



## Clinical trial results:

### A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

#### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2008-004753-14                               |
| Trial protocol           | BE CZ SK DE IE LV ES FR EE GR AT NL BG IT GB |
| Global end of trial date | 08 November 2019                             |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 22 February 2021 |
| First version publication date | 06 November 2020 |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 109MS303 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00835770 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Biogen  |
| Sponsor organisation address | 250 Binney Street, Cambridge, United States, 02142                  |
| Public contact               | Biogen Study Medical Director, Biogen,<br>clinicaltrials@biogen.com |
| Scientific contact           | Biogen Study Medical Director, Biogen,<br>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                       | 08 November 2019 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 08 November 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the long-term safety profile of BG00012.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 03 February 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                          |
|--------------------------------------|--------------------------|
| Country: Number of subjects enrolled | Poland: 308              |
| Country: Number of subjects enrolled | United States: 267       |
| Country: Number of subjects enrolled | India: 162               |
| Country: Number of subjects enrolled | Germany: 160             |
| Country: Number of subjects enrolled | Ukraine: 104             |
| Country: Number of subjects enrolled | Czechia: 98              |
| Country: Number of subjects enrolled | Serbia: 86               |
| Country: Number of subjects enrolled | France: 69               |
| Country: Number of subjects enrolled | Belgium: 41              |
| Country: Number of subjects enrolled | Canada: 40               |
| Country: Number of subjects enrolled | Mexico: 38               |
| Country: Number of subjects enrolled | Bulgaria: 33             |
| Country: Number of subjects enrolled | Australia: 26            |
| Country: Number of subjects enrolled | Spain: 26                |
| Country: Number of subjects enrolled | Moldova, Republic of: 24 |
| Country: Number of subjects enrolled | Romania: 23              |
| Country: Number of subjects enrolled | United Kingdom: 22       |
| Country: Number of subjects enrolled | Belarus: 20              |
| Country: Number of subjects enrolled | Estonia: 19              |

|                                      |                            |
|--------------------------------------|----------------------------|
| Country: Number of subjects enrolled | Greece: 19                 |
| Country: Number of subjects enrolled | North Macedonia: 19        |
| Country: Number of subjects enrolled | Slovakia: 18               |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 15 |
| Country: Number of subjects enrolled | Croatia: 14                |
| Country: Number of subjects enrolled | New Zealand: 14            |
| Country: Number of subjects enrolled | Switzerland: 14            |
| Country: Number of subjects enrolled | Latvia: 11                 |
| Country: Number of subjects enrolled | Austria: 10                |
| Country: Number of subjects enrolled | Israel: 9                  |
| Country: Number of subjects enrolled | South Africa: 8            |
| Country: Number of subjects enrolled | Italy: 6                   |
| Country: Number of subjects enrolled | Guatemala: 5               |
| Country: Number of subjects enrolled | Netherlands: 4             |
| Country: Number of subjects enrolled | Ireland: 3                 |
| Country: Number of subjects enrolled | Puerto Rico: 3             |
| Worldwide total number of subjects   | 1738                       |
| EEA total number of subjects         | 862                        |

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)                      | 1738 |
| From 65 to 84 years                       | 0    |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 298 investigative sites from 03 February 2009 to 08 November 2019.

### Pre-assignment

Screening details:

The study included subjects who completed studies 2006-003696-12 and 2006-003697-10. A total of 1736 subjects were treated in the open-label phase extension study 2008-004753-14, out of which 759 completed the study.

### 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, Monitor, Carer, Data analyst, Assessor |

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | BG00012 240 mg BID |

Arm description:

Subjects received BG00012 240 milligrams (mg) (120 mg each) 2 capsules orally, twice a day (BID) and 2 matching placebo capsules once a day (QD) up to 8 years.

|  |                   |
|--|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | BG00012           |
| Investigational medicinal product code |                   |
| Other name                             | Dimethly fumarate |
| Pharmaceutical forms                   | Capsule           |
| Routes of administration               | Oral use          |

Dosage and administration details:

Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, BID up to 8 years.

|  |          |
|--|----------|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use |

Dosage and administration details:

Subjects received 2 matching placebo to BG00012 capsules QD up to 8 years.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | BG00012 240 mg TID |
|------------------|--------------------|

Arm description:

Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, three times a day (TID) up to 8 years.

|  |                   |
|--|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | BG00012           |
| Investigational medicinal product code |                   |
| Other name                             | Dimethly fumarate |
| Pharmaceutical forms                   | Capsule           |
| Routes of administration               | Oral use          |

Dosage and administration details:

Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, TID up to 8 years.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | BG00012 240 mg<br>BID | BG00012 240 mg<br>TID |
|---|-----------------------|-----------------------|
| Started   | 868                   | 868                   |
| Completed   | 384                   | 375                   |
| Not completed                                       | 484                   | 493                   |
| Subject Non-Compliance                              | 11                    | 9                     |
| MS progression                                      | 14                    | 9                     |
| Adverse Event                                       | 113                   | 124                   |
| Death   | 4                     | 6                     |
| Not specified                                       | 115                   | 104                   |
| Unknown   | 2                     | 1                     |
| Investigator decision                               | 42                    | 42                    |
| Lost to follow-up                                   | 22                    | 19                    |
| Consent withdrawn                                   | 144                   | 156                   |
| MS relapse  | 17                    | 23                    |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported in the baseline period is for intent to treat population (868 subjects in BG00012 240 mg BID, 868 subjects in BG00012 240 mg TID).

## Baseline characteristics

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | BG00012 240 mg BID |
|-----------------------|--------------------|

Reporting group description:

Subjects received BG00012 240 milligrams (mg) (120 mg each) 2 capsules orally, twice a day (BID) and 2 matching placebo capsules once a day (QD) up to 8 years.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | BG00012 240 mg TID |
|-----------------------|--------------------|

Reporting group description:

Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, three times a day (TID) up to 8 years.

| Reporting group values             | BG00012 240 mg<br>BID | BG00012 240 mg<br>TID | Total |
|------------------------------------|-----------------------|-----------------------|-------|
| Number of subjects                 | 868                   | 868                   | 1736  |
| Age categorical<br>Units: Subjects |                       |                       |       |

|   |                |                |      |
|---|----------------|----------------|------|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 39.6<br>± 8.93 | 40.1<br>± 9.23 | -    |
| Sex: Female, Male<br>Units: subjects                                    |                |                |      |
| Female  | 616            | 596            | 1212 |
| Male  | 252            | 272            | 524  |
| Race/Ethnicity, Customized<br>Units: Subjects                           |                |                |      |
| White   | 285            | 309            | 594  |
| Black or African American   | 10             | 16             | 26   |
| Asian   | 82             | 80             | 162  |
| American Indian or Alaska Native  | 0              | 0              | 0    |
| Native Hawaiian or Other Pacific Islander                               | 0              | 0              | 0    |
| Other   | 32             | 24             | 56   |
| Not Reported Due To Confidentiality Regulations                         | 459            | 439            | 898  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | BG00012 240 mg BID                                 |
| Reporting group description:<br>Subjects received BG00012 240 milligrams (mg) (120 mg each) 2 capsules orally, twice a day (BID) and 2 matching placebo capsules once a day (QD) up to 8 years.   |  |
| Reporting group title   | BG00012 240 mg TID                                 |
| Reporting group description:<br>Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, three times a day (TID) up to 8 years.  |  |
| Subject analysis set title  | BG00012 240 mg BID (Prior BG00012 240 mg BID)      |
| Subject analysis set type   | Intention-to-treat                                 |
| Subject analysis set description:<br>Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received BG00012 240 mg BID in the previous studies were included in this arm group.         |  |
| Subject analysis set title  | BG00012 240 mg TID (Prior BG00012 240 mg TID)      |
| Subject analysis set type   | Intention-to-treat                                 |
| Subject analysis set description:<br>Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received BG00012 240 mg TID in the previous studies were included in this arm group.  |  |
| Subject analysis set title  | BG00012 240 mg BID (Prior BG00012 Matched Placebo) |
| Subject analysis set type   | Intention-to-treat                                 |
| Subject analysis set description:<br>Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received placebo matched to BG00012 in the previous studies were included in this arm group. |  |
| Subject analysis set title  | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
| Subject analysis set type   | Intention-to-treat                                 |
| Subject analysis set description:<br>Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received placebo matched to BG00012 in the previous studies were included in this arm group.                                    |  |
| Subject analysis set title  | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) |
| Subject analysis set type   | Intention-to-treat                                 |
| Subject analysis set description:<br>Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received Glatiramer Acetate (GA) in the previous studies were included in this arm group.    |  |
| Subject analysis set title  | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |
| Subject analysis set type   | Intention-to-treat                                 |
| Subject analysis set description:<br>Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received GA in the previous studies were included in this arm group.  |  |
| Subject analysis set title  | BG00012 240 mg BID (Prior BG00012 240 mg BID)      |
| Subject analysis set type   | Sub-group analysis                                 |
| Subject analysis set description:<br>Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received BG00012 240 mg BID in the previous studies were included in this arm group.         |  |
| Subject analysis set title  | BG00012 240 mg TID (Prior BG00012 240 mg TID)      |
| Subject analysis set type   | Sub-group analysis                                 |
| Subject analysis set description:<br>Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received BG00012 240 mg TID in the previous studies were included in this arm group.  |  |

|  |  |
|--|--|
| Subject analysis set title   | BG00012 240 mg BID (Prior BG00012 Matched Placebo) |
| Subject analysis set type  | Sub-group analysis                                 |
| Subject analysis set description:  |  |
| Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received placebo matched to BG00012 in the previous studies were included in this arm group. |  |
| Subject analysis set title   | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
| Subject analysis set type  | Sub-group analysis                                 |
| Subject analysis set description:  |  |
| Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received placebo matched to BG00012 in the previous studies were included in this arm group.                                    |  |
| Subject analysis set title   | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) |
| Subject analysis set type  | Sub-group analysis                                 |
| Subject analysis set description:  |  |
| Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received Glatiramer Acetate (GA) in the previous studies were included in this arm group.    |  |
| Subject analysis set title   | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |
| Subject analysis set type  | Sub-group analysis                                 |
| Subject analysis set description:  |  |
| Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received GA in the previous studies were included in this arm group.  |  |

### Primary: Number of Subjects with Treatment-Emergent Adverse Events (AEs)

|   |  |
|---|--|
| End point title   | Number of Subjects with Treatment-Emergent Adverse Events (AEs) <sup>[1]</sup> |
| End point description:  |  |
| An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Safety population included all subjects who had any post-baseline safety follow-up in study 2008-004753-14, defined as any treatment emergent AE in study 2008-004753-14 or any post-baseline laboratory, vital signs, or physical exam assessment in study 2008-004753-14, and received at least one dose of study treatment in study 2008-004753-14. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Day 1 up to Week 561  |  |
| 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: Only descriptive analysis was planned to be performed.   |  |

| End point values            | BG00012 240 mg BID | BG00012 240 mg TID |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 868                | 868                |  |  |
| Units: subjects             | 824                | 814                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Had Relapses

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Had Relapses |
|-----------------|---|



**End point description:**

Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Day 1 up to Week 384

| End point values              | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|-------------------------------|---|---|--|--|
| Subject group type            | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed   | 501   | 502   | 249  | 248  |
| Units: percentage of subjects | 40  | 41  | 34   | 36   |

| End point values              | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed   | 118  | 118  |  |  |
| Units: percentage of subjects | 31   | 31   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Annualized Relapse Rate (ARR)**

|                 |                               |
|-----------------|-------------------------------|
| End point title | Annualized Relapse Rate (ARR) |
|-----------------|-------------------------------|

**End point description:**

The annualized relapse rate is calculated as the total number of relapses occurred during the period for all subjects, divided by the total number of subject-years followed in the period. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Day 1 up to Week 384

| End point values                  | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|-----------------------------------|---|---|--|--|
| Subject group type                | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed       | 501   | 502   | 249  | 248  |
| Units: relapses per subject-years |   |   |  |  |
| number (not applicable)           | 0.159   | 0.179   | 0.200  | 0.199  |

| End point values                  | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed       | 118  | 118  |  |  |
| Units: relapses per subject-years |  |  |  |  |
| number (not applicable)           | 0.184  | 0.212  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Expanded Disability Status Scale (EDSS) at Week 384

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the Expanded Disability Status Scale (EDSS) at Week 384 |
|-----------------|---|

End point description:

The EDSS scale ranges from 0 (Normal neurological exam, no disability) to 10 (Death) in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist. Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS  $\geq 1.0$  that was sustained for at least 24 weeks, or a 1.5 point increase on the EDSS from a baseline EDSS =0 that was sustained for at least 24 weeks. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Baseline, Week 384

| End point values                     | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed          | 501   | 502   | 249  | 248  |
| Units: score on a scale              |   |   |  |  |
| arithmetic mean (standard deviation) |   |   |  |  |

|  |                |                |                |                |
|--|----------------|----------------|----------------|----------------|
| Baseline (n =499, 502, 249, 248, 118, 118)       | 2.44 (± 1.251) | 2.43 (± 1.144) | 2.50 (± 1.135) | 2.54 (± 1.218) |
| Change at Week 384 (n =226, 219, 90, 98, 42, 50) | 0.28 (± 1.160) | 0.26 (± 1.213) | 0.37 (± 1.328) | 0.53 (± 1.278) |

| End point values                                 | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|--|--|--|--|--|
| Subject group type                               | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed                      | 118  | 118  |  |  |
| Units: score on a scale                          |  |  |  |  |
| arithmetic mean (standard deviation)             |  |  |  |  |
| Baseline (n =499, 502, 249, 248, 118, 118)       | 2.57 (± 1.249)                                     | 2.68 (± 1.231)                                     |  |  |
| Change at Week 384 (n =226, 219, 90, 98, 42, 50) | 0.39 (± 1.217)                                     | 0.49 (± 1.319)                                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Gadolinium (Gd)-Enhancing Lesions as Measured by Magnetic Resonance Imaging (MRI)

|                 |   |
|-----------------|---|
| End point title | Number of Gadolinium (Gd)-Enhancing Lesions as Measured by Magnetic Resonance Imaging (MRI) |
|-----------------|---|

End point description:

The Gd-enhancing lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Baseline up to Week 288

| End point values                       | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                     | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed            | 213   | 222   | 105  | 103  |
| Units: lesions                         |   |   |  |  |
| arithmetic mean (standard deviation)   |   |   |  |  |
| Week 48 (n =191, 195, 83, 78, 41, 48)  | 0.4 (± 1.87)                                  | 0.4 (± 1.29)                                  | 0.2 (± 0.66)                                       | 0.3 (± 1.14)                                       |
| Week 96 (n =183, 186, 77, 75, 39, 46)  | 0.4 (± 1.77)                                  | 0.4 (± 1.28)                                  | 0.1 (± 0.38)                                       | 0.2 (± 0.82)                                       |
| Week 144 (n =156, 159, 66, 60, 32, 41) | 0.3 (± 1.66)                                  | 0.4 (± 1.30)                                  | 0.2 (± 0.44)                                       | 0.1 (± 0.29)                                       |

|  |              |              |              |              |
|--|--------------|--------------|--------------|--------------|
| Week 192 (n =144, 149, 59, 55, 33, 38) | 0.4 (± 2.02) | 0.5 (± 1.85) | 0.5 (± 1.72) | 0.3 (± 0.96) |
| Week 240 (n =135, 134, 55, 53, 29, 34) | 0.5 (± 3.14) | 0.5 (± 2.29) | 0.2 (± 0.50) | 0.2 (± 0.51) |
| Week 288 (n =89, 97, 30, 31, 6, 16)    | 0.2 (± 0.74) | 0.5 (± 1.81) | 0.1 (± 0.40) | 0.7 (± 2.76) |

| End point values                       | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|--|--|--|--|--|
| Subject group type                     | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed            | 49   | 60   |  |  |
| Units: lesions                         |  |  |  |  |
| arithmetic mean (standard deviation)   |  |  |  |  |
| Week 48 (n =191, 195, 83, 78, 41, 48)  | 0.5 (± 1.19)                                       | 0.4 (± 1.14)                                       |  |  |
| Week 96 (n =183, 186, 77, 75, 39, 46)  | 0.6 (± 1.33)                                       | 0.3 (± 0.73)                                       |  |  |
| Week 144 (n =156, 159, 66, 60, 32, 41) | 0.5 (± 2.48)                                       | 0.3 (± 1.59)                                       |  |  |
| Week 192 (n =144, 149, 59, 55, 33, 38) | 0.2 (± 0.60)                                       | 0.6 (± 2.01)                                       |  |  |
| Week 240 (n =135, 134, 55, 53, 29, 34) | 0.2 (± 0.58)                                       | 0.3 (± 0.75)                                       |  |  |
| Week 288 (n =89, 97, 30, 31, 6, 16)    | 0.0 (± 0.00)                                       | 0.3 (± 0.77)                                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Volume of Gd-Enhancing Lesions as Measured by Magnetic Resonance Imaging (MRI)

|   |  |
|---|--|
| End point title   | Volume of Gd-Enhancing Lesions as Measured by Magnetic Resonance Imaging (MRI) |
| End point description:<br>The Gd-enhancing lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10). |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline up to Week 288   |  |

| End point values                          | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|---|---|---|--|--|
| Subject group type                        | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed               | 213   | 222   | 105  | 103  |
| Units: millimetre cube (mm <sup>3</sup> ) |   |   |  |  |
| arithmetic mean (standard deviation)      |   |   |  |  |
| Baseline (n =209, 220, 104, 99, 47, 60)   | 31.7 (± 179.28)                               | 48.6 (± 205.43)                               | 96.0 (± 260.79)                                    | 142.5 (± 459.76)                                   |
| Week 48 (n =190, 197, 83, 77, 40, 48)     | 59.6 (± 526.51)                               | 70.0 (± 366.63)                               | 18.8 (± 91.47)                                     | 25.3 (± 108.19)                                    |
| Week 96 (n =182, 185, 77, 73, 38, 46)     | 49.1 (± 245.14)                               | 56.1 (± 271.29)                               | 27.7 (± 204.80)                                    | 13.3 (± 67.01)                                     |
| Week 144 (n =155, 160, 66, 59, 31, 41)    | 44.1 (± 291.14)                               | 47.0 (± 169.68)                               | 18.8 (± 66.15)                                     | 3.8 (± 25.03)                                      |
| Week 192 (n =143, 148, 59, 54, 32, 38)    | 39.1 (± 217.89)                               | 54.5 (± 251.31)                               | 45.8 (± 156.88)                                    | 19.9 (± 79.19)                                     |
| Week 240 (n =134, 133, 55, 52, 28, 34)    | 96.8 (± 650.06)                               | 69.3 (± 374.67)                               | 21.7 (± 77.87)                                     | 14.1 (± 45.22)                                     |
| Week 288 (n =89, 97, 30, 31, 6, 16)       | 18.2 (± 93.28)                                | 53.1 (± 250.87)                               | 7.9 (± 30.09)                                      | 230.2 (± 1092.11)                                  |

| End point values                          | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|---|--|--|--|--|
| Subject group type                        | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed               | 49   | 60   |  |  |
| Units: millimetre cube (mm <sup>3</sup> ) |  |  |  |  |
| arithmetic mean (standard deviation)      |  |  |  |  |
| Baseline (n =209, 220, 104, 99, 47, 60)   | 37.1 (± 138.82)                                    | 41.7 (± 116.55)                                    |  |  |
| Week 48 (n =190, 197, 83, 77, 40, 48)     | 42.5 (± 123.67)                                    | 42.7 (± 148.11)                                    |  |  |
| Week 96 (n =182, 185, 77, 73, 38, 46)     | 64.3 (± 183.16)                                    | 22.3 (± 60.83)                                     |  |  |
| Week 144 (n =155, 160, 66, 59, 31, 41)    | 42.6 (± 142.55)                                    | 92.9 (± 397.69)                                    |  |  |
| Week 192 (n =143, 148, 59, 54, 32, 38)    | 12.0 (± 40.56)                                     | 55.1 (± 169.16)                                    |  |  |
| Week 240 (n =134, 133, 55, 52, 28, 34)    | 17.5 (± 46.19)                                     | 17.1 (± 48.41)                                     |  |  |
| Week 288 (n =89, 97, 30, 31, 6, 16)       | 0.0 (± 0.00)                                       | 34.1 (± 102.87)                                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of New or Newly Enlarging T2 Lesions as Measured by Magnetic Resonance Imaging (MRI)

|   |   |
|---|---|
| End point title   | Number of New or Newly Enlarging T2 Lesions as Measured by Magnetic Resonance Imaging (MRI) |
| End point description:<br>The T2 lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12, 2006-003697-10 or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10). |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline up to Week 288   |   |

| End point values                       | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                     | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed            | 213   | 222   | 105  | 103  |
| Units: lesions                         |   |   |  |  |
| arithmetic mean (standard deviation)   |   |   |  |  |
| Week 48 (n =198, 201, 84, 81, 42, 50)  | 1.6 (± 4.07)                                  | 2.2 (± 6.15)                                  | 2.7 (± 4.96)                                       | 2.4 (± 5.45)                                       |
| Week 96 (n =191, 192, 78, 77, 40, 47)  | 3.4 (± 8.35)                                  | 4.1 (± 10.01)                                 | 3.8 (± 7.24)                                       | 2.9 (± 6.78)                                       |
| Week 144 (n =163, 168, 67, 63, 35, 44) | 4.2 (± 9.81)                                  | 5.2 (± 10.01)                                 | 4.0 (± 7.27)                                       | 4.3 (± 10.12)                                      |
| Week 192 (n =151, 155, 61, 56, 33, 40) | 5.8 (± 14.04)                                 | 7.5 (± 15.14)                                 | 5.6 (± 10.09)                                      | 5.6 (± 14.19)                                      |
| Week 240 (n =139, 142, 55, 55, 30, 37) | 7.4 (± 17.09)                                 | 9.5 (± 20.33)                                 | 8.2 (± 14.87)                                      | 7.7 (± 17.89)                                      |
| Week 288 (n =123, 123, 45, 49, 26, 32) | 8.2 (± 18.53)                                 | 12.4 (± 28.23)                                | 7.5 (± 13.89)                                      | 10.4 (± 22.05)                                     |

| End point values                       | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|--|--|--|--|--|
| Subject group type                     | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed            | 49   | 60   |  |  |
| Units: lesions                         |  |  |  |  |
| arithmetic mean (standard deviation)   |  |  |  |  |
| Week 48 (n =198, 201, 84, 81, 42, 50)  | 3.4 (± 6.57)                                       | 2.1 (± 3.83)                                       |  |  |
| Week 96 (n =191, 192, 78, 77, 40, 47)  | 4.9 (± 8.51)                                       | 3.4 (± 5.13)                                       |  |  |
| Week 144 (n =163, 168, 67, 63, 35, 44) | 5.7 (± 9.45)                                       | 5.2 (± 9.68)                                       |  |  |
| Week 192 (n =151, 155, 61, 56, 33, 40) | 5.5 (± 9.94)                                       | 5.6 (± 13.35)                                      |  |  |
| Week 240 (n =139, 142, 55, 55, 30, 37) | 6.8 (± 11.74)                                      | 7.5 (± 16.76)                                      |  |  |
| Week 288 (n =123, 123, 45, 49, 26, 32) | 8.9 (± 15.04)                                      | 6.0 (± 8.90)                                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Volume of New or Newly Enlarging T2 Lesions as Measured by Magnetic Resonance Imaging (MRI)

|                 |   |
|-----------------|---|
| End point title | Volume of New or Newly Enlarging T2 Lesions as Measured by Magnetic Resonance Imaging (MRI) |
|-----------------|---|

End point description:

The T2 lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12, 2006-003697-10 or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Baseline up to Week 288

| End point values                        | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|---|---|---|--|--|
| Subject group type                      | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed             | 213   | 222   | 105  | 103  |
| Units: mm <sup>3</sup>                  |   |   |  |  |
| arithmetic mean (standard deviation)    |   |   |  |  |
| Baseline (n =209, 220, 104, 99, 47, 60) | 10231.9 (± 11214.17)                          | 10408.3 (± 12166.80)                          | 8883.7 (± 8570.10)                                 | 10806.3 (± 12060.05)                               |
| Week 48 (n =194, 199, 84, 78, 40, 50)   | 9951.9 (± 10750.15)                           | 9849.6 (± 10986.36)                           | 8992.1 (± 7952.13)                                 | 10114.5 (± 10121.61)                               |
| Week 96 (n =187, 190, 78, 74, 38, 47)   | 10331.3 (± 11359.81)                          | 10434.0 (± 12201.38)                          | 8645.2 (± 7787.60)                                 | 9985.7 (± 10715.73)                                |
| Week 144 (n =162, 167, 67, 61, 34, 44)  | 9930.1 (± 10686.26)                           | 10280.7 (± 11324.58)                          | 8829.4 (± 7482.93)                                 | 9792.3 (± 9842.28)                                 |
| Week 192 (n =149, 154, 61, 55, 32, 40)  | 9837.7 (± 10845.04)                           | 10760.0 (± 11987.16)                          | 9077.6 (± 7794.52)                                 | 10576.3 (± 12029.26)                               |
| Week 240 (n =138, 141, 55, 54, 29, 37)  | 10611.2 (± 11633.95)                          | 11087.5 (± 12464.90)                          | 9711.1 (± 8709.46)                                 | 10591.4 (± 11613.26)                               |
| Week 288 (n =121, 122, 45, 49, 26, 32)  | 9611.8 (± 9447.18)                            | 9800.8 (± 11279.84)                           | 8819.8 (± 8866.90)                                 | 10537.6 (± 10684.47)                               |

|                  |  |  |  |  |
|------------------|--|--|--|--|
| End point values | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|------------------|--|--|--|--|

|   |                      |                      |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                      | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed             | 49                   | 60                   |  |  |
| Units: mm <sup>3</sup>                  |                      |                      |  |  |
| arithmetic mean (standard deviation)    |                      |                      |  |  |
| Baseline (n =209, 220, 104, 99, 47, 60) | 12628.9 (± 11258.69) | 13044.4 (± 14608.50) |  |  |
| Week 48 (n =194, 199, 84, 78, 40, 50)   | 11160.7 (± 9565.55)  | 12979.0 (± 14415.86) |  |  |
| Week 96 (n =187, 190, 78, 74, 38, 47)   | 11318.1 (± 9873.73)  | 13974.1 (± 15432.10) |  |  |
| Week 144 (n =162, 167, 67, 61, 34, 44)  | 10188.5 (± 8064.09)  | 12949.7 (± 14036.15) |  |  |
| Week 192 (n =149, 154, 61, 55, 32, 40)  | 10421.9 (± 8773.41)  | 11671.5 (± 13124.47) |  |  |
| Week 240 (n =138, 141, 55, 54, 29, 37)  | 11009.9 (± 9551.94)  | 12254.4 (± 13732.10) |  |  |
| Week 288 (n =121, 122, 45, 49, 26, 32)  | 11586.3 (± 9728.19)  | 10404.8 (± 12245.75) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of T1 Hypointense Lesions as Measured by Magnetic Resonance Imaging (MRI)

|                 |  |
|-----------------|--|
| End point title | Number of T1 Hypointense Lesions as Measured by Magnetic Resonance Imaging (MRI) |
|-----------------|--|

End point description:

The T1 hypointense lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Baseline up to Week 288

| End point values                       | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                     | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed            | 213   | 222   | 105  | 103  |
| Units: lesions                         |   |   |  |  |
| arithmetic mean (standard deviation)   |   |   |  |  |
| Week 48 (n =183, 184, 79, 76, 41, 48)  | 0.8 (± 2.13)                                  | 1.0 (± 2.37)                                  | 1.8 (± 3.81)                                       | 1.7 (± 3.71)                                       |
| Week 96 (n =171, 178, 75, 72, 39, 45)  | 1.7 (± 3.63)                                  | 1.9 (± 3.91)                                  | 1.8 (± 3.33)                                       | 2.1 (± 5.00)                                       |
| Week 144 (n =148, 155, 63, 53, 32, 41) | 2.0 (± 4.61)                                  | 2.8 (± 5.19)                                  | 2.0 (± 3.69)                                       | 2.6 (± 7.02)                                       |
| Week 192 (n =141, 145, 58, 53, 33, 38) | 2.9 (± 7.03)                                  | 3.4 (± 6.79)                                  | 2.9 (± 5.12)                                       | 3.8 (± 10.71)                                      |



|  |              |               |              |               |
|--|--------------|---------------|--------------|---------------|
| Week 240 (n =134, 136, 55, 53, 29, 34) | 3.4 (± 8.25) | 4.8 (± 9.39)  | 4.0 (± 7.52) | 4.9 (± 13.30) |
| Week 288 (n =88, 94, 30, 32, 6, 16)    | 2.7 (± 5.72) | 5.9 (± 12.02) | 4.5 (± 7.38) | 3.6 (± 4.51)  |

| End point values                       | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|--|--|--|--|--|
| Subject group type                     | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed            | 49   | 60   |  |  |
| Units: lesions                         |  |  |  |  |
| arithmetic mean (standard deviation)   |  |  |  |  |
| Week 48 (n =183, 184, 79, 76, 41, 48)  | 2.0 (± 4.22)                                       | 1.3 (± 2.64)                                       |  |  |
| Week 96 (n =171, 178, 75, 72, 39, 45)  | 3.0 (± 5.85)                                       | 1.9 (± 3.44)                                       |  |  |
| Week 144 (n =148, 155, 63, 53, 32, 41) | 3.1 (± 6.20)                                       | 2.9 (± 5.19)                                       |  |  |
| Week 192 (n =141, 145, 58, 53, 33, 38) | 3.3 (± 6.74)                                       | 3.0 (± 7.14)                                       |  |  |
| Week 240 (n =134, 136, 55, 53, 29, 34) | 4.0 (± 8.06)                                       | 4.2 (± 10.20)                                      |  |  |
| Week 288 (n =88, 94, 30, 32, 6, 16)    | 1.0 (± 1.10)                                       | 5.6 (± 6.81)                                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Volume of T1 Hypointense Lesions as Measured by Magnetic Resonance Imaging (MRI)

|                 |  |
|-----------------|--|
| End point title | Volume of T1 Hypointense Lesions as Measured by Magnetic Resonance Imaging (MRI) |
|-----------------|--|

End point description:

The T1 hypointense lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12, 2006-003697-10 or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Baseline up to Week 288

| End point values                     | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed          | 213   | 222   | 105  | 103  |
| Units: mm <sup>3</sup>               |   |   |  |  |
| arithmetic mean (standard deviation) |   |   |  |  |

|   |                    |                    |                    |                    |
|---|--------------------|--------------------|--------------------|--------------------|
| Baseline (n =209, 220, 104, 99, 47, 60) | 3640.1 (± 5598.31) | 3447.3 (± 4900.96) | 2754.2 (± 3552.30) | 3623.1 (± 5549.13) |
| Week 48 (n =190, 197, 83, 77, 40, 48)   | 3829.5 (± 5824.26) | 3715.5 (± 5112.21) | 2891.9 (± 3034.00) | 3936.0 (± 5271.89) |
| Week 96 (n =183, 186, 77, 73, 38, 46)   | 3841.2 (± 5682.74) | 3853.7 (± 5428.66) | 2921.0 (± 3327.93) | 3849.4 (± 5167.13) |
| Week 144 (n =157, 164, 67, 58, 33, 42)  | 3767.4 (± 4969.23) | 4074.0 (± 5413.85) | 3145.6 (± 3366.27) | 4006.9 (± 5062.08) |
| Week 192 (n =145, 149, 60, 54, 32, 38)  | 3834.9 (± 4942.19) | 4177.4 (± 5301.68) | 3385.4 (± 3575.44) | 4330.0 (± 5136.67) |
| Week 240 (n =135, 137, 55, 52, 28, 34)  | 4038.6 (± 5145.85) | 4238.2 (± 5248.84) | 3406.4 (± 3936.73) | 3823.9 (± 4274.82) |
| Week 288 (n =113, 121, 40, 45, 20, 29)  | 3603.3 (± 4394.60) | 3973.1 (± 5202.05) | 3350.6 (± 4140.34) | 4187.5 (± 4835.43) |

| End point values                        | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|---|--|--|--|--|
| Subject group type                      | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed             | 49   | 60   |  |  |
| Units: mm <sup>3</sup>                  |  |  |  |  |
| arithmetic mean (standard deviation)    |  |  |  |  |
| Baseline (n =209, 220, 104, 99, 47, 60) | 3204.3 (± 4221.55)                                 | 3572.6 (± 4915.24)                                 |  |  |
| Week 48 (n =190, 197, 83, 77, 40, 48)   | 3271.0 (± 4157.24)                                 | 3743.3 (± 5374.24)                                 |  |  |
| Week 96 (n =183, 186, 77, 73, 38, 46)   | 3510.4 (± 4672.80)                                 | 3949.7 (± 5018.63)                                 |  |  |
| Week 144 (n =157, 164, 67, 58, 33, 42)  | 3499.2 (± 4198.50)                                 | 4126.1 (± 5695.44)                                 |  |  |
| Week 192 (n =145, 149, 60, 54, 32, 38)  | 3592.0 (± 4069.39)                                 | 4089.3 (± 4996.13)                                 |  |  |
| Week 240 (n =135, 137, 55, 52, 28, 34)  | 3503.4 (± 3933.75)                                 | 4057.7 (± 5223.62)                                 |  |  |
| Week 288 (n =113, 121, 40, 45, 20, 29)  | 3264.9 (± 3639.91)                                 | 2959.1 (± 3918.62)                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change from Baseline in Brain Atrophy

|   |   |
|---|---|
| End point title   | Percent Change from Baseline in Brain Atrophy |
| End point description:  |   |
| Brain atrophy was measured using magnetic resonance imaging (MRI) technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10). |   |
| End point type  | Secondary                                     |
| End point timeframe:  |   |
| Baseline up to Week 288   |   |

| <b>End point values</b>                          | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                               | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed                      | 213   | 222   | 105  | 103  |
| Units: percent change                            |   |   |  |  |
| arithmetic mean (standard deviation)             |   |   |  |  |
| Change at Week 48 (n =162, 162, 56, 64, 33, 42)  | -1.206 (± 1.1006)                             | -1.263 (± 1.0848)                             | -1.487 (± 1.3086)                                  | -1.320 (± 1.4021)                                  |
| Change at Week 96 (n =144, 145, 50, 56, 30, 37)  | -1.372 (± 1.1382)                             | -1.500 (± 1.0893)                             | -1.589 (± 1.3630)                                  | -1.775 (± 1.7191)                                  |
| Change at Week 144 (n =122, 133, 44, 49, 28, 36) | -1.708 (± 1.4109)                             | -1.876 (± 1.2604)                             | -2.139 (± 1.5884)                                  | -2.353 (± 1.7897)                                  |
| Change at Week 192 (n =114, 120, 41, 45, 29, 36) | -2.138 (± 1.6831)                             | -2.117 (± 1.4000)                             | -2.230 (± 1.7755)                                  | -2.476 (± 1.7062)                                  |
| Change at Week 240 (n =92, 95, 37, 40, 18, 26)   | -2.313 (± 1.6309)                             | -2.253 (± 1.3721)                             | -2.271 (± 1.4817)                                  | -2.593 (± 1.9043)                                  |
| Change at Week 288 (n =71, 72, 25, 30, 15, 23)   | -2.216 (± 1.5744)                             | -2.271 (± 1.2193)                             | -2.470 (± 1.6757)                                  | -2.849 (± 1.9648)                                  |

| <b>End point values</b>                          | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|--|--|--|--|--|
| Subject group type                               | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed                      | 49   | 60   |  |  |
| Units: percent change                            |  |  |  |  |
| arithmetic mean (standard deviation)             |  |  |  |  |
| Change at Week 48 (n =162, 162, 56, 64, 33, 42)  | -1.496 (± 1.1316)                                  | -1.414 (± 1.1882)                                  |  |  |
| Change at Week 96 (n =144, 145, 50, 56, 30, 37)  | -1.883 (± 1.2383)                                  | -1.810 (± 1.4556)                                  |  |  |
| Change at Week 144 (n =122, 133, 44, 49, 28, 36) | -2.386 (± 1.3168)                                  | -2.252 (± 2.2124)                                  |  |  |
| Change at Week 192 (n =114, 120, 41, 45, 29, 36) | -2.645 (± 1.2284)                                  | -2.417 (± 2.0486)                                  |  |  |
| Change at Week 240 (n =92, 95, 37, 40, 18, 26)   | -2.249 (± 1.2985)                                  | -2.790 (± 2.2188)                                  |  |  |
| Change at Week 288 (n =71, 72, 25, 30, 15, 23)   | -2.657 (± 1.7051)                                  | -2.496 (± 1.3699)                                  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change from Baseline in Magnetization Transfer Ratio (MTR)

|                 |  |
|-----------------|--|
| End point title | Percent Change from Baseline in Magnetization Transfer Ratio |
|-----------------|--|

## End point description:

Magnetization Transfer Ratio (MTR) was measured using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12, 2006-003697-10 or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

## End point type

Secondary

## End point timeframe:

Baseline up to Week 288

| End point values                                 | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                               | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed                      | 213   | 222   | 105  | 103  |
| Units: percent change                            |   |   |  |  |
| arithmetic mean (standard deviation)             |   |   |  |  |
| Change at Week 48 (n =126, 118, 49, 56, 20, 23)  | -0.325 (± 5.4932)                             | -0.383 (± 4.8621)                             | 1.034 (± 7.3548)                                   | -0.567 (± 4.4766)                                  |
| Change at Week 96 (n =118, 113, 46, 50, 20, 20)  | -0.427 (± 6.6493)                             | -0.532 (± 4.9880)                             | 1.630 (± 7.6584)                                   | -0.947 (± 7.0771)                                  |
| Change at Week 144 (n =103, 107, 45, 37, 19, 24) | -0.042 (± 9.2548)                             | 0.509 (± 7.2692)                              | 1.525 (± 8.6421)                                   | 1.411 (± 12.2825)                                  |
| Change at Week 192 (n =100, 100, 42, 41, 25, 23) | 1.038 (± 10.8680)                             | 0.955 (± 8.6105)                              | 3.012 (± 9.3831)                                   | 3.103 (± 13.0046)                                  |
| Change at Week 240 (n =91, 90, 40, 42, 23, 20)   | -0.002 (± 15.6190)                            | 1.647 (± 8.3094)                              | 3.213 (± 9.6621)                                   | 4.108 (± 13.8103)                                  |
| Change at Week 288 (n =65, 71, 19, 25, 5, 14)    | 0.002 (± 4.0206)                              | -0.391 (± 4.6415)                             | -0.666 (± 2.0741)                                  | -0.622 (± 2.2922)                                  |

| End point values                                 | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|--|--|--|--|--|
| Subject group type                               | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed                      | 49   | 60   |  |  |
| Units: percent change                            |  |  |  |  |
| arithmetic mean (standard deviation)             |  |  |  |  |
| Change at Week 48 (n =126, 118, 49, 56, 20, 23)  | -0.081 (± 13.6416)                                 | -0.334 (± 1.5103)                                  |  |  |
| Change at Week 96 (n =118, 113, 46, 50, 20, 20)  | -4.269 (± 12.6065)                                 | 0.215 (± 1.4270)                                   |  |  |
| Change at Week 144 (n =103, 107, 45, 37, 19, 24) | -4.460 (± 10.3887)                                 | 3.119 (± 8.1676)                                   |  |  |
| Change at Week 192 (n =100, 100, 42, 41, 25, 23) | 1.384 (± 15.7611)                                  | 3.841 (± 10.8600)                                  |  |  |
| Change at Week 240 (n =91, 90, 40, 42, 23, 20)   | 2.959 (± 16.8386)                                  | 0.673 (± 25.9962)                                  |  |  |
| Change at Week 288 (n =65, 71, 19, 25, 5, 14)    | -0.466 (± 0.9410)                                  | -1.114 (± 2.4539)                                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Short Form-36 Health Survey (SF-36®) at Week 384

|  |  |
|--|--|
| End point title  | Change From Baseline in Short Form-36 Health Survey (SF-36®) at Week 384 |
| End point description:   |  |
| <p>The SF-36 is a brief (36-item) scale reflecting the impact of both dysfunctions and general health perception the questionnaire measures: 1.physical function (PF),2. role physical (RF),3. bodily pain (BP),4. role emotional (RE),5. social function (SF), 6. general health (GH),7. vitality (VT), 8. mental health (MH). Items 1-4 primarily contribute to the PCS score of the SF-36. Items 5-8 primarily contribute to the mental component summary (MCS) score of the SF-36. The questions related to each dimension are scored on a scale from 0 (worst score) to 100 (best score), with higher scores indicating better function. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).</p> |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline, Week 384   |  |

| End point values                               | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                             | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed                    | 501   | 502   | 249  | 248  |
| Units: score on a scale                        |   |   |  |  |
| arithmetic mean (standard deviation)           |   |   |  |  |
| Baseline: PF (n=494,487,244,240,115,112)       | 68.48 (± 25.938)                              | 71.78 (± 24.849)                              | 69.67 (± 24.481)                                   | 67.97 (± 26.279)                                   |
| Change at Week 384: PF (n=236,215,90,97,43,48) | 0.73 (± 21.972)                               | -4.79 (± 24.641)                              | -7.37 (± 22.253)                                   | -6.89 (± 23.194)                                   |
| Baseline: RF (n=494,486,244,238,114,112)       | 56.46 (± 41.254)                              | 58.42 (± 41.280)                              | 56.35 (± 40.896)                                   | 59.87 (± 41.747)                                   |
| Change at Week 384: RF (n=232,215,90,94,43,48) | 3.20 (± 48.259)                               | -2.75 (± 47.283)                              | -10.00 (± 43.188)                                  | -8.24 (± 53.177)                                   |
| Baseline: BP (n=494,490,244,240,115,112)       | 69.68 (± 25.587)                              | 70.42 (± 24.688)                              | 68.51 (± 26.163)                                   | 69.44 (± 26.016)                                   |
| Change at Week 384: BP (n=237,216,90,97,43,48) | 1.32 (± 28.525)                               | -1.47 (± 25.779)                              | -2.92 (± 23.486)                                   | -4.36 (± 25.935)                                   |
| Baseline: GH (n=493,489,240,238,115,110)       | 53.99 (± 21.563)                              | 55.44 (± 20.768)                              | 54.45 (± 18.690)                                   | 52.42 (± 20.028)                                   |
| Change at Week 384: GH (n=234,213,86,95,42,47) | 0.87 (± 18.744)                               | -2.12 (± 20.595)                              | -2.28 (± 16.752)                                   | -0.52 (± 22.035)                                   |

|   |                     |                     |                      |                     |
|---|---------------------|---------------------|----------------------|---------------------|
| Baseline: VT (n<br>=492,486,242,239,115,111)      | 50.48 (±<br>20.966) | 52.21 (±<br>19.842) | 50.63 (±<br>19.130)  | 50.64 (±<br>21.069) |
| Change at Week 384: VT<br>(n=235,214,87,96,41,47) | 1.11 (±<br>19.857)  | -0.73 (±<br>19.033) | -4.67 (±<br>17.934)  | 0.40 (±<br>20.822)  |
| Baseline: SF (n<br>=494,490,244,239,115,112)      | 71.46 (±<br>24.451) | 71.53 (±<br>24.394) | 69.67 (±<br>24.581)  | 72.23 (±<br>24.699) |
| Change at Week 384: SF<br>(n=237,216,90,96,43,48) | -2.16 (±<br>25.575) | -3.30 (±<br>24.912) | -5.69 (±<br>22.184)  | -2.08 (±<br>27.724) |
| Baseline: RE (n<br>=491,485,241,238,115,111)      | 64.87 (±<br>40.653) | 65.57 (±<br>40.015) | 62.86 (±<br>42.715)  | 62.61 (±<br>41.280) |
| Change at Week 384: RE<br>(n=233,214,90,96,43,47) | 0.43 (±<br>49.950)  | 0.47 (±<br>43.513)  | -12.22 (±<br>42.532) | 4.17 (±<br>44.656)  |
| Baseline: MH (n<br>=492,486,242,239,115,111)      | 65.01 (±<br>19.818) | 66.24 (±<br>19.060) | 65.42 (±<br>17.658)  | 65.15 (±<br>19.233) |
| Change at Week 384: MH<br>(n=235,214,87,96,41,47) | 1.32 (±<br>19.715)  | 2.31 (±<br>18.095)  | -3.91 (±<br>19.897)  | 2.33 (±<br>17.524)  |
| Baseline:MCS(n=488,480,237,235,114,<br>108)       | 45.40 (±<br>11.130) | 45.63 (±<br>10.272) | 45.13 (±<br>10.932)  | 45.31 (±<br>10.907) |
| Change at Week<br>384:MCS(n=226,211,85,92,41,45)  | 0.05 (±<br>12.415)  | 0.87 (±<br>10.028)  | -2.55 (±<br>10.328)  | 1.97 (±<br>10.657)  |
| Baseline:PCS(n=488,480,237,235,114,1<br>08)       | 43.53 (±<br>9.884)  | 44.44 (±<br>10.048) | 43.74 (±<br>9.739)   | 43.56 (±<br>10.267) |
| Change at Week 384:PCS<br>(n=226,211,85,92,41,45) | 0.55 (± 9.373)      | -1.94 (±<br>10.532) | -2.29 (±<br>8.929)   | -3.25 (±<br>9.998)  |

| End point values                                  | BG00012 240<br>mg BID (Prior<br>Glatiramer<br>Acetate [GA]) | BG00012 240<br>mg TID (Prior<br>Glatiramer<br>Acetate [GA]) |  |  |
|---|---|---|--|--|
| Subject group type                                | Subject analysis set  | Subject analysis set  |  |  |
| Number of subjects analysed                       | 118   | 118   |  |  |
| Units: score on a scale                           |   |   |  |  |
| arithmetic mean (standard deviation)              |   |   |  |  |
| Baseline: PF<br>(n=494,487,244,240,115,112)       | 69.10 (±<br>25.226)   | 68.20 (±<br>25.370)   |  |  |
| Change at Week 384: PF<br>(n=236,215,90,97,43,48) | -6.19 (±<br>21.719)   | -6.25 (±<br>28.350)   |  |  |
| Baseline: RF (n<br>=494,486,244,238,114,112)      | 55.26 (±<br>40.390)   | 53.57 (±<br>42.029)   |  |  |
| Change at Week 384: RF<br>(n=232,215,90,94,43,48) | -12.21 (±<br>40.595)  | -1.04 (±<br>54.568)   |  |  |
| Baseline: BP (n<br>=494,490,244,240,115,112)      | 69.30 (±<br>25.766)   | 68.59 (±<br>26.102)   |  |  |
| Change at Week 384: BP<br>(n=237,216,90,97,43,48) | -3.60 (±<br>22.138)   | -4.46 (±<br>33.297)   |  |  |
| Baseline: GH (n<br>=493,489,240,238,115,110)      | 51.21 (±<br>18.707)   | 52.58 (±<br>19.675)   |  |  |
| Change at Week 384: GH<br>(n=234,213,86,95,42,47) | -5.64 (±<br>18.270)   | 1.21 (±<br>21.674)  |  |  |
| Baseline: VT (n<br>=492,486,242,239,115,111)      | 51.30 (±<br>19.703)   | 50.33 (±<br>20.019)   |  |  |
| Change at Week 384: VT<br>(n=235,214,87,96,41,47) | -6.71 (±<br>20.236)   | 1.03 (±<br>19.829)  |  |  |
| Baseline: SF (n<br>=494,490,244,239,115,112)      | 69.02 (±<br>24.688)   | 69.53 (±<br>25.100)   |  |  |
| Change at Week 384: SF<br>(n=237,216,90,96,43,48) | -10.76 (±<br>34.350)  | -0.52 (±<br>25.780)   |  |  |

|  |                   |                  |  |  |
|--|-------------------|------------------|--|--|
| Baseline: RE (n =491,485,241,238,115,111)      | 60.29 (± 41.393)  | 64.26 (± 41.854) |  |  |
| Change at Week 384: RE (n=233,214,90,96,43,47) | -13.18 (± 42.501) | -3.55 (± 48.769) |  |  |
| Baseline: MH (n =492,486,242,239,115,111)      | 62.30 (± 17.347)  | 63.61 (± 18.414) |  |  |
| Change at Week 384: MH (n=235,214,87,96,41,47) | -0.29 (± 21.989)  | -2.06 (± 20.066) |  |  |
| Baseline:MCS(n=488,480,237,235,114,108)        | 44.00 (± 10.702)  | 45.03 (± 10.642) |  |  |
| Change at Week 384:MCS(n=226,211,85,92,41,45)  | -2.59 (± 12.895)  | 0.08 (± 10.328)  |  |  |
| Baseline:PCS(n=488,480,237,235,114,108)        | 43.68 (± 10.359)  | 43.15 (± 10.091) |  |  |
| Change at Week 384:PCS (n=226,211,85,92,41,45) | -2.70 (± 8.860)   | -1.59 (± 10.765) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D) Health Survey - EQ-5D Index Score at Week 384

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D) Health Survey - EQ-5D Index Score at Week 384 |
|-----------------|--|

End point description:

The EQ-5D is a generic health-related quality of life instrument consisting of 2 components, EQ-5D index score and EQ-VAS. The EQ-5D provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject is instructed to indicate whether he or she has (1) "no problems", (2) "some problems", or (3) "severe problems". A positive change from baseline indicates improvement. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Baseline, Week 384

| End point values                                 | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                               | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed                      | 501   | 502   | 249  | 248  |
| Units: score on a scale                          |   |   |  |  |
| arithmetic mean (standard deviation)             |   |   |  |  |
| Baseline (n =488, 484, 239, 239, 115, 112)       | 0.73 (± 0.210)                                | 0.73 (± 0.222)                                | 0.72 (± 0.223)                                     | 0.71 (± 0.244)                                     |
| Change at Week 384 (n =230, 212, 86, 96, 42, 48) | 0.01 (± 0.251)                                | 0.00 (± 0.233)                                | -0.07 (± 0.269)                                    | 0.00 (± 0.249)                                     |

| End point values                                 | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|--|--|--|--|--|
| Subject group type                               | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed                      | 118  | 118  |  |  |
| Units: score on a scale                          |  |  |  |  |
| arithmetic mean (standard deviation)             |  |  |  |  |
| Baseline (n =488, 484, 239, 239, 115, 112)       | 0.71 (± 0.246)                                     | 0.72 (± 0.189)                                     |  |  |
| Change at Week 384 (n =230, 212, 86, 96, 42, 48) | -0.04 (± 0.253)                                    | -0.03 (± 0.241)                                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D) Health Survey - Visual Analog Scale (VAS) at Week 384

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D) Health Survey - Visual Analog Scale (VAS) at Week 384 |
|-----------------|--|

End point description:

The EQ-5D is a generic health-related quality of life instrument consisting of 2 components, EQ-5D index score and EQ-VAS. In EQ-VAS subjects are asked to rate their current health on a 20 centimetre (cm) scale from 0 to 100 where 0 represents "worst imaginable health state" and 100 represents "best imaginable health state". A positive change from baseline indicates improvement. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

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

End point timeframe:

Baseline, Week 384

| End point values                                 | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                               | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed                      | 501   | 502   | 249  | 248  |
| Units: score on a scale                          |   |   |  |  |
| arithmetic mean (standard deviation)             |   |   |  |  |
| Baseline (n =492, 488, 243, 238, 113, 112)       | 70.97 (± 18.460)                              | 70.48 (± 19.993)                              | 70.40 (± 17.630)                                   | 69.44 (± 19.907)                                   |
| Change at Week 384 (n =235, 215, 91, 95, 42, 48) | -0.48 (± 19.631)                              | -1.67 (± 18.855)                              | -7.24 (± 18.419)                                   | -3.17 (± 22.003)                                   |



| End point values                                 | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|--|--|--|--|--|
| Subject group type                               | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed                      | 118  | 118  |  |  |
| Units: score on a scale                          |  |  |  |  |
| arithmetic mean (standard deviation)             |  |  |  |  |
| Baseline (n =492, 488, 243, 238, 113, 112)       | 66.80 (± 18.846)                                   | 69.07 (± 20.094)                                   |  |  |
| Change at Week 384 (n =235, 215, 91, 95, 42, 48) | -1.71 (± 25.330)                                   | -4.11 (± 16.270)                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Visual Function Test Scores at Week 384

|   |   |
|---|---|
| End point title   | Change From Baseline in Visual Function Test Scores at Week 384 |
| End point description:  |   |
| Subjects were tested using the contrast level of 100%, 2.5%, and 1.25% charts, and the scores were defined as the number of letters identified correctly for each chart (the maximum score was 60). Higher scores indicate better functioning. A positive change from baseline indicates better functioning. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10). |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Baseline, Week 384  |   |

| End point values                               | BG00012 240 mg BID (Prior BG00012 240 mg BID) | BG00012 240 mg TID (Prior BG00012 240 mg TID) | BG00012 240 mg BID (Prior BG00012 Matched Placebo) | BG00012 240 mg TID (Prior BG00012 Matched Placebo) |
|--|---|---|--|--|
| Subject group type                             | Subject analysis set                          | Subject analysis set                          | Subject analysis set                               | Subject analysis set                               |
| Number of subjects analysed                    | 501   | 502   | 249  | 248  |
| Units: score on a scale                        |   |   |  |  |
| arithmetic mean (standard deviation)           |   |   |  |  |
| Baseline:100%Chart (n=501,502,249,248,118,118) | 54.7 (± 7.95)                                 | 55.0 (± 7.84)                                 | 55.1 (± 7.26)                                      | 54.8 (± 7.12)                                      |
| Change at Week384:100%Chart(n=231,216,87,99)   | -0.4 (± 6.76)                                 | -1.9 (± 6.81)                                 | -1.4 (± 8.48)                                      | -1.2 (± 7.53)                                      |
| Baseline:2.5%Chart(n=501,502,249,248,118,118)  | 32.4 (± 12.17)                                | 32.6 (± 11.76)                                | 32.4 (± 11.42)                                     | 32.3 (± 11.99)                                     |
| Change at Week384:2.5%Chart(n=231,216,87,99,   | -2.4 (± 10.77)                                | -3.3 (± 10.43)                                | -1.5 (± 11.77)                                     | -4.9 (± 11.14)                                     |

|   |                                  |                                  |                                  |                                  |
|---|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Baseline:1.25%Chart(n=501,502,249,248,118,118)<br>Change atWeek384:1.25%Chart(n=231,216,87, | 24.1 (± 12.45)<br>-5.8 (± 13.39) | 24.2 (± 12.28)<br>-6.0 (± 11.77) | 23.8 (± 12.11)<br>-4.1 (± 13.04) | 23.7 (± 12.96)<br>-7.4 (± 12.42) |
|---|----------------------------------|----------------------------------|----------------------------------|----------------------------------|

| End point values  | BG00012 240 mg BID (Prior Glatiramer Acetate [GA]) | BG00012 240 mg TID (Prior Glatiramer Acetate [GA]) |  |  |
|---|--|--|--|--|
| Subject group type  | Subject analysis set                               | Subject analysis set                               |  |  |
| Number of subjects analysed   | 118  | 118  |  |  |
| Units: score on a scale   |  |  |  |  |
| arithmetic mean (standard deviation)  |  |  |  |  |
| Baseline:100%Chart (n=501,502,249,248,118,118)<br>Change at Week384:100%Chart(n=231,216,87,99 | 54.3 (± 8.26)<br>-1.6 (± 8.05)                     | 55.0 (± 6.73)<br>-0.7 (± 5.17)                     |  |  |
| Baseline:2.5%Chart(n=501,502,249,248,118,118)<br>Change at Week384:2.5%Chart(n=231,216,87,99, | 31.8 (± 12.36)<br>-4.0 (± 11.90)                   | 31.7 (± 12.41)<br>-2.1 (± 9.86)                    |  |  |
| Baseline:1.25%Chart(n=501,502,249,248,118,118)<br>Change atWeek384:1.25%Chart(n=231,216,87,   | 23.4 (± 11.76)<br>-6.7 (± 13.78)                   | 22.2 (± 13.25)<br>-5.0 (± 12.74)                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of the study up to follow-up (Day 1 up to Week 561)

Adverse event reporting additional description:

Safety population included all subjects who had any post-baseline safety follow-up in study 2008-004753-14, defined as any treatment emergent AE in study 2008-004753-14 or any post-baseline laboratory, vital signs, or physical exam assessment in study 2008-004753-14, and received at least one dose of study treatment in study 2008-004753-14.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 13.1 |
|--------------------|------|

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | BG00012 240 mg BID |
|-----------------------|--------------------|

Reporting group description:

Subjects received BG00012 240 mg (120 mg each) capsules orally, BID and 2 matching placebo capsules QD up to 8 years.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | BG00012 240 mg TID |
|-----------------------|--------------------|

Reporting group description:

Subjects received BG00012 240 mg (120 mg each) capsules orally, TID up to 8 years.

| Serious adverse events  | BG00012 240 mg<br>BID | BG00012 240 mg<br>TID |  |
|---|-----------------------|-----------------------|--|
| Total subjects affected by serious adverse events                   |                       |                       |  |
| subjects affected / exposed   | 279 / 868 (32.14%)    | 272 / 868 (31.34%)    |  |
| number of deaths (all causes)                                       | 5                     | 6                     |  |
| number of deaths resulting from adverse events                      | 0                     | 0                     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                       |                       |  |
| Adenolymphoma   |                       |                       |  |
| subjects affected / exposed   | 0 / 868 (0.00%)       | 1 / 868 (0.12%)       |  |
| occurrences causally related to treatment / all                     | 0 / 0                 | 0 / 1                 |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0                 |  |
| Anal cancer   |                       |                       |  |
| subjects affected / exposed   | 2 / 868 (0.23%)       | 0 / 868 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 1 / 2                 | 0 / 0                 |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0                 |  |
| Basal cell carcinoma  |                       |                       |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 868 (0.35%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Benign breast neoplasm                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bowenoid papulosis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain cancer metastatic                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cancer                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 868 (0.46%) | 8 / 868 (0.92%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 2 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cancer in situ                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cancer stage II                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast neoplasm                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carcinoid tumour of the pancreas                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervix neoplasm                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic myeloid leukaemia                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endometrial cancer                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fibroma   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Glioma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemangioma                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leiomyoma                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung adenocarcinoma stage II                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung squamous cell carcinoma stage unspecified  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant melanoma                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningioma                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mesothelioma malignant                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic malignant melanoma                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic neoplasm                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic carcinoma                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngeal neoplasm benign                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal cancer                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cell carcinoma                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 868 (0.35%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Salivary gland cancer                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of the cervix           |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous endometrial carcinoma                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thyroid cancer                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transitional cell carcinoma                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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                     | 6 / 868 (0.69%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Circulatory collapse                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Venous thrombosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Venous thrombosis limb                          |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Abdominoplasty                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic valve replacement                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicectomy                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder neck suspension                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bunion operation                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Caesarean section                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carpal tunnel decompression                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystectomy                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cochlea implant                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystocele repair                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Female sterilisation                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip arthroplasty                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hysterectomy                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Knee arthroplasty                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mammoplasty                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Medical device change                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Medical device removal                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Percutaneous coronary intervention              |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative care                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgery   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thyroidectomy                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia repair                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Varicose vein operation                         |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pregnancy, puerperium and perinatal conditions       |                 |                 |  |
| Abortion missed                                      |                 |                 |  |
| subjects affected / exposed                          | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Abortion spontaneous                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Complication of pregnancy                            |                 |                 |  |
| subjects affected / exposed                          | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Capsular contracture associated with breast implant  |                 |                 |  |
| subjects affected / exposed                          | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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                          | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Impaired healing                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                     | 3 / 868 (0.35%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Serositis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Treatment failure                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Anaphylactic reaction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug hypersensitivity                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Breast necrosis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervical dysplasia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystocele                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysfunctional uterine bleeding                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endometrial hyperplasia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 0 / 868 (0.00%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fibrocystic breast disease                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Menorrhagia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metrorrhagia                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian cyst                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian cyst ruptured                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic adhesions                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic pain                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterine polyp                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Choking   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paranasal cyst                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleurisy  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary artery thrombosis                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary sarcoidosis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Acute psychosis                                 |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alcoholism                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anorexia nervosa                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anxiety disorder                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Burnout syndrome                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Catatonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Completed suicide                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Delirium  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Depression                                      |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                      | 0 / 868 (0.00%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Drug abuse                                       |                 |                 |  |
| subjects affected / exposed                      | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Hallucination                                    |                 |                 |  |
| subjects affected / exposed                      | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Major depression                                 |                 |                 |  |
| subjects affected / exposed                      | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Mood disorder due to a general medical condition |                 |                 |  |
| subjects affected / exposed                      | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Morbid thoughts                                  |                 |                 |  |
| subjects affected / exposed                      | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Neurosis   |                 |                 |  |
| subjects affected / exposed                      | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Psychiatric decompensation                       |                 |                 |  |
| subjects affected / exposed                      | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Psychotic behaviour                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                           | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Psychotic disorder                                    |                 |                 |  |
| subjects affected / exposed                           | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Psychotic disorder due to a general medical condition |                 |                 |  |
| subjects affected / exposed                           | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Stress  |                 |                 |  |
| subjects affected / exposed                           | 1 / 868 (0.12%) | 0 / 868 (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                           | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                               |                 |                 |  |
| Bile duct stone                                       |                 |                 |  |
| subjects affected / exposed                           | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Biliary colic   |                 |                 |  |
| subjects affected / exposed                           | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Cholecystitis   |                 |                 |  |
| subjects affected / exposed                           | 3 / 868 (0.35%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all       | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis chronic                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 7 / 868 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic hepatitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Anticoagulation drug level above therapeutic    |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigation                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphocyte count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Accident  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Accident at work                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acetabulum fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Animal bite                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ankle fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Avulsion fracture                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain contusion                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clavicle fracture                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Comminuted fracture                             |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%)  | 1 / 868 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Concussion                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 868 (0.00%)  | 1 / 868 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Contusion                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 868 (0.35%)  | 1 / 868 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug toxicity                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 868 (0.00%)  | 1 / 868 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fall  |                  |                  |  |
| subjects affected / exposed                     | 13 / 868 (1.50%) | 18 / 868 (2.07%) |  |
| occurrences causally related to treatment / all | 0 / 16           | 0 / 19           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral neck fracture                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 868 (0.35%)  | 4 / 868 (0.46%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femur fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 868 (0.35%)  | 0 / 868 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibula fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 868 (0.00%)  | 3 / 868 (0.35%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot fracture                                   |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hand fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 4 / 868 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incision site haematoma                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incisional hernia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint injury                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint sprain                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ligament injury                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ligament rupture                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar vertebral fracture                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meniscus lesion                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multiple injuries                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscle rupture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Overdose  |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative hernia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pubis fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radius fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 868 (0.35%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory fume inhalation disorder            |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 4 / 868 (0.46%) | 5 / 868 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skeletal injury                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Splenic rupture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 5 / 868 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ulna fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Cytogenetic abnormality                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Limb malformation                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mitral valve prolapse                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 5 / 868 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wolff-parkinson-white syndrome                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular insufficiency                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Complex partial seizures                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Convulsion                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 868 (0.35%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dementia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disturbance in attention                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysarthria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hemiparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoaesthesia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracranial aneurysm                           |                 |                 |  |

|   |                    |                    |
|---|--------------------|--------------------|
| subjects affected / exposed                     | 1 / 868 (0.12%)    | 0 / 868 (0.00%)    |
| occurrences causally related to treatment / all | 0 / 1              | 0 / 0              |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |
| Lumbar radiculopathy                            |                    |                    |
| subjects affected / exposed                     | 0 / 868 (0.00%)    | 1 / 868 (0.12%)    |
| occurrences causally related to treatment / all | 0 / 0              | 0 / 1              |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |
| Migraine  |                    |                    |
| subjects affected / exposed                     | 1 / 868 (0.12%)    | 1 / 868 (0.12%)    |
| occurrences causally related to treatment / all | 1 / 1              | 0 / 1              |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |
| Multiple sclerosis                              |                    |                    |
| subjects affected / exposed                     | 4 / 868 (0.46%)    | 2 / 868 (0.23%)    |
| occurrences causally related to treatment / all | 0 / 4              | 0 / 2              |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |
| Multiple sclerosis relapse                      |                    |                    |
| subjects affected / exposed                     | 116 / 868 (13.36%) | 122 / 868 (14.06%) |
| occurrences causally related to treatment / all | 3 / 229            | 9 / 217            |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |
| Muscle spasticity                               |                    |                    |
| subjects affected / exposed                     | 1 / 868 (0.12%)    | 0 / 868 (0.00%)    |
| occurrences causally related to treatment / all | 0 / 1              | 0 / 0              |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |
| Neuralgia                                       |                    |                    |
| subjects affected / exposed                     | 1 / 868 (0.12%)    | 2 / 868 (0.23%)    |
| occurrences causally related to treatment / all | 0 / 1              | 0 / 2              |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |
| Optic neuritis                                  |                    |                    |
| subjects affected / exposed                     | 0 / 868 (0.00%)    | 2 / 868 (0.23%)    |
| occurrences causally related to treatment / all | 0 / 0              | 0 / 2              |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |
| Paraesthesia                                    |                    |                    |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parkinson's disease                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Quadriparesis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radiculitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient global amnesia                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Trigeminal neuralgia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uhthoff's phenomenon                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eosinophilia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Iron deficiency anaemia                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphopenia                                     |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Hypoacusis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden hearing loss                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertigo positional                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Cataract  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Glaucoma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinal ischaemia                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ulcerative keratitis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vision blurred                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal hernia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis ulcerative                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Crohn's disease                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer perforation                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 2 / 868 (0.23%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal inflammation                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal mucosal disorder               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal necrosis                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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 / 868 (0.12%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal haemorrhage                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subileus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Volvulus  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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          |                 |                 |  |
| Decubitus ulcer                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermatitis allergic                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrotic syndrome                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neurogenic bladder                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Autoimmune thyroiditis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Basedow's disease                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Goitre  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperthyroidism                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 4 / 868 (0.46%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bursitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chondropathy                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foot deformity                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc degeneration                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc disorder                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 5 / 868 (0.58%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myositis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 5 / 868 (0.58%) | 4 / 868 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periarthritis                                   |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rotator cuff syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal deformity                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spondylolisthesis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Synovitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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                     | 2 / 868 (0.23%) | 4 / 868 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteriuria                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopulmonary aspergillosis                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (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                     | 2 / 868 (0.23%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic sinusitis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 2 / 868 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic tonsillitis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dengue fever                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea infectious                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endometritis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis norovirus                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis rotavirus                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal bacterial infection            |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Genital herpes                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematoma infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes simplex                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 3 / 868 (0.35%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infected skin ulcer                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nasopharyngitis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal candidiasis                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oral candidiasis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Papilloma viral infection                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic abscess                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonsillar abscess                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonsillitis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 6 / 868 (0.69%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 1 / 7           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia bacterial                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural infection                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary tuberculoma                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| 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                     | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis chronic                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyothorax                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal abscess                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection viral               |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 868 (0.12%)  | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Scrub typhus                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%)  | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Septic shock                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%)  | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sinusitis                                       |                  |                 |  |
| subjects affected / exposed                     | 2 / 868 (0.23%)  | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Subcutaneous abscess                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%)  | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Tooth abscess                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%)  | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Upper respiratory tract infection               |                  |                 |  |
| subjects affected / exposed                     | 1 / 868 (0.12%)  | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urinary tract infection                         |                  |                 |  |
| subjects affected / exposed                     | 10 / 868 (1.15%) | 4 / 868 (0.46%) |  |
| occurrences causally related to treatment / all | 1 / 11           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urosepsis                                       |                  |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                      | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Vaginal infection                                |                 |                 |  |
| subjects affected / exposed                      | 1 / 868 (0.12%) | 0 / 868 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Vestibular neuronitis                            |                 |                 |  |
| subjects affected / exposed                      | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Viral infection                                  |                 |                 |  |
| subjects affected / exposed                      | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Progressive multifocal leukoencephalopathy (PML) |                 |                 |  |
| subjects affected / exposed                      | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders               |                 |                 |  |
| Dehydration                                      |                 |                 |  |
| subjects affected / exposed                      | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                                |                 |                 |  |
| subjects affected / exposed                      | 1 / 868 (0.12%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                   |                 |                 |  |
| subjects affected / exposed                      | 0 / 868 (0.00%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Obesity  |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 868 (0.23%) | 1 / 868 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | BG00012 240 mg<br>BID | BG00012 240 mg<br>TID |  |
|---|-----------------------|-----------------------|--|
| Total subjects affected by non-serious adverse events |                       |                       |  |
| subjects affected / exposed                           | 779 / 868 (89.75%)    | 767 / 868 (88.36%)    |  |
| Vascular disorders                                    |                       |                       |  |
| Flushing  |                       |                       |  |
| subjects affected / exposed                           | 170 / 868 (19.59%)    | 165 / 868 (19.01%)    |  |
| occurrences (all)                                     | 264                   | 227                   |  |
| Hot flush   |                       |                       |  |
| subjects affected / exposed                           | 44 / 868 (5.07%)      | 53 / 868 (6.11%)      |  |
| occurrences (all)                                     | 62                    | 71                    |  |
| Hypertension  |                       |                       |  |
| subjects affected / exposed                           | 51 / 868 (5.88%)      | 43 / 868 (4.95%)      |  |
| occurrences (all)                                     | 60                    | 46                    |  |
| General disorders and administration site conditions  |                       |                       |  |
| Fatigue   |                       |                       |  |
| subjects affected / exposed                           | 100 / 868 (11.52%)    | 102 / 868 (11.75%)    |  |
| occurrences (all)                                     | 126                   | 139                   |  |
| Pyrexia   |                       |                       |  |
| subjects affected / exposed                           | 47 / 868 (5.41%)      | 43 / 868 (4.95%)      |  |
| occurrences (all)                                     | 62                    | 55                    |  |
| Respiratory, thoracic and mediastinal disorders       |                       |                       |  |
| Cough   |                       |                       |  |
| subjects affected / exposed                           | 54 / 868 (6.22%)      | 66 / 868 (7.60%)      |  |
| occurrences (all)                                     | 71                    | 82                    |  |
| Psychiatric disorders                                 |                       |                       |  |
| Anxiety   |                       |                       |  |
| subjects affected / exposed                           | 31 / 868 (3.57%)      | 46 / 868 (5.30%)      |  |
| occurrences (all)                                     | 37                    | 54                    |  |
| Depression  |                       |                       |  |

|   |                           |                           |  |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 102 / 868 (11.75%)<br>125 | 87 / 868 (10.02%)<br>114  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 52 / 868 (5.99%)<br>59    | 51 / 868 (5.88%)<br>59    |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)      | 53 / 868 (6.11%)<br>74    | 59 / 868 (6.80%)<br>80    |  |
| Albumin urine present<br>subjects affected / exposed<br>occurrences (all)                                     | 66 / 868 (7.60%)<br>107   | 62 / 868 (7.14%)<br>86    |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                                | 56 / 868 (6.45%)<br>85    | 42 / 868 (4.84%)<br>71    |  |
| Injury, poisoning and procedural<br>complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 60 / 868 (6.91%)<br>113   | 63 / 868 (7.26%)<br>108   |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                     | 60 / 868 (6.91%)<br>86    | 45 / 868 (5.18%)<br>61    |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 145 / 868 (16.71%)<br>247 | 131 / 868 (15.09%)<br>205 |  |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)   | 64 / 868 (7.37%)<br>86    | 49 / 868 (5.65%)<br>78    |  |
| Multiple sclerosis relapse<br>subjects affected / exposed<br>occurrences (all)                                | 324 / 868 (37.33%)<br>724 | 335 / 868 (38.59%)<br>769 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)  | 57 / 868 (6.57%)<br>78    | 59 / 868 (6.80%)<br>72    |  |
| Blood and lymphatic system disorders  |                           |                           |  |

|  |                           |                           |  |
|--|---------------------------|---------------------------|--|
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)          | 52 / 868 (5.99%)<br>83    | 42 / 868 (4.84%)<br>59    |  |
| Gastrointestinal disorders   |                           |                           |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 50 / 868 (5.76%)<br>75    | 55 / 868 (6.34%)<br>67    |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 69 / 868 (7.95%)<br>90    | 76 / 868 (8.76%)<br>108   |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 111 / 868 (12.79%)<br>159 | 118 / 868 (13.59%)<br>162 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 56 / 868 (6.45%)<br>71    | 61 / 868 (7.03%)<br>77    |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 42 / 868 (4.84%)<br>52    | 45 / 868 (5.18%)<br>54    |  |
| Skin and subcutaneous tissue disorders                                   |                           |                           |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)             | 47 / 868 (5.41%)<br>57    | 32 / 868 (3.69%)<br>36    |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)             | 50 / 868 (5.76%)<br>61    | 38 / 868 (4.38%)<br>50    |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                 | 45 / 868 (5.18%)<br>68    | 40 / 868 (4.61%)<br>53    |  |
| Renal and urinary disorders  |                           |                           |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)           | 49 / 868 (5.65%)<br>71    | 61 / 868 (7.03%)<br>90    |  |
| Microalbuminuria<br>subjects affected / exposed<br>occurrences (all)     | 55 / 868 (6.34%)<br>78    | 61 / 868 (7.03%)<br>103   |  |
| Proteinuria  |                           |                           |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 76 / 868 (8.76%)<br>108 | 81 / 868 (9.33%)<br>127 |  |
| Musculoskeletal and connective tissue disorders  |                         |                         |  |
| Arthralgia                                       |                         |                         |  |
| subjects affected / exposed                      | 97 / 868 (11.18%)       | 115 / 868 (13.25%)      |  |
| occurrences (all)                                | 146                     | 169                     |  |
| Back pain  |                         |                         |  |
| subjects affected / exposed                      | 125 / 868 (14.40%)      | 125 / 868 (14.40%)      |  |
| occurrences (all)                                | 179                     | 170                     |  |
| Muscle spasms                                    |                         |                         |  |
| subjects affected / exposed                      | 38 / 868 (4.38%)        | 49 / 868 (5.65%)        |  |
| occurrences (all)                                | 46                      | 78                      |  |
| Musculoskeletal pain                             |                         |                         |  |
| subjects affected / exposed                      | 35 / 868 (4.03%)        | 49 / 868 (5.65%)        |  |
| occurrences (all)                                | 42                      | 59                      |  |
| Pain in extremity                                |                         |                         |  |
| subjects affected / exposed                      | 102 / 868 (11.75%)      | 92 / 868 (10.60%)       |  |
| occurrences (all)                                | 157                     | 128                     |  |
| Infections and infestations                      |                         |                         |  |
| Bronchitis                                       |                         |                         |  |
| subjects affected / exposed                      | 82 / 868 (9.45%)        | 98 / 868 (11.29%)       |  |
| occurrences (all)                                | 121                     | 150                     |  |
| Gastroenteritis                                  |                         |                         |  |
| subjects affected / exposed                      | 52 / 868 (5.99%)        | 33 / 868 (3.80%)        |  |
| occurrences (all)                                | 65                      | 40                      |  |
| Herpes zoster                                    |                         |                         |  |
| subjects affected / exposed                      | 47 / 868 (5.41%)        | 38 / 868 (4.38%)        |  |
| occurrences (all)                                | 51                      | 43                      |  |
| Influenza  |                         |                         |  |
| subjects affected / exposed                      | 87 / 868 (10.02%)       | 67 / 868 (7.72%)        |  |
| occurrences (all)                                | 113                     | 87                      |  |
| Nasopharyngitis                                  |                         |                         |  |
| subjects affected / exposed                      | 220 / 868 (25.35%)      | 226 / 868 (26.04%)      |  |
| occurrences (all)                                | 564                     | 528                     |  |
| Pharyngitis                                      |                         |                         |  |

|                                   |                    |                    |  |
|-----------------------------------|--------------------|--------------------|--|
| subjects affected / exposed       | 44 / 868 (5.07%)   | 50 / 868 (5.76%)   |  |
| occurrences (all)                 | 63                 | 62                 |  |
| Sinusitis                         |                    |                    |  |
| subjects affected / exposed       | 65 / 868 (7.49%)   | 63 / 868 (7.26%)   |  |
| occurrences (all)                 | 107                | 128                |  |
| Upper respiratory tract infection |                    |                    |  |
| subjects affected / exposed       | 143 / 868 (16.47%) | 136 / 868 (15.67%) |  |
| occurrences (all)                 | 296                | 253                |  |
| Urinary tract infection           |                    |                    |  |
| subjects affected / exposed       | 196 / 868 (22.58%) | 164 / 868 (18.89%) |  |
| occurrences (all)                 | 394                | 319                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 15 September 2010 | Extension of the duration of the study from 2 years to 5 years or marketing authorization (if approved), whichever occurs first.   |
| 17 March 2014     | Extended the study duration for each subject from 5 years to 8 years and to change the dosing regimen from dose-blind dosing with BG00012 240 mg twice a day (BID) or three times a day (TID) to open-label dosing with BG00012 at a dose of 240 mg BID for all subjects.  |
| 02 September 2014 | Updated the safety reporting information.  |
| 16 November 2014  | Progressive multifocal leukoencephalopathy (PML) has occurred in the setting of severe, prolonged lymphopenia following BG00012 administration. Severe, prolonged lymphopenia is a known risk factor for PML. In the controlled and uncontrolled BG00012 clinical studies, 2% of subjects experienced lymphocyte counts $<0.5 \times 10^9$ per litre (/L) for at least six months. In these subjects, the majority of lymphocyte counts remained $<0.5 \times 10^9$ /L with continued therapy. The study protocol is being amended to enable the early identification of subjects who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on the management of such subjects. |
| 21 January 2016   | - Extended the study duration by an additional 4 years to collect data on long-term efficacy and safety of BG00012. - Increased the minimal duration of follow-up for lymphopenic subjects upon discontinuation of treatment with BG00012, per Committee for Medicinal Products for Human Use (CHMP) recommendations.  |
| 07 November 2016  | Removed the discontinuation criteria of elevated serum creatinine (either $>1.2 \times$ baseline serum creatinine or $>1.2 \times$ upper limit of normal [ULN]), positive urinalysis, and low white blood cell (WBC) count.  |
| 05 February 2018  | Changed the length of the study from 12 years to 8 years.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported