained for 12 weeks, or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks. The EDSS measures the disability status of people with multiple sclerosis on a scale that ranges from 0 to 10, with higher scores indicating more disability. Estimated proportion of subjects with progression is based on the Kaplan-Meier product limit method. Subjects were censored at the time of withdrawal/switch if they withdrew from study or switched to alternative MS medication without a progression. Subjects with a tentative progression at the End of Treatment Period Visit (or the last EDSS assessment prior to alternative MS start date) and no confirmation assessment were censored at their last EDSS assessment.

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

End point timeframe:

Baseline through 144 weeks

| End point values | Interferon beta-1a | Daclizumab High Yield Process | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 922 | 919 | | |
| Units: proportion of participants | | | | |
| number (not applicable) | 0.203 | 0.162 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects Relapse-free at Week 144

| End point title | Proportion of Subjects Relapse-free at Week 144 |
|---|---|

End point description:

Relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist. Only relapses confirmed by INEC are included in this analysis. Data after subjects switched to alternative MS medications are excluded. The estimated proportion of subjects relapse-free at Week 144 is based on the Kaplan-Meier product limit method.

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

End point timeframe:

144 weeks

| End point values | Interferon beta-1a | Daclizumab High Yield Process | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 922 | 919 | | |
| Units: proportion of participants | | | | |
| number (not applicable) | 0.508 | 0.673 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With a ≥ 7.5 Point Worsening From Baseline in the Multiple Sclerosis Impact Scale (MSIS-29) Physical Impact Score at 96 Weeks

| End point title | Percentage of Subjects With a ≥ 7.5 Point Worsening From Baseline in the Multiple Sclerosis Impact Scale (MSIS-29) Physical Impact Score at 96 Weeks |
|---|---|

End point description:

The MSIS-29 is a 29-item disease-specific patient-reported outcome measure that has been developed and validated to examine the physical and psychological impact of MS from a patient's perspective; it measures physical and psychological items. Worsening in the MSIS-29 physical score is defined as an increase of ≥ 7.5 points in the MSIS-29 physical score at 96 weeks compared to baseline. If a subject was missing data for less than 10 of the 20 items that make up the physical score, then the mean of the non-missing items were used for the missing items. If a subject was missing 10 or more of the 20 items that make up the physical score, or missing the questionnaire entirely, or if the questionnaire was completed after the subject switched to alternative MS medication, a random effects model was used to estimate the MSIS-29 physical score.

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

End point timeframe:

Baseline and 96 weeks

| End point values | Interferon beta-1a | Daclizumab High Yield Process | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 912[6] | 906[7] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 23 | 19 | | |

Notes:

[6] - subjects with an assessment at baseline and Week 96

[7] - subjects with an assessment at baseline and Week 96

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All events were collected from Baseline through Week 164 (end of Post-dosing period).

Adverse event reporting additional description:

Treatment emergent events are reported. Events are considered treatment emergent if they occurred on or after the first dosing date and up to 180 days after the last dosing date.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | IFN beta-1a 30 mcg |

Reporting group description:

IFN β-1a 30 µg IM injection once weekly plus placebo to DAC HYP SC once every 4 weeks for 96 to 144 weeks

| | |
|---|---|
| Reporting group title | DAC HYP 150 mg |

Reporting group description:

DAC HYP 150 mg subcutaneous (SC) injection once every 4 weeks plus placebo to IFN β-1a intramuscular (IM) injection once weekly for 96 to 144 weeks

| Serious adverse events | IFN beta-1a 30 mcg | DAC HYP 150 mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 194 / 922 (21.04%) | 221 / 919 (24.05%) | |
| number of deaths (all causes) | 4 | 1 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenoma benign | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign neoplasm | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign ovarian tumour | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Benign salivary gland neoplasm | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain neoplasm malignant | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial cancer | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibroadenoma of breast | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningioma | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian germ cell teratoma benign | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma metastatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of the cervix | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of the oral cavity | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Testicular seminoma (pure) | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tongue neoplasm malignant stage unspecified | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 922 (0.11%) | 3 / 919 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicose vein | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kawasaki's disease | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |

| | | | |
|---|---|---|---|
| Abortion induced | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angioplasty | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 / 922 (0.11%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rehabilitation therapy | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cystectomy | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal decompression | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 | 1 / 922 (0.11%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 3 / 922 (0.33%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (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** | | | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Adjustment disorder with mixed disturbance of emotion and conduct | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bipolar disorder | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 2 / 922 (0.22%) | 3 / 919 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Depression suicidal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Emotional distress | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mood disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Substance abuse | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 2 / 922 (0.22%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 922 (0.33%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis acute | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 922 (0.22%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 922 (0.22%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Smear cervix abnormal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 | 2 / 922 (0.22%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Face injury | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 2 / 922 (0.22%) | 4 / 919 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foreign body | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament injury | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple injuries | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nail avulsion | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 922 (0.22%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Dermoid cyst | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 3 / 922 (0.33%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Palpitations | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 4 / 919 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Complex partial seizures | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple sclerosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 922 (0.33%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 124 / 922 (13.45%) | 97 / 919 (10.55%) | |
| occurrences causally related to treatment / all | 1 / 206 | 3 / 150 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle spasticity | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenia gravis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Optic neuritis | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Relapsing-remitting multiple sclerosis | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Speech disorder | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tension headache | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic encephalopathy | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uhthoff's phenomenon | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Agranulocytosis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 922 (0.11%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 5 / 919 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 3 / 919 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoid tissue hyperplasia | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cystoid macular oedema | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 1 / 919 (0.11%) | |
| 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 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis microscopic | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (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 | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth cyst | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oroantral fistula | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (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 | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dermal cyst | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 3 / 919 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytoclastic vasculitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lichenoid keratosis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pityriasis rubra pilaris | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoriasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pustular psoriasis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 3 / 919 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibromyalgia | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patellofemoral pain syndrome | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lupus-like syndrome | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Plica syndrome | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondyloarthropathy | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic tonsillitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis infectious | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis a | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ludwig angina | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lyme disease | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuroborreliosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis viral | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parotitis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 922 (0.22%) | 5 / 919 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reiter's syndrome | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Strongyloidiasis | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 922 (0.22%) | 8 / 919 (0.87%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral myocarditis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 922 (0.11%) | 0 / 919 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 922 (0.11%) | 2 / 919 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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 / 922 (0.00%) | 1 / 919 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tetany | | | |
| subjects affected / exposed | 0 / 922 (0.00%) | 1 / 919 (0.11%) | |
| 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** | IFN beta-1a 30 mcg | DAC HYP 150 mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 783 / 922 (84.92%) | 731 / 919 (79.54%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 66 / 922 (7.16%) | 69 / 919 (7.51%) | |
| occurrences (all) | 86 | 96 | |
| Aspartate aminotransferase | | | |

| | | | |
|---|---|---|---|
| increased | | | |
| subjects affected / exposed | 44 / 922 (4.77%) | 48 / 919 (5.22%) | |
| occurrences (all) | 51 | 69 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 37 / 922 (4.01%) | 48 / 919 (5.22%) | |
| occurrences (all) | 58 | 66 | |
| Headache | | | |
| subjects affected / exposed | 175 / 922 (18.98%) | 159 / 919 (17.30%) | |
| occurrences (all) | 925 | 443 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 54 / 922 (5.86%) | 54 / 919 (5.88%) | |
| occurrences (all) | 76 | 71 | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 428 / 922 (46.42%) | 293 / 919 (31.88%) | |
| occurrences (all) | 748 | 480 | |
| Paraesthesia | | | |
| subjects affected / exposed | 57 / 922 (6.18%) | 42 / 919 (4.57%) | |
| occurrences (all) | 101 | 59 | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 7 / 922 (0.76%) | 46 / 919 (5.01%) | |
| occurrences (all) | 7 | 58 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 55 / 922 (5.97%) | 37 / 919 (4.03%) | |
| occurrences (all) | 232 | 66 | |
| Fatigue | | | |
| subjects affected / exposed | 76 / 922 (8.24%) | 69 / 919 (7.51%) | |
| occurrences (all) | 125 | 103 | |
| Influenza like illness | | | |
| subjects affected / exposed | 345 / 922 (37.42%) | 88 / 919 (9.58%) | |
| occurrences (all) | 3172 | 166 | |
| Injection site pain | | | |
| subjects affected / exposed | 102 / 922 (11.06%) | 96 / 919 (10.45%) | |
| occurrences (all) | 376 | 331 | |

| | | | |
|---|---|---|---|
| Injection site erythema | | | |
| subjects affected / exposed | 47 / 922 (5.10%) | 40 / 919 (4.35%) | |
| occurrences (all) | 243 | 62 | |
| Pyrexia | | | |
| subjects affected / exposed | 134 / 922 (14.53%) | 104 / 919 (11.32%) | |
| occurrences (all) | 624 | 170 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 55 / 922 (5.97%) | 67 / 919 (7.29%) | |
| occurrences (all) | 71 | 82 | |
| Nausea | | | |
| subjects affected / exposed | 46 / 922 (4.99%) | 46 / 919 (5.01%) | |
| occurrences (all) | 60 | 80 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 46 / 922 (4.99%) | 53 / 919 (5.77%) | |
| occurrences (all) | 56 | 68 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 41 / 922 (4.45%) | 69 / 919 (7.51%) | |
| occurrences (all) | 53 | 86 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 26 / 922 (2.82%) | 64 / 919 (6.96%) | |
| occurrences (all) | 29 | 80 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 56 / 922 (6.07%) | 72 / 919 (7.83%) | |
| occurrences (all) | 68 | 85 | |
| Insomnia | | | |
| subjects affected / exposed | 54 / 922 (5.86%) | 42 / 919 (4.57%) | |
| occurrences (all) | 62 | 52 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 62 / 922 (6.72%) | 71 / 919 (7.73%) | |
| occurrences (all) | 113 | 96 | |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 70 / 922 (7.59%) | 86 / 919 (9.36%) | |
| occurrences (all) | 106 | 146 | |
| Myalgia | | | |
| subjects affected / exposed | 49 / 922 (5.31%) | 42 / 919 (4.57%) | |
| occurrences (all) | 167 | 67 | |
| Pain in extremity | | | |
| subjects affected / exposed | 58 / 922 (6.29%) | 55 / 919 (5.98%) | |
| occurrences (all) | 134 | 90 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 43 / 922 (4.66%) | 61 / 919 (6.64%) | |
| occurrences (all) | 48 | 76 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 197 / 922 (21.37%) | 226 / 919 (24.59%) | |
| occurrences (all) | 319 | 499 | |
| Influenza | | | |
| subjects affected / exposed | 56 / 922 (6.07%) | 82 / 919 (8.92%) | |
| occurrences (all) | 77 | 113 | |
| Oral herpes | | | |
| subjects affected / exposed | 44 / 922 (4.77%) | 57 / 919 (6.20%) | |
| occurrences (all) | 63 | 106 | |
| Pharyngitis | | | |
| subjects affected / exposed | 69 / 922 (7.48%) | 77 / 919 (8.38%) | |
| occurrences (all) | 89 | 109 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 124 / 922 (13.45%) | 148 / 919 (16.10%) | |
| occurrences (all) | 183 | 259 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 96 / 922 (10.41%) | 92 / 919 (10.01%) | |
| occurrences (all) | 136 | 150 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 27 May 2011 | The primary reasons for this amendment to Protocol 205MS301 were to:<br>- Increase subject monitoring for laboratory signals related to hepatic function (liver function tests [LFTs] will be assessed monthly throughout the treatment period), and update criteria for temporary suspension and discontinuation of study treatment for subjects who develop elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin. Subjects who must permanently discontinue study treatment due to elevated LFTs will be evaluated for possible toxicological, infectious, immunological, and metabolic causes of liver injury.<br>- Provide additional guidance to Investigators on the evaluation and management of cutaneous events.<br>- Increase the sample size for the study from 1500 to 1800 subjects based on recent clinical studies that suggested a lower annualized relapse rate for the IFN β-1a group. |
| 10 March 2012 | The primary reasons for this amendment to Protocol 205MS301 were to:<br>- Prohibit concomitant treatment with medications that have an established association with hepatotoxicity or cutaneous hypersensitivity reactions.<br>- Provide monthly liver function testing results to the Treating Neurologist prior to administration of study treatment. |
| 29 April 2013 | The primary reasons for this amendment to Protocol 205MS301 were to:<br>- Modify the definition and rank ordering of some secondary and additional endpoints<br>- Update the statistical analysis section in the protocol: In the protocol version 1 for Study 205MS301, it was stated that efficacy analyses in the trial would first be tested at the 0.04 significance level, and if they were negative, they would then be tested at the 0.01 significance level in the subgroup of subjects who were positive at Baseline for the DAC HYP response signature. Based on the results from exploratory analyses that were performed on Study 205MS201 biomarker data, and in accordance with the original design of Study 205MS301, the sponsor then amended protocol for Study 205MS301 on 29 April 2013 (approximately 11 months prior to the end of Study 205MS301 Treatment Period) to document this result, removed the reference to the response signature from the analysis plan, and clarifed that all efficacy analyses in Study 205MS301 would be performed at the standard 0.05 significance level. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported