



## Clinical trial results:

### Multicenter, Randomized, Double-blind, Placebo-controlled Study to Compare the Efficacy and Safety of Romosozumab With Placebo in Men With Osteoporosis

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-005551-32 |
| Trial protocol           | CZ BE DK PL    |
| Global end of trial date | 20 April 2016  |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 13 April 2017 |
| First version publication date | 13 April 2017 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20110174 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02186171 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Amgen Inc.  |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, United States, 91320                           |
| Public contact               | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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                       | 20 April 2016 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 20 April 2016 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of treatment with romosozumab for 12 months compared with placebo on percent changes from baseline in bone mineral density (BMD) at the lumbar spine as assessed by dual-energy x-ray absorptiometry (DXA) in men with osteoporosis.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 16 June 2014 |
| 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: 47             |
| Country: Number of subjects enrolled | Czech Republic: 27     |
| Country: Number of subjects enrolled | Denmark: 35            |
| Country: Number of subjects enrolled | Belgium: 18            |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Switzerland: 15        |
| Country: Number of subjects enrolled | Colombia: 35           |
| Country: Number of subjects enrolled | Japan: 27              |
| Country: Number of subjects enrolled | United States: 21      |
| Worldwide total number of subjects   | 245                    |
| EEA total number of subjects         | 127                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 42  |
| From 65 to 84 years                       | 197 |
| 85 years and over                         | 6   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 31 centers in Europe, North America, Latin America, and Japan. Participants were enrolled from 16 June 2014 to 27 January 2015.

### Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to receive 210 mg romosozumab or matched placebo in a blinded fashion for the duration of the 12-month treatment period. Randomization was stratified by geographic region (Europe, North America, Latin America, and Japan).

### 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          |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Participants received placebo subcutaneous injections once a month (QM) for 12 months.

|  |  |
|--|--|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Administered by subcutaneous injection once a month

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Romosozumab |
|------------------|-------------|

Arm description:

Participants received 210 mg romosozumab administered by subcutaneous injection once a month for 12 months.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Romosozumab                                  |
| Investigational medicinal product code | AMG 785                                      |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Administered by subcutaneous injection once a month

| <b>Number of subjects in period 1</b> | Placebo | Romosozumab |
|---------------------------------------|---------|-------------|
| Started                               | 82      | 163         |
| Received Treatment                    | 81      | 163         |
| Completed                             | 78      | 148         |
| Not completed                         | 4       | 15          |
| Consent withdrawn by subject          | 1       | 9           |
| Death                                 | 1       | 2           |
| Lost to follow-up                     | 2       | 2           |
| Protocol-specified criteria           | -       | 2           |

## Baseline characteristics

### Reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Placebo     |
| Reporting group description:  |             |
| Participants received placebo subcutaneous injections once a month (QM) for 12 months.                      |             |
| Reporting group title   | Romosozumab |
| Reporting group description:  |             |
| Participants received 210 mg romosozumab administered by subcutaneous injection once a month for 12 months. |             |

| Reporting group values  | Placebo | Romosozumab | Total |
|---|---------|-------------|-------|
| Number of subjects  | 82      | 163         | 245   |
| Age Categorical   |         |             |       |
| Units: Subjects   |         |             |       |
| Adults (18-64 years)  | 11      | 31          | 42    |
| From 65-74 years  | 42      | 62          | 104   |
| 75 years and over   | 29      | 70          | 99    |
| Age Continuous  |         |             |       |
| Units: years  |         |             |       |
| arithmetic mean   | 71.5    | 72.4        | -     |
| standard deviation  | ± 6.9   | ± 7.4       | -     |
| Gender Categorical  |         |             |       |
| Units: Subjects   |         |             |       |
| Female  | 0       | 0           | 0     |
| Male  | 82      | 163         | 245   |
| Race  |         |             |       |
| Units: Subjects   |         |             |       |
| White   | 60      | 120         | 180   |
| Asian   | 9       | 18          | 27    |
| Black or African American   | 0       | 1           | 1     |
| Other   | 13      | 23          | 36    |
| Multiple  | 0       | 1           | 1     |
| Geographic Region   |         |             |       |
| Units: Subjects   |         |             |       |
| Europe  | 54      | 108         | 162   |
| Japan   | 9       | 18          | 27    |
| Latin America   | 12      | 23          | 35    |
| North America   | 7       | 14          | 21    |
| Lumbar Spine BMD T-score  |         |             |       |
| The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old. Normal is a T-score of -1.0 or higher; Osteopenia is defined as between -1.0 and -2.5; Osteoporosis is defined as -2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman. |         |             |       |
| Units: T-score  |         |             |       |
| arithmetic mean   | -2.33   | -2.22       | -     |
| standard deviation  | ± 1.41  | ± 1.19      | -     |
| Total Hip BMD T-score   |         |             |       |
| Units: T-score  |         |             |       |
| arithmetic mean   | -1.92   | -1.92       | -     |

|                          |        |        |   |
|--------------------------|--------|--------|---|
| standard deviation       | ± 0.65 | ± 0.59 | - |
| Femoral Neck BMD T-score |        |        |   |
| Units: T-score           |        |        |   |
| arithmetic mean          | -2.3   | -2.34  |   |
| standard deviation       | ± 0.52 | ± 0.52 | - |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Placebo     |
| Reporting group description:  |             |
| Participants received placebo subcutaneous injections once a month (QM) for 12 months.                      |             |
| Reporting group title   | Romosozumab |
| Reporting group description:  |             |
| Participants received 210 mg romosozumab administered by subcutaneous injection once a month for 12 months. |             |

### Primary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density (BMD) at Month 12

|  |   |
|--|---|
| End point title  | Percent Change From Baseline in Lumbar Spine Bone Mineral Density (BMD) at Month 12 |
| End point description:   |   |
| Lumbar spine bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.  |   |
| This endpoint was analyzed using the primary efficacy analysis subset which includes all randomized participants who had a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the lumbar spine; last observation carried forward (LOCF) imputation was used. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Baseline and month 12  |   |

| End point values                    | Placebo         | Romosozumab     |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 79              | 157             |  |  |
| Units: percent change               |                 |                 |  |  |
| least squares mean (standard error) | 1.2 (± 0.5)     | 12.1 (± 0.5)    |  |  |

### Statistical analyses

|   |                         |
|---|-------------------------|
| Statistical analysis title              | Primary Analysis        |
| Comparison groups                       | Placebo v Romosozumab   |
| Number of subjects included in analysis | 236                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[1]</sup> |
| Method                                  | ANCOVA                  |
| Parameter estimate                      | LS Mean Difference      |
| Point estimate                          | 10.9                    |



|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | 9.6                        |
| upper limit          | 12.2                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.6                        |

Notes:

[1] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

### Secondary: Percent Change from Baseline in BMD at the Total Hip at Month 12

|                 |  |
|-----------------|--|
| End point title | Percent Change from Baseline in BMD at the Total Hip at Month 12 |
|-----------------|--|

End point description:

Total hip bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

This endpoint was analyzed using the primary efficacy analysis subset which includes all randomized participants who had a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the total hip; LOCF imputation was used.

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

End point timeframe:

Baseline and month 12

| End point values                    | Placebo         | Romosozumab     |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 79              | 158             |  |  |
| Units: percent change               |                 |                 |  |  |
| least squares mean (standard error) | -0.5 (± 0.3)    | 2.5 (± 0.2)     |  |  |

### Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title              | Primary Analysis             |
| Comparison groups                       | Placebo v Romosozumab        |
| Number of subjects included in analysis | 237                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority <sup>[2]</sup>   |
| P-value                                 | < 0.0001 <sup>[3]</sup>      |
| Method                                  | ANCOVA                       |
| Parameter estimate                      | LS Mean Treatment Difference |
| Point estimate                          | 3                            |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 2.3                          |
| upper limit                             | 3.7                          |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.4                        |

Notes:

[2] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 12 months in total hip and femoral neck to maintain the overall significance level at 0.05.

[3] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

## Secondary: Percent Change from Baseline in BMD at the Femoral Neck at Month 12

|                 |   |
|-----------------|---|
| End point title | Percent Change from Baseline in BMD at the Femoral Neck at Month 12 |
|-----------------|---|

End point description:

Femoral neck bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

This endpoint was analyzed using the primary efficacy analysis subset which includes all randomized participants who had a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the femoral neck; LOCF imputation was used.

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

End point timeframe:

Baseline and month 12

| End point values                    | Placebo         | Romosozumab     |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 79              | 158             |  |  |
| Units: percent change               |                 |                 |  |  |
| least squares mean (standard error) | -0.2 (± 0.4)    | 2.2 (± 0.4)     |  |  |

## Statistical analyses

|   |                            |
|---|----------------------------|
| Statistical analysis title              | Primary Analysis           |
| Comparison groups                       | Placebo v Romosozumab      |
| Number of subjects included in analysis | 237                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[4]</sup> |
| P-value                                 | < 0.0001 <sup>[5]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | Treatment Difference       |
| Point estimate                          | 2.4                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.5                        |
| upper limit                             | 3.3                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.5                        |

Notes:

[4] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 12 months in total hip and femoral neck to maintain the overall significance level at 0.05.

[5] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

## Secondary: Percent Change From Baseline in Lumbar Spine BMD at Month 6

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Lumbar Spine BMD at Month 6 |
|-----------------|---|

End point description:

Lumbar spine bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

This endpoint was analyzed using the primary efficacy analysis subset with available data at baseline and month 6.

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

End point timeframe:

Baseline and month 6

| End point values                    | Placebo         | Romosozumab     |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 78              | 156             |  |  |
| Units: percent change               |                 |                 |  |  |
| least squares mean (standard error) | 0.3 (± 0.4)     | 9 (± 0.4)       |  |  |

## Statistical analyses

|   |                            |
|---|----------------------------|
| Statistical analysis title              | Primary Analysis           |
| Comparison groups                       | Placebo v Romosozumab      |
| Number of subjects included in analysis | 234                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[6]</sup> |
| P-value                                 | < 0.0001 <sup>[7]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | 8.7                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 7.6                        |
| upper limit                             | 9.7                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.5                        |

Notes:

[6] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 6 months at the lumbar spine, total hip and femoral neck BMD in order to maintain the overall significance level at 0.05.

[7] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-

baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

## Secondary: Percent Change from Baseline in BMD at the Total Hip at Month 6

|                 |   |
|-----------------|---|
| End point title | Percent Change from Baseline in BMD at the Total Hip at Month 6 |
|-----------------|---|

End point description:

Bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

This endpoint was analyzed using the primary efficacy analysis subset with available data at baseline and month 6.

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

End point timeframe:

Baseline and month 6

| End point values                    | Placebo          | Romosozumab      |  |  |
|-------------------------------------|------------------|------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed         | 78               | 157              |  |  |
| Units: percent change               |                  |                  |  |  |
| least squares mean (standard error) | 0.2 ( $\pm$ 0.2) | 1.6 ( $\pm$ 0.2) |  |  |

## Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title              | Primary Analysis             |
| Comparison groups                       | Placebo v Romosozumab        |
| Number of subjects included in analysis | 235                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority <sup>[8]</sup>   |
| P-value                                 | < 0.0001 <sup>[9]</sup>      |
| Method                                  | ANCOVA                       |
| Parameter estimate                      | LS Mean Treatment Difference |
| Point estimate                          | 1.4                          |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.8                          |
| upper limit                             | 2                            |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 0.3                          |

Notes:

[8] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 6 months at the lumbar spine, total hip and femoral neck BMD in order to maintain the overall significance level at 0.05.

[9] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

## Secondary: Percent Change from Baseline in BMD at the Femoral Neck at Month 6

|  |  |
|--|--|
| End point title  | Percent Change from Baseline in BMD at the Femoral Neck at Month 6 |
| End point description:<br>Bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.<br>This endpoint was analyzed using the primary efficacy analysis subset with available data at baseline and month 6. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Baseline and month 6   |  |

| End point values                    | Placebo         | Romosozumab      |  |  |
|-------------------------------------|-----------------|------------------|--|--|
| Subject group type                  | Reporting group | Reporting group  |  |  |
| Number of subjects analysed         | 78              | 157              |  |  |
| Units: percent change               |                 |                  |  |  |
| least squares mean (standard error) | 0 ( $\pm$ 0.4)  | 1.2 ( $\pm$ 0.3) |  |  |

## Statistical analyses

|   |                             |
|---|-----------------------------|
| Statistical analysis title              | Primary Analysis            |
| Comparison groups                       | Placebo v Romosozumab       |
| Number of subjects included in analysis | 235                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[10]</sup> |
| P-value                                 | = 0.0033 <sup>[11]</sup>    |
| Method                                  | ANCOVA                      |
| Parameter estimate                      | LS Mean Difference          |
| Point estimate                          | 1.3                         |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.4                         |
| upper limit                             | 2.1                         |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.4                         |

### Notes:

[10] - The Hochberg procedure was employed to control the overall type 1 error for the percent change from baseline at 6 months at the lumbar spine, total hip and femoral neck BMD in order to maintain the overall significance level at 0.05.

[11] - ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region, and using a variance structure allowing for heterogeneity between treatment groups.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

15 months

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Romosozumab |
|-----------------------|-------------|

Reporting group description:

Participants received 210 mg romosozumab administered by subcutaneous injection once a month for 12 months.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received placebo subcutaneous injections once a month (QM) for 12 months.

| Serious adverse events  | Romosozumab       | Placebo          |  |
|---|-------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                   |                  |  |
| subjects affected / exposed   | 23 / 163 (14.11%) | 10 / 81 (12.35%) |  |
| number of deaths (all causes)                                       | 2                 | 1                |  |
| number of deaths resulting from adverse events                      |                   |                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                  |  |
| Basal cell carcinoma  |                   |                  |  |
| subjects affected / exposed   | 1 / 163 (0.61%)   | 0 / 81 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0            |  |
| Oropharyngeal cancer  |                   |                  |  |
| subjects affected / exposed   | 1 / 163 (0.61%)   | 0 / 81 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0            |  |
| Injury, poisoning and procedural complications                      |                   |                  |  |
| Anaemia postoperative   |                   |                  |  |
| subjects affected / exposed   | 1 / 163 (0.61%)   | 0 / 81 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0            |  |
| Femur fracture  |                   |                  |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Humerus fracture                                |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Laceration                                      |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Rib fracture                                    |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Subdural haematoma                              |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Thoracic vertebral fracture                     |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Upper limb fracture                             |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cardiac disorders                               |                 |                |  |
| Angina unstable                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (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                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Atrial flutter                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cardiac failure                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cardiac valve disease                           |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cardio-respiratory arrest                       |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Coronary artery stenosis                        |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Myocardial ischaemia                            |                 |                |  |
| subjects affected / exposed                     | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Wolff-Parkinson-White syndrome                  |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (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                        |                 |                |  |
| Carotid arteriosclerosis                        |                 |                |  |



|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Carotid artery stenosis                         |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (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                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cerebrovascular accident                        |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Dementia Alzheimer's type                       |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Epilepsy  |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Haemorrhagic stroke                             |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Lacunar infarction                              |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Syncope   |                 |                |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| subjects affected / exposed                          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Vascular encephalopathy                              |                 |                |  |
| subjects affected / exposed                          | 1 / 163 (0.61%) | 0 / 81 (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 |                 |                |  |
| Death  |                 |                |  |
| subjects affected / exposed                          | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1          |  |
| Implant site haematoma                               |                 |                |  |
| subjects affected / exposed                          | 1 / 163 (0.61%) | 0 / 81 (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                          | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                           |                 |                |  |
| Abdominal pain                                       |                 |                |  |
| subjects affected / exposed                          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Abdominal pain upper                                 |                 |                |  |
| subjects affected / exposed                          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Gastrooesophageal reflux disease                     |                 |                |  |
| subjects affected / exposed                          | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Intra-abdominal haemorrhage<br>subjects affected / exposed  | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1          |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          |  |
| Reproductive system and breast<br>disorders                 |                 |                |  |
| Benign prostatic hyperplasia<br>subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          |  |
| Hepatobiliary disorders                                     |                 |                |  |
| Cholecystitis<br>subjects affected / exposed                | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal<br>disorders          |                 |                |  |
| Chronic obstructive pulmonary<br>disease                    |                 |                |  |
| subjects affected / exposed                                 | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 2          |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          |  |
| Emphysema   |                 |                |  |
| subjects affected / exposed                                 | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1          |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          |  |
| Psychiatric disorders                                       |                 |                |  |
| Depressed mood  |                 |                |  |
| subjects affected / exposed                                 | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          |  |
| Depression  |                 |                |  |
| subjects affected / exposed                                 | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0          |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0          |  |
| Musculoskeletal and connective tissue<br>disorders          |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Osteoarthritis                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Infections and infestations                     |                 |                |  |
| Appendicitis                                    |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Appendicitis perforated                         |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Atypical pneumonia                              |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Device related infection                        |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Escherichia sepsis                              |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pneumonia                                       |                 |                |  |
| subjects affected / exposed                     | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pneumonia bacterial                             |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Urinary tract infection                         |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | Romosozumab        | Placebo          |  |
|---|--------------------|------------------|--|
| Total subjects affected by non-serious adverse events               |                    |                  |  |
| subjects affected / exposed   | 122 / 163 (74.85%) | 65 / 81 (80.25%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                  |  |
| Basal cell carcinoma  |                    |                  |  |
| subjects affected / exposed   | 2 / 163 (1.23%)    | 0 / 81 (0.00%)   |  |
| occurrences (all)   | 2                  | 0                |  |
| Benign lung neoplasm  |                    |                  |  |
| subjects affected / exposed   | 0 / 163 (0.00%)    | 1 / 81 (1.23%)   |  |
| occurrences (all)   | 0                  | 1                |  |
| Benign neoplasm of adrenal gland                                    |                    |                  |  |
| subjects affected / exposed   | 0 / 163 (0.00%)    | 2 / 81 (2.47%)   |  |
| occurrences (all)   | 0                  | 2                |  |
| Benign renal neoplasm   |                    |                  |  |
| subjects affected / exposed   | 0 / 163 (0.00%)    | 1 / 81 (1.23%)   |  |
| occurrences (all)   | 0                  | 1                |  |
| Lipoma  |                    |                  |  |
| subjects affected / exposed   | 1 / 163 (0.61%)    | 0 / 81 (0.00%)   |  |
| occurrences (all)   | 1                  | 0                |  |
| Paranasal sinus benign neoplasm                                     |                    |                  |  |
| subjects affected / exposed   | 1 / 163 (0.61%)    | 0 / 81 (0.00%)   |  |
| occurrences (all)   | 1                  | 0                |  |
| Prostatic adenoma   |                    |                  |  |
| subjects affected / exposed   | 1 / 163 (0.61%)    | 0 / 81 (0.00%)   |  |
| occurrences (all)   | 1                  | 0                |  |
| Seborrhoeic keratosis   |                    |                  |  |
| subjects affected / exposed   | 1 / 163 (0.61%)    | 0 / 81 (0.00%)   |  |
| occurrences (all)   | 1                  | 0                |  |
| Skin papilloma  |                    |                  |  |

|                                       |                  |                |  |
|---------------------------------------|------------------|----------------|--|
| subjects affected / exposed           | 2 / 163 (1.23%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                     | 3                | 0              |  |
| Squamous cell carcinoma of skin       |                  |                |  |
| subjects affected / exposed           | 0 / 163 (0.00%)  | 2 / 81 (2.47%) |  |
| occurrences (all)                     | 0                | 2              |  |
| Vascular disorders                    |                  |                |  |
| Aortic aneurysm                       |                  |                |  |
| subjects affected / exposed           | 0 / 163 (0.00%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                     | 0                | 1              |  |
| Aortic dilatation                     |                  |                |  |
| subjects affected / exposed           | 0 / 163 (0.00%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                     | 0                | 2              |  |
| Arteriosclerosis                      |                  |                |  |
| subjects affected / exposed           | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                     | 1                | 0              |  |
| Essential hypertension                |                  |                |  |
| subjects affected / exposed           | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                     | 1                | 0              |  |
| Haematoma                             |                  |                |  |
| subjects affected / exposed           | 3 / 163 (1.84%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                     | 3                | 0              |  |
| Hypertension                          |                  |                |  |
| subjects affected / exposed           | 14 / 163 (8.59%) | 5 / 81 (6.17%) |  |
| occurrences (all)                     | 17               | 5              |  |
| Peripheral arterial occlusive disease |                  |                |  |
| subjects affected / exposed           | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                     | 1                | 0              |  |
| Peripheral venous disease             |                  |                |  |
| subjects affected / exposed           | 4 / 163 (2.45%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                     | 4                | 0              |  |
| Subclavian artery stenosis            |                  |                |  |
| subjects affected / exposed           | 0 / 163 (0.00%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                     | 0                | 1              |  |
| Varicose vein                         |                  |                |  |
| subjects affected / exposed           | 1 / 163 (0.61%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                     | 1                | 1              |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| Surgical and medical procedures                      |                 |                |  |
| Osteosynthesis                                       |                 |                |  |
| subjects affected / exposed                          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| General disorders and administration site conditions |                 |                |  |
| Application site dermatitis                          |                 |                |  |
| subjects affected / exposed                          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Asthenia   |                 |                |  |
| subjects affected / exposed                          | 0 / 163 (0.00%) | 2 / 81 (2.47%) |  |
| occurrences (all)                                    | 0               | 2              |  |
| Chills   |                 |                |  |
| subjects affected / exposed                          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Discomfort   |                 |                |  |
| subjects affected / exposed                          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Drug withdrawal syndrome                             |                 |                |  |
| subjects affected / exposed                          | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                    | 1               | 0              |  |
| Fatigue  |                 |                |  |
| subjects affected / exposed                          | 3 / 163 (1.84%) | 4 / 81 (4.94%) |  |
| occurrences (all)                                    | 3               | 4              |  |
| Influenza like illness                               |                 |                |  |
| subjects affected / exposed                          | 6 / 163 (3.68%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                    | 6               | 0              |  |
| Injection site bruising                              |                 |                |  |
| subjects affected / exposed                          | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                    | 1               | 0              |  |
| Injection site erythema                              |                 |                |  |
| subjects affected / exposed                          | 3 / 163 (1.84%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                    | 5               | 1              |  |
| Injection site haematoma                             |                 |                |  |
| subjects affected / exposed                          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Injection site hypersensitivity                      |                 |                |  |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Injection site induration   |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Injection site pain         |                 |                |  |
| subjects affected / exposed | 4 / 163 (2.45%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 9               | 0              |  |
| Injection site pruritus     |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 2 / 81 (2.47%) |  |
| occurrences (all)           | 3               | 2              |  |
| Injection site swelling     |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Local swelling              |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Malaise                     |                 |                |  |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 2               | 0              |  |
| Non-cardiac chest pain      |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 2               | 1              |  |
| Immune system disorders     |                 |                |  |
| Allergy to arthropod bite   |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Drug hypersensitivity       |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| House dust allergy          |                 |                |  |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 2               | 0              |  |
| Seasonal allergy            |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 2 / 81 (2.47%) |  |
| occurrences (all)           | 1               | 2              |  |



|   |                 |                |  |
|---|-----------------|----------------|--|
| Reproductive system and breast disorders        |                 |                |  |
| Balanoposthitis                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1               | 0              |  |
| Benign prostatic hyperplasia                    |                 |                |  |
| subjects affected / exposed                     | 5 / 163 (3.07%) | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 5               | 0              |  |
| Breast pain                                     |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 2 / 81 (2.47%) |  |
| occurrences (all)                               | 0               | 2              |  |
| Breast swelling                                 |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                               | 0               | 1              |  |
| Nipple disorder                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1               | 0              |  |
| Prostatitis                                     |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1               | 0              |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Allergic pharyngitis                            |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1               | 0              |  |
| Asthma  |                 |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1               | 0              |  |
| Bronchiectasis                                  |                 |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                               | 0               | 1              |  |
| Chronic obstructive pulmonary disease           |                 |                |  |
| subjects affected / exposed                     | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 2               | 0              |  |
| Cough   |                 |                |  |
| subjects affected / exposed                     | 5 / 163 (3.07%) | 1 / 81 (1.23%) |  |
| occurrences (all)                               | 5               | 1              |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Dyspnoea                                |                 |                |  |
| subjects affected / exposed             | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)                       | 2               | 1              |  |
| Dyspnoea exertional                     |                 |                |  |
| subjects affected / exposed             | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                       | 0               | 1              |  |
| Emphysema                               |                 |                |  |
| subjects affected / exposed             | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)                       | 1               | 1              |  |
| Epistaxis                               |                 |                |  |
| subjects affected / exposed             | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                       | 1               | 0              |  |
| Oropharyngeal pain                      |                 |                |  |
| subjects affected / exposed             | 2 / 163 (1.23%) | 1 / 81 (1.23%) |  |
| occurrences (all)                       | 2               | 1              |  |
| Productive cough                        |                 |                |  |
| subjects affected / exposed             | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                       | 0               | 1              |  |
| Pulmonary embolism                      |                 |                |  |
| subjects affected / exposed             | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                       | 1               | 0              |  |
| Pulmonary fibrosis                      |                 |                |  |
| subjects affected / exposed             | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                       | 1               | 0              |  |
| Rhinitis allergic                       |                 |                |  |
| subjects affected / exposed             | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                       | 2               | 0              |  |
| Rhinorrhoea                             |                 |                |  |
| subjects affected / exposed             | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                       | 0               | 2              |  |
| Psychiatric disorders                   |                 |                |  |
| Adjustment disorder with depressed mood |                 |                |  |
| subjects affected / exposed             | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                       | 1               | 0              |  |
| Affective disorder                      |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                           | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                     | 0               | 1              |  |
| Confusional state                                     |                 |                |  |
| subjects affected / exposed                           | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                     | 1               | 0              |  |
| Depressed mood  |                 |                |  |
| subjects affected / exposed                           | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                     | 1               | 0              |  |
| Depression  |                 |                |  |
| subjects affected / exposed                           | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                     | 2               | 0              |  |
| Insomnia  |                 |                |  |
| subjects affected / exposed                           | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                     | 1               | 1              |  |
| Personality change due to a general medical condition |                 |                |  |
| subjects affected / exposed                           | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                     | 1               | 0              |  |
| Restlessness  |                 |                |  |
| subjects affected / exposed                           | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                     | 1               | 0              |  |
| Investigations  |                 |                |  |
| Blood bilirubin increased                             |                 |                |  |
| subjects affected / exposed                           | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                     | 0               | 1              |  |
| Blood glucose increased                               |                 |                |  |
| subjects affected / exposed                           | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                     | 2               | 0              |  |
| Blood uric acid increased                             |                 |                |  |
| subjects affected / exposed                           | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                                     | 1               | 0              |  |
| Cardiac murmur  |                 |                |  |
| subjects affected / exposed                           | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                                     | 0               | 1              |  |
| Heart rate irregular                                  |                 |                |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| subjects affected / exposed                    | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                              | 1               | 0              |  |
| Vitamin D decreased                            |                 |                |  |
| subjects affected / exposed                    | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                              | 1               | 0              |  |
| Vitamin D increased                            |                 |                |  |
| subjects affected / exposed                    | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                              | 1               | 0              |  |
| Injury, poisoning and procedural complications |                 |                |  |
| Arthropod bite                                 |                 |                |  |
| subjects affected / exposed                    | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                              | 0               | 1              |  |
| Arthropod sting                                |                 |                |  |
| subjects affected / exposed                    | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                              | 1               | 0              |  |
| Chest injury                                   |                 |                |  |
| subjects affected / exposed                    | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                              | 1               | 0              |  |
| Contusion                                      |                 |                |  |
| subjects affected / exposed                    | 0 / 163 (0.00%) | 3 / 81 (3.70%) |  |
| occurrences (all)                              | 0               | 3              |  |
| Face injury                                    |                 |                |  |
| subjects affected / exposed                    | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                              | 0               | 1              |  |
| Fall   |                 |                |  |
| subjects affected / exposed                    | 6 / 163 (3.68%) | 2 / 81 (2.47%) |  |
| occurrences (all)                              | 7               | 4              |  |
| Head injury                                    |                 |                |  |
| subjects affected / exposed                    | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                              | 0               | 1              |  |
| Joint injury                                   |                 |                |  |
| subjects affected / exposed                    | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                              | 0               | 1              |  |
| Laceration                                     |                 |                |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| subjects affected / exposed                | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| Ligament sprain                            |                 |                |  |
| subjects affected / exposed                | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| Lumbar vertebral fracture                  |                 |                |  |
| subjects affected / exposed                | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| Meniscus injury                            |                 |                |  |
| subjects affected / exposed                | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| Muscle strain                              |                 |                |  |
| subjects affected / exposed                | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                          | 0               | 1              |  |
| Post procedural haematoma                  |                 |                |  |
| subjects affected / exposed                | 2 / 163 (1.23%) | 1 / 81 (1.23%) |  |
| occurrences (all)                          | 2               | 1              |  |
| Post procedural haemorrhage                |                 |                |  |
| subjects affected / exposed                | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)                          | 1               | 1              |  |
| Procedural pain                            |                 |                |  |
| subjects affected / exposed                | 8 / 163 (4.91%) | 6 / 81 (7.41%) |  |
| occurrences (all)                          | 9               | 7              |  |
| Skin abrasion                              |                 |                |  |
| subjects affected / exposed                | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| Tendon rupture                             |                 |                |  |
| subjects affected / exposed                | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                          | 1               | 0              |  |
| Tooth fracture                             |                 |                |  |
| subjects affected / exposed                | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                          | 0               | 3              |  |
| Congenital, familial and genetic disorders |                 |                |  |
| Hydrocele                                  |                 |                |  |

|                                     |                 |                |  |
|-------------------------------------|-----------------|----------------|--|
| subjects affected / exposed         | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                   | 1               | 0              |  |
| Cardiac disorders                   |                 |                |  |
| Angina pectoris                     |                 |                |  |
| subjects affected / exposed         | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)                   | 2               | 0              |  |
| Aortic valve incompetence           |                 |                |  |
| subjects affected / exposed         | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                   | 0               | 1              |  |
| Arteriosclerosis coronary artery    |                 |                |  |
| subjects affected / exposed         | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)                   | 1               | 1              |  |
| Atrial fibrillation                 |                 |                |  |
| subjects affected / exposed         | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)                   | 1               | 1              |  |
| Atrial flutter                      |                 |                |  |
| subjects affected / exposed         | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                   | 0               | 1              |  |
| Atrioventricular block first degree |                 |                |  |
| subjects affected / exposed         | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                   | 1               | 0              |  |
| Cardiac failure chronic             |                 |                |  |
| subjects affected / exposed         | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)                   | 1               | 1              |  |
| Extrasystoles                       |                 |                |  |
| subjects affected / exposed         | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)                   | 0               | 1              |  |
| Left atrial dilatation              |                 |                |  |
| subjects affected / exposed         | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                   | 1               | 0              |  |
| Mitral valve incompetence           |                 |                |  |
| subjects affected / exposed         | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                   | 1               | 0              |  |
| Myocardial ischaemia                |                 |                |  |
| subjects affected / exposed         | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)                   | 1               | 0              |  |

|                                |                  |                |  |
|--------------------------------|------------------|----------------|--|
| Palpitations                   |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 1                | 0              |  |
| Supraventricular extrasystoles |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 2                | 0              |  |
| Supraventricular tachycardia   |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 1                | 0              |  |
| Ventricular extrasystoles      |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 2                | 0              |  |
| Nervous system disorders       |                  |                |  |
| Cerebral arteriosclerosis      |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 1                | 0              |  |
| Cognitive disorder             |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 1                | 0              |  |
| Disturbance in attention       |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 1                | 0              |  |
| Dizziness                      |                  |                |  |
| subjects affected / exposed    | 5 / 163 (3.07%)  | 1 / 81 (1.23%) |  |
| occurrences (all)              | 5                | 1              |  |
| Dysaesthesia                   |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 1                | 0              |  |
| Headache                       |                  |                |  |
| subjects affected / exposed    | 10 / 163 (6.13%) | 6 / 81 (7.41%) |  |
| occurrences (all)              | 12               | 7              |  |
| Hypoaesthesia                  |                  |                |  |
| subjects affected / exposed    | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)              | 1                | 0              |  |
| IIIrd nerve paralysis          |                  |                |  |

|                             |                 |                |
|-----------------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| IVth nerve paralysis        |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Loss of consciousness       |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |
| Migraine                    |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |
| Paraesthesia                |                 |                |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)           | 2               | 0              |
| Polyneuropathy              |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |
| occurrences (all)           | 1               | 1              |
| Radicular syndrome          |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |
| Radiculopathy               |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |
| Sciatica                    |                 |                |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)           | 2               | 0              |
| Seizure                     |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Somnolence                  |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Syncope                     |                 |                |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)           | 2               | 0              |
| Transient ischaemic attack  |                 |                |



|   |                      |                     |  |
|---|----------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| With nerve paralysis<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 163 (0.61%)<br>1 | 2 / 81 (2.47%)<br>2 |  |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)         | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)   | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Vertigo positional<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Eye disorders<br>Arteriosclerotic retinopathy<br>subjects affected / exposed<br>occurrences (all)   | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Blepharitis<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Cataract<br>subjects affected / exposed<br>occurrences (all)  | 4 / 163 (2.45%)<br>4 | 1 / 81 (1.23%)<br>1 |  |
| Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Ectropion   |                      |                     |  |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Eye allergy                 |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Eye pain                    |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Glaucoma                    |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Macular degeneration        |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Vision blurred              |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 1               | 1              |  |
| Gastrointestinal disorders  |                 |                |  |
| Abdominal discomfort        |                 |                |  |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 2               | 0              |  |
| Abdominal hernia            |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Abdominal pain              |                 |                |  |
| subjects affected / exposed | 3 / 163 (1.84%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 3               | 0              |  |
| Abdominal pain upper        |                 |                |  |
| subjects affected / exposed | 3 / 163 (1.84%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 5               | 0              |  |
| Ascites                     |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Cheilitis                   |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |

|                                      |                 |                |
|--------------------------------------|-----------------|----------------|
| Cheilosis                            |                 |                |
| subjects affected / exposed          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)                    | 0               | 1              |
| Coeliac artery stenosis              |                 |                |
| subjects affected / exposed          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)                    | 0               | 1              |
| Constipation                         |                 |                |
| subjects affected / exposed          | 9 / 163 (5.52%) | 1 / 81 (1.23%) |
| occurrences (all)                    | 10              | 1              |
| Dental caries                        |                 |                |
| subjects affected / exposed          | 3 / 163 (1.84%) | 0 / 81 (0.00%) |
| occurrences (all)                    | 3               | 0              |
| Diarrhoea                            |                 |                |
| subjects affected / exposed          | 6 / 163 (3.68%) | 4 / 81 (4.94%) |
| occurrences (all)                    | 6               | 4              |
| Diverticulum                         |                 |                |
| subjects affected / exposed          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)                    | 0               | 1              |
| Diverticulum intestinal              |                 |                |
| subjects affected / exposed          | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)                    | 1               | 0              |
| Dyspepsia                            |                 |                |
| subjects affected / exposed          | 3 / 163 (1.84%) | 3 / 81 (3.70%) |
| occurrences (all)                    | 4               | 4              |
| Eructation                           |                 |                |
| subjects affected / exposed          | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)                    | 1               | 0              |
| Functional gastrointestinal disorder |                 |                |
| subjects affected / exposed          | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)                    | 2               | 0              |
| Gastric ulcer                        |                 |                |
| subjects affected / exposed          | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)                    | 0               | 1              |
| Haemorrhagic erosive gastritis       |                 |                |
| subjects affected / exposed          | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)                    | 1               | 0              |

|                             |                 |                |
|-----------------------------|-----------------|----------------|
| Haemorrhoids                |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Hiatus hernia               |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |
| Inguinal hernia             |                 |                |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)           | 2               | 0              |
| Intestinal dilatation       |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Irritable bowel syndrome    |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Large intestine polyp       |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Loose tooth                 |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all)           | 0               | 2              |
| Mesenteric artery stenosis  |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |
| Nausea                      |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |
| occurrences (all)           | 1               | 1              |
| Odynophagia                 |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Oesophagitis                |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Pancreatic cyst             |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |

|   |                      |                     |  |
|---|----------------------|---------------------|--|
| Periodontal disease<br>subjects affected / exposed<br>occurrences (all)   | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Teeth brittle<br>subjects affected / exposed<br>occurrences (all)   | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)   | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Truncus coeliacus thrombosis<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Hepatobiliary disorders<br>Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 163 (0.00%)<br>0 | 2 / 81 (2.47%)<br>2 |  |
| Gallbladder polyp<br>subjects affected / exposed<br>occurrences (all)   | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Hepatic cyst<br>subjects affected / exposed<br>occurrences (all)  | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Hepatomegaly<br>subjects affected / exposed<br>occurrences (all)  | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Actinic keratosis<br>subjects affected / exposed<br>occurrences (all) | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Blister   |                      |                     |  |

|                             |                 |                |
|-----------------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Dermatitis allergic         |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Dermatitis contact          |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Dry skin                    |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Ecchymosis                  |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Eczema                      |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all)           | 0               | 2              |
| Erythema                    |                 |                |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)           | 2               | 0              |
| Hyperhidrosis               |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |
| Miliaria                    |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |
| occurrences (all)           | 1               | 1              |
| Papule                      |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Pruritus                    |                 |                |
| subjects affected / exposed | 2 / 163 (1.23%) | 1 / 81 (1.23%) |
| occurrences (all)           | 2               | 1              |
| Pruritus generalised        |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |
| occurrences (all)           | 1               | 1              |
| Psoriasis                   |                 |                |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Rash                        |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 1               | 1              |  |
| Rosacea                     |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Seborrhoeic dermatitis      |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Skin mass                   |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Urticaria                   |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Vitiligo                    |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Renal and urinary disorders |                 |                |  |
| Dysuria                     |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Haematuria                  |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Nephrolithiasis             |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Nephropathy                 |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Renal artery stenosis       |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 2              |  |

|   |                  |                |  |
|---|------------------|----------------|--|
| Renal cyst                                      |                  |                |  |
| subjects affected / exposed                     | 3 / 163 (1.84%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                               | 3                | 1              |  |
| Renal injury                                    |                  |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                               | 0                | 1              |  |
| Urinary bladder polyp                           |                  |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1                | 0              |  |
| Urinary retention                               |                  |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                               | 1                | 1              |  |
| Endocrine disorders                             |                  |                |  |
| Goitre  |                  |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1                | 0              |  |
| Hypothyroidism                                  |                  |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1                | 0              |  |
| Musculoskeletal and connective tissue disorders |                  |                |  |
| Arthralgia                                      |                  |                |  |
| subjects affected / exposed                     | 10 / 163 (6.13%) | 8 / 81 (9.88%) |  |
| occurrences (all)                               | 13               | 9              |  |
| Arthritis                                       |                  |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                               | 0                | 1              |  |
| Back pain                                       |                  |                |  |
| subjects affected / exposed                     | 15 / 163 (9.20%) | 4 / 81 (4.94%) |  |
| occurrences (all)                               | 15               | 4              |  |
| Bone pain                                       |                  |                |  |
| subjects affected / exposed                     | 1 / 163 (0.61%)  | 0 / 81 (0.00%) |  |
| occurrences (all)                               | 1                | 0              |  |
| Bursa disorder                                  |                  |                |  |
| subjects affected / exposed                     | 0 / 163 (0.00%)  | 1 / 81 (1.23%) |  |
| occurrences (all)                               | 0                | 1              |  |
| Intervertebral disc degeneration                |                  |                |  |



|                              |                 |                |
|------------------------------|-----------------|----------------|
| subjects affected / exposed  | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)            | 2               | 0              |
| Intervertebral disc disorder |                 |                |
| subjects affected / exposed  | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)            | 0               | 1              |
| Limb discomfort              |                 |                |
| subjects affected / exposed  | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)            | 1               | 0              |
| Muscle spasms                |                 |                |
| subjects affected / exposed  | 3 / 163 (1.84%) | 5 / 81 (6.17%) |
| occurrences (all)            | 3               | 7              |
| Muscular weakness            |                 |                |
| subjects affected / exposed  | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)            | 1               | 0              |
| Musculoskeletal chest pain   |                 |                |
| subjects affected / exposed  | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)            | 1               | 0              |
| Musculoskeletal pain         |                 |                |
| subjects affected / exposed  | 5 / 163 (3.07%) | 0 / 81 (0.00%) |
| occurrences (all)            | 7               | 0              |
| Myalgia                      |                 |                |
| subjects affected / exposed  | 4 / 163 (2.45%) | 5 / 81 (6.17%) |
| occurrences (all)            | 6               | 5              |
| Osteitis deformans           |                 |                |
| subjects affected / exposed  | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)            | 1               | 0              |
| Osteoarthritis               |                 |                |
| subjects affected / exposed  | 8 / 163 (4.91%) | 2 / 81 (2.47%) |
| occurrences (all)            | 8               | 2              |
| Pain in extremity            |                 |                |
| subjects affected / exposed  | 6 / 163 (3.68%) | 2 / 81 (2.47%) |
| occurrences (all)            | 7               | 2              |
| Periarthritis                |                 |                |
| subjects affected / exposed  | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)            | 3               | 0              |
| Rheumatoid arthritis         |                 |                |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Rib deformity               |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Spinal osteoarthritis       |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 2 / 81 (2.47%) |  |
| occurrences (all)           | 2               | 2              |  |
| Spinal pain                 |                 |                |  |
| subjects affected / exposed | 2 / 163 (1.23%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 2               | 1              |  |
| Trigger finger              |                 |                |  |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 2               | 0              |  |
| Infections and infestations |                 |                |  |
| Acute sinusitis             |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Bronchitis                  |                 |                |  |
| subjects affected / exposed | 3 / 163 (1.84%) | 3 / 81 (3.70%) |  |
| occurrences (all)           | 3               | 3              |  |
| Bronchitis viral            |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Cellulitis                  |                 |                |  |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Conjunctivitis              |                 |                |  |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |  |
| occurrences (all)           | 2               | 0              |  |
| Fungal infection            |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |
| Furuncle                    |                 |                |  |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |  |
| occurrences (all)           | 0               | 1              |  |

|                                   |                   |                  |
|-----------------------------------|-------------------|------------------|
| Gastroenteritis                   |                   |                  |
| subjects affected / exposed       | 3 / 163 (1.84%)   | 2 / 81 (2.47%)   |
| occurrences (all)                 | 4                 | 4                |
| Gastroenteritis viral             |                   |                  |
| subjects affected / exposed       | 1 / 163 (0.61%)   | 0 / 81 (0.00%)   |
| occurrences (all)                 | 1                 | 0                |
| Herpes zoster                     |                   |                  |
| subjects affected / exposed       | 2 / 163 (1.23%)   | 0 / 81 (0.00%)   |
| occurrences (all)                 | 2                 | 0                |
| Influenza                         |                   |                  |
| subjects affected / exposed       | 4 / 163 (2.45%)   | 0 / 81 (0.00%)   |
| occurrences (all)                 | 4                 | 0                |
| Laryngitis                        |                   |                  |
| subjects affected / exposed       | 1 / 163 (0.61%)   | 0 / 81 (0.00%)   |
| occurrences (all)                 | 1                 | 0                |
| Localised infection               |                   |                  |
| subjects affected / exposed       | 0 / 163 (0.00%)   | 1 / 81 (1.23%)   |
| occurrences (all)                 | 0                 | 1                |
| Lower respiratory tract infection |                   |                  |
| subjects affected / exposed       | 1 / 163 (0.61%)   | 0 / 81 (0.00%)   |
| occurrences (all)                 | 1                 | 0                |
| Nasopharyngitis                   |                   |                  |
| subjects affected / exposed       | 35 / 163 (21.47%) | 22 / 81 (27.16%) |
| occurrences (all)                 | 45                | 23               |
| Onychomycosis                     |                   |                  |
| subjects affected / exposed       | 1 / 163 (0.61%)   | 0 / 81 (0.00%)   |
| occurrences (all)                 | 1                 | 0                |
| Oral fungal infection             |                   |                  |
| subjects affected / exposed       | 0 / 163 (0.00%)   | 1 / 81 (1.23%)   |
| occurrences (all)                 | 0                 | 1                |
| Otitis externa                    |                   |                  |
| subjects affected / exposed       | 1 / 163 (0.61%)   | 0 / 81 (0.00%)   |
| occurrences (all)                 | 1                 | 0                |
| Otitis externa bacterial          |                   |                  |
| subjects affected / exposed       | 0 / 163 (0.00%)   | 1 / 81 (1.23%)   |
| occurrences (all)                 | 0                 | 1                |

|                                   |                 |                |
|-----------------------------------|-----------------|----------------|
| Otitis media                      |                 |                |
| subjects affected / exposed       | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)                 | 0               | 1              |
| Paronychia                        |                 |                |
| subjects affected / exposed       | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)                 | 1               | 0              |
| Periodontitis                     |                 |                |
| subjects affected / exposed       | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)                 | 1               | 0              |
| Pharyngitis                       |                 |                |
| subjects affected / exposed       | 4 / 163 (2.45%) | 1 / 81 (1.23%) |
| occurrences (all)                 | 4               | 1              |
| Pharyngitis streptococcal         |                 |                |
| subjects affected / exposed       | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)                 | 0               | 1              |
| Pulpitis dental                   |                 |                |
| subjects affected / exposed       | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)                 | 1               | 0              |
| Pneumonia                         |                 |                |
| subjects affected / exposed       | 4 / 163 (2.45%) | 0 / 81 (0.00%) |
| occurrences (all)                 | 4               | 0              |
| Respiratory tract infection viral |                 |                |
| subjects affected / exposed       | 0 / 163 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all)                 | 0               | 2              |
| Respiratory tract infection       |                 |                |
| subjects affected / exposed       | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)                 | 2               | 0              |
| Rhinitis                          |                 |                |
| subjects affected / exposed       | 1 / 163 (0.61%) | 2 / 81 (2.47%) |
| occurrences (all)                 | 1               | 2              |
| Sinusitis                         |                 |                |
| subjects affected / exposed       | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)                 | 3               | 0              |
| Tonsillitis                       |                 |                |
| subjects affected / exposed       | 0 / 163 (0.00%) | 2 / 81 (2.47%) |
| occurrences (all)                 | 0               | 2              |

|  |                      |                     |  |
|--|----------------------|---------------------|--|
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)  | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 5 / 163 (3.07%)<br>5 | 4 / 81 (4.94%)<br>4 |  |
| Upper respiratory tract infection<br>bacterial<br>subjects affected / exposed<br>occurrences (all)           | 1 / 163 (0.61%)<br>2 | 3 / 81 (3.70%)<br>4 |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 163 (0.61%)<br>1 | 2 / 81 (2.47%)<br>2 |  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Viral rhinitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 163 (0.61%)<br>1 | 1 / 81 (1.23%)<br>1 |  |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 163 (0.61%)<br>1 | 0 / 81 (0.00%)<br>0 |  |
| Wound infection staphylococcal<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 0 / 163 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |  |
| Diabetes mellitus inadequate control   |                      |                     |  |

|                             |                 |                |
|-----------------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Dyslipidaemia               |                 |                |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)           | 2               | 0              |
| Glucose tolerance impaired  |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |
| occurrences (all)           | 1               | 1              |
| Gout                        |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 2              |
| Hypercholesterolaemia       |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Hyperglycaemia              |                 |                |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 81 (0.00%) |
| occurrences (all)           | 2               | 0              |
| Hypermagnesaemia            |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |
| Hypomagnesaemia             |                 |                |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all)           | 0               | 1              |
| Type 2 diabetes mellitus    |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 81 (1.23%) |
| occurrences (all)           | 1               | 1              |
| Vitamin B12 deficiency      |                 |                |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 81 (0.00%) |
| occurrences (all)           | 1               | 0              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 15 July 2014 | <ul style="list-style-type: none"><li>- Inclusion criteria: Number 103: added assessment by the central imaging vendor at screening for BMD T-scores</li><li>- Exclusion criteria and Excluded treatments: deleted tibolone.</li><li>- Study procedures: Clarified intervals for DXA scans taken for the screening period; defined day 1 and subsequent visit dates.</li></ul> |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported