



## Clinical trial results:

### Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy and Safety of Denosumab Compared With Risedronate in Glucocorticoid-treated Individuals

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2010-024393-19             |
| Trial protocol           | BE HU NL CZ ES PL DE DK FR |
| Global end of trial date | 29 June 2017               |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 29 June 2018 |
| First version publication date | 29 June 2018 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20101217 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01575873 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                       |
|------------------------------|---------------------------------------------------------------------------------------|
| Sponsor organisation name    | Amgen Inc.                                                                            |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, 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                       | 29 June 2017 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 29 June 2017 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective in the glucocorticoid-continuing (GC-C) subpopulation treated with chronic glucocorticoid therapy ( $\geq 7.5$  mg daily prednisone or its equivalent for  $\geq 3$  months and planning to continue treatment for a total of at least 6 months) is to demonstrate that treatment with denosumab 60 mg subcutaneously (SC) every 6 months (Q6M) is not inferior to treatment with oral risedronate 5 mg every day (QD) with respect to the percent change from baseline in lumbar spine BMD by dual X-ray absorptiometry (DXA) at 12 months.

The primary objective in the glucocorticoid-initiating (GC-I) subpopulation treated with glucocorticoid therapy ( $\geq 7.5$  mg daily prednisone or its equivalent for  $< 3$  months and planning to continue treatment for a total of at least 6 months) is to demonstrate that treatment with denosumab 60 mg SC Q6M is not inferior to treatment with oral risedronate 5 mg QD with respect to the percent change from baseline in lumbar spine BMD by DXA at 12 months.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

The protocol, proposed informed consent form, other written subject information, and any proposed advertising material was submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for written approval.

The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 28 March 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Czech Republic: 141    |
| Country: Number of subjects enrolled | Poland: 96             |
| Country: Number of subjects enrolled | Russian Federation: 75 |
| Country: Number of subjects enrolled | Belgium: 59            |
| Country: Number of subjects enrolled | Spain: 42              |
| Country: Number of subjects enrolled | Hungary: 37            |
| Country: Number of subjects enrolled | France: 35             |
| Country: Number of subjects enrolled | Denmark: 25            |
| Country: Number of subjects enrolled | Netherlands: 13        |
| Country: Number of subjects enrolled | Germany: 8             |
| Country: Number of subjects enrolled | Argentina: 74          |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Mexico: 32             |
| Country: Number of subjects enrolled | Colombia: 13           |
| Country: Number of subjects enrolled | United States: 76      |
| Country: Number of subjects enrolled | Canada: 36             |
| Country: Number of subjects enrolled | Korea, Republic of: 33 |
| Worldwide total number of subjects   | 795                    |
| EEA total number of subjects         | 456                    |

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)                      | 440 |
| From 65 to 84 years                       | 344 |
| 85 years and over                         | 11  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 79 centers in Europe, North America, Latin America, and Korea from 28 March 2012 to 30 June 2015.

Participants who had been taking glucocorticoids for at least 3 months were classed as glucocorticoid continuing; those who were taking glucocorticoids for less than 3 months were classed as glucocorticoid initiating.

### Pre-assignment

Screening details:

Eligible patients were randomly assigned in a 1:1 ratio to receive 60 mg denosumab every 6 months or 5 mg oral risedronate daily for 24 months within each subpopulation. Randomization was stratified by sex within each subpopulation.

### 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>             | Risedronate: Glucocorticoid-initiating |

Arm description:

Participants received 5 mg risedronate orally once a day for 24 months and placebo to denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18.

|                                        |                                              |
|----------------------------------------|----------------------------------------------|
| Arm type                               | Active comparator                            |
| Investigational medicinal product name | Placebo for denosumab                        |
| 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 every 6 months

|                                        |                  |
|----------------------------------------|------------------|
| Investigational medicinal product name | Risedronate      |
| Investigational medicinal product code |                  |
| Other name                             | Actonel, Atelvia |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Administered orally once a day

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Denosumab: Glucocorticoid-initiating |
|------------------|--------------------------------------|

Arm description:

Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.

|                                        |                                              |
|----------------------------------------|----------------------------------------------|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Denosumab                                    |
| Investigational medicinal product code | AMG 162                                      |
| Other name                             | Prolia®                                      |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

|                                                                                                                                                                                          |                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Dosage and administration details:                                                                                                                                                       |                                              |
| Administered by subcutaneous injection once every 6 months                                                                                                                               |                                              |
| Investigational medicinal product name                                                                                                                                                   | Placebo for risendronate                     |
| Investigational medicinal product code                                                                                                                                                   |                                              |
| Other name                                                                                                                                                                               |                                              |
| Pharmaceutical forms                                                                                                                                                                     | Tablet                                       |
| Routes of administration                                                                                                                                                                 | Oral use                                     |
| Dosage and administration details:                                                                                                                                                       |                                              |
| Administered orally once a day                                                                                                                                                           |                                              |
| <b>Arm title</b>                                                                                                                                                                         | Risedronate: Glucocorticoid-continuing       |
| Arm description:                                                                                                                                                                         |                                              |
| Participants received 5 mg risedronate orally once a day for 24 months and placebo to denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18.                          |                                              |
| Arm type                                                                                                                                                                                 | Active comparator                            |
| Investigational medicinal product name                                                                                                                                                   | Risedronate                                  |
| Investigational medicinal product code                                                                                                                                                   |                                              |
| Other name                                                                                                                                                                               | Actonel, Atelvia                             |
| Pharmaceutical forms                                                                                                                                                                     | Tablet                                       |
| Routes of administration                                                                                                                                                                 | Oral use                                     |
| Dosage and administration details:                                                                                                                                                       |                                              |
| Administered orally once a day                                                                                                                                                           |                                              |
| Investigational medicinal product name                                                                                                                                                   | Placebo for denosumab                        |
| 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 every 6 months                                                                                                                               |                                              |
| <b>Arm title</b>                                                                                                                                                                         | Denosumab: Glucocorticoid-continuing         |
| Arm description:                                                                                                                                                                         |                                              |
| Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months. |                                              |
| Arm type                                                                                                                                                                                 | Experimental                                 |
| Investigational medicinal product name                                                                                                                                                   | Denosumab                                    |
| Investigational medicinal product code                                                                                                                                                   | AMG 162                                      |
| Other name                                                                                                                                                                               | Prolia®                                      |
| Pharmaceutical forms                                                                                                                                                                     | Solution for injection in pre-filled syringe |
| Routes of administration                                                                                                                                                                 | Subcutaneous use                             |
| Dosage and administration details:                                                                                                                                                       |                                              |
| Administered by subcutaneous injection once every 6 months                                                                                                                               |                                              |
| Investigational medicinal product name                                                                                                                                                   | Placebo for risendronate                     |
| Investigational medicinal product code                                                                                                                                                   |                                              |
| Other name                                                                                                                                                                               |                                              |
| Pharmaceutical forms                                                                                                                                                                     | Tablet                                       |
| Routes of administration                                                                                                                                                                 | Oral use                                     |
| Dosage and administration details:                                                                                                                                                       |                                              |
| Administered orally once a day                                                                                                                                                           |                                              |

| <b>Number of subjects in period 1</b> | <b>Risedronate:<br/>Glucocorticoid-<br/>initiating</b> | <b>Denosumab:<br/>Glucocorticoid-<br/>initiating</b> | <b>Risedronate:<br/>Glucocorticoid-<br/>continuing</b> |
|---------------------------------------|--------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|
| Started                               | 145                                                    | 145                                                  | 252                                                    |
| Received Study Drug                   | 140                                                    | 142                                                  | 246                                                    |
| Completed                             | 117                                                    | 109                                                  | 178                                                    |
| Not completed                         | 28                                                     | 36                                                   | 74                                                     |
| Consent withdrawn by subject          | 15                                                     | 20                                                   | 34                                                     |
| Adverse Event                         | 7                                                      | 7                                                    | 9                                                      |
| Administrative decision               | 1                                                      | 1                                                    | 1                                                      |
| Death                                 | 3                                                      | 2                                                    | 8                                                      |
| Other                                 | -                                                      | -                                                    | 4                                                      |
| Protocol deviation                    | -                                                      | 1                                                    | -                                                      |
| Lost to follow-up                     | 1                                                      | 3                                                    | 13                                                     |
| Requirement for Alternative Therapy   | -                                                      | -                                                    | 1                                                      |
| Noncompliance                         | 1                                                      | 2                                                    | 4                                                      |

| <b>Number of subjects in period 1</b> | <b>Denosumab:<br/>Glucocorticoid-<br/>continuing</b> |
|---------------------------------------|------------------------------------------------------|
| Started                               | 253                                                  |
| Received Study Drug                   | 251                                                  |
| Completed                             | 186                                                  |
| Not completed                         | 67                                                   |
| Consent withdrawn by subject          | 34                                                   |
| Adverse Event                         | 12                                                   |
| Administrative decision               | -                                                    |
| Death                                 | 9                                                    |
| Other                                 | 2                                                    |
| Protocol deviation                    | 1                                                    |
| Lost to follow-up                     | 5                                                    |
| Requirement for Alternative Therapy   | 1                                                    |
| Noncompliance                         | 3                                                    |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                          |                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Reporting group title                                                                                                                                                                    | Risedronate: Glucocorticoid-initiating |
| Reporting group description:                                                                                                                                                             |                                        |
| Participants received 5 mg risedronate orally once a day for 24 months and placebo to denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18.                          |                                        |
| Reporting group title                                                                                                                                                                    | Denosumab: Glucocorticoid-initiating   |
| Reporting group description:                                                                                                                                                             |                                        |
| Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months. |                                        |
| Reporting group title                                                                                                                                                                    | Risedronate: Glucocorticoid-continuing |
| Reporting group description:                                                                                                                                                             |                                        |
| Participants received 5 mg risedronate orally once a day for 24 months and placebo to denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18.                          |                                        |
| Reporting group title                                                                                                                                                                    | Denosumab: Glucocorticoid-continuing   |
| Reporting group description:                                                                                                                                                             |                                        |
| Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months. |                                        |

| Reporting group values           | Risedronate:<br>Glucocorticoid-<br>initiating | Denosumab:<br>Glucocorticoid-<br>initiating | Risedronate:<br>Glucocorticoid-<br>continuing |
|----------------------------------|-----------------------------------------------|---------------------------------------------|-----------------------------------------------|
| Number of subjects               | 145                                           | 145                                         | 252                                           |
| Age Categorical                  |                                               |                                             |                                               |
| Units: Subjects                  |                                               |                                             |                                               |
| < 50 years                       | 5                                             | 2                                           | 26                                            |
| 50 - 64 years                    | 75                                            | 55                                          | 130                                           |
| 65 - 74 years                    | 38                                            | 50                                          | 62                                            |
| ≥ 75 years                       | 27                                            | 38                                          | 34                                            |
| Age Continuous                   |                                               |                                             |                                               |
| Units: years                     |                                               |                                             |                                               |
| arithmetic mean                  | 64.4                                          | 67.5                                        | 61.3                                          |
| standard deviation               | ± 10.0                                        | ± 10.1                                      | ± 11.1                                        |
| Gender Categorical               |                                               |                                             |                                               |
| Units: Subjects                  |                                               |                                             |                                               |
| Female                           | 93                                            | 93                                          | 185                                           |
| Male                             | 52                                            | 52                                          | 67                                            |
| Race                             |                                               |                                             |                                               |
| Units: Subjects                  |                                               |                                             |                                               |
| White                            | 123                                           | 122                                         | 223                                           |
| Other                            | 11                                            | 12                                          | 11                                            |
| Asian                            | 9                                             | 9                                           | 12                                            |
| Black or African American        | 2                                             | 2                                           | 4                                             |
| American Indian or Alaska Native | 0                                             | 0                                           | 1                                             |
| Multiple                         | 0                                             | 0                                           | 1                                             |
| Ethnicity                        |                                               |                                             |                                               |
| Units: Subjects                  |                                               |                                             |                                               |
| Hispanic or Latino               | 18                                            | 20                                          | 54                                            |
| Not Hispanic or Latino           | 127                                           | 125                                         | 198                                           |
| Menopausal Status                |                                               |                                             |                                               |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |            |            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|------------|------------|
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |            |            |
| Premenopause                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 7          | 10         | 25         |
| Postmenopause                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 83         | 82         | 157        |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 3          | 1          | 3          |
| NA - Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 52         | 52         | 67         |
| Lumbar Spine Bone Mineral Density (BMD) T-score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |            |            |
| <p>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 <math>-1.0</math> or higher; Osteopenia is defined as between <math>-1.0</math> and <math>-2.5</math>; Osteoporosis is defined as <math>-2.5</math> or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.</p> <p>Data are reported for participants with observed values (143, 144, 252, and 249 subjects in each reporting group respectively).</p> |            |            |            |
| Units: T-score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |            |            |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -1.06      | -0.92      | -1.96      |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $\pm 1.57$ | $\pm 1.86$ | $\pm 1.38$ |
| Total Hip BMD T-score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |            |            |            |
| <p>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 <math>-1.0</math> or higher; Osteopenia is defined as between <math>-1.0</math> and <math>-2.5</math>; Osteoporosis is defined as <math>-2.5</math> or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.</p> <p>Data are reported for participants with observed values (142, 142, 250, and 249 subjects in each reporting group respectively).</p> |            |            |            |
| Units: T-score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |            |            |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -0.98      | -1.14      | -1.56      |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $\pm 1.07$ | $\pm 1.00$ | $\pm 0.96$ |

| Reporting group values           | Denosumab:<br>Glucocorticoid-<br>continuing | Total |  |
|----------------------------------|---------------------------------------------|-------|--|
| Number of subjects               | 253                                         | 795   |  |
| Age Categorical                  |                                             |       |  |
| Units: Subjects                  |                                             |       |  |
| < 50 years                       | 33                                          | 66    |  |
| 50 - 64 years                    | 114                                         | 374   |  |
| 65 - 74 years                    | 73                                          | 223   |  |
| $\geq 75$ years                  | 33                                          | 132   |  |
| Age Continuous                   |                                             |       |  |
| Units: years                     |                                             |       |  |
| arithmetic mean                  | 61.5                                        | -     |  |
| standard deviation               | $\pm 11.6$                                  |       |  |
| Gender Categorical               |                                             |       |  |
| Units: Subjects                  |                                             |       |  |
| Female                           | 185                                         | 556   |  |
| Male                             | 68                                          | 239   |  |
| Race                             |                                             |       |  |
| Units: Subjects                  |                                             |       |  |
| White                            | 230                                         | 698   |  |
| Other                            | 13                                          | 47    |  |
| Asian                            | 6                                           | 36    |  |
| Black or African American        | 4                                           | 12    |  |
| American Indian or Alaska Native | 0                                           | 1     |  |
| Multiple                         | 0                                           | 1     |  |
| Ethnicity                        |                                             |       |  |
| Units: Subjects                  |                                             |       |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |     |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----|--|
| Hispanic or Latino                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 43         | 135 |  |
| Not Hispanic or Latino                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 210        | 660 |  |
| Menopausal Status                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |            |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |     |  |
| Premenopause                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 24         | 66  |  |
| Postmenopause                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 159        | 481 |  |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 2          | 9   |  |
| NA - Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 68         | 239 |  |
| Lumbar Spine Bone Mineral Density (BMD) T-score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |     |  |
| <p>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 <math>-1.0</math> or higher; Osteopenia is defined as between <math>-1.0</math> and <math>-2.5</math>; Osteoporosis is defined as <math>-2.5</math> or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.</p> <p>Data are reported for participants with observed values (143, 144, 252, and 249 subjects in each reporting group respectively).</p> |            |     |  |
| Units: T-score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |     |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -1.92      |     |  |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $\pm 1.38$ | -   |  |
| Total Hip BMD T-score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |            |     |  |
| <p>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 <math>-1.0</math> or higher; Osteopenia is defined as between <math>-1.0</math> and <math>-2.5</math>; Osteoporosis is defined as <math>-2.5</math> or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.</p> <p>Data are reported for participants with observed values (142, 142, 250, and 249 subjects in each reporting group respectively).</p> |            |     |  |
| Units: T-score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |     |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -1.66      |     |  |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $\pm 0.96$ | -   |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                          |                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Reporting group title                                                                                                                                                                                                    | Risedronate: Glucocorticoid-initiating |
| Reporting group description:<br>Participants received 5 mg risedronate orally once a day for 24 months and placebo to denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18.                          |                                        |
| Reporting group title                                                                                                                                                                                                    | Denosumab: Glucocorticoid-initiating   |
| Reporting group description:<br>Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months. |                                        |
| Reporting group title                                                                                                                                                                                                    | Risedronate: Glucocorticoid-continuing |
| Reporting group description:<br>Participants received 5 mg risedronate orally once a day for 24 months and placebo to denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18.                          |                                        |
| Reporting group title                                                                                                                                                                                                    | Denosumab: Glucocorticoid-continuing   |
| Reporting group description:<br>Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months. |                                        |

### Primary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 (Non-inferiority Analysis)

|                                                                                                                            |                                                                                                          |
|----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| End point title                                                                                                            | Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 (Non-inferiority Analysis) |
| End point description:<br>Bone mineral density at the lumbar spine was measured by dual-energy x-ray absorptiometry (DXA). |                                                                                                          |
| End point type                                                                                                             | Primary                                                                                                  |
| End point timeframe:<br>Baseline and month 12                                                                              |                                                                                                          |

| End point values                             | Risedronate: Glucocorticoid-initiating | Denosumab: Glucocorticoid-initiating | Risedronate: Glucocorticoid-continuing | Denosumab: Glucocorticoid-continuing |
|----------------------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|
| Subject group type                           | Reporting group                        | Reporting group                      | Reporting group                        | Reporting group                      |
| Number of subjects analysed                  | 126 <sup>[1]</sup>                     | 119 <sup>[2]</sup>                   | 211 <sup>[3]</sup>                     | 209 <sup>[4]</sup>                   |
| Units: percent change                        |                                        |                                      |                                        |                                      |
| least squares mean (confidence interval 95%) | 0.8 (0.2 to 1.5)                       | 3.8 (3.1 to 4.5)                     | 2.3 (1.7 to 2.9)                       | 4.4 (3.8 to 5.0)                     |

Notes:

- [1] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.
- [2] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.
- [3] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.
- [4] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

### Statistical analyses

|                                                                                                                                          |                                             |
|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Statistical analysis title                                                                                                               | GC-I Subpopulation Non-inferiority Analysis |
| Statistical analysis description:<br>Analyses of the primary and secondary endpoints were performed independently in the glucocorticoid- |                                             |

continuing and glucocorticoid-initiating subpopulations. A fixed-sequence testing procedure was used to control the experiment-wise type 1 error rate at a two-sided 5% significance level within each subpopulation.

The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for treatment, baseline BMD, sex, machine type, and baseline BMD-by-machine type interaction.

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating |
| Number of subjects included in analysis | 245                                                                           |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           | non-inferiority <sup>[5]</sup>                                                |
| P-value                                 | < 0.001 <sup>[6]</sup>                                                        |
| Method                                  | ANCOVA                                                                        |
| Parameter estimate                      | LS Mean Difference                                                            |
| Point estimate                          | 2.9                                                                           |
| Confidence interval                     |                                                                               |
| level                                   | 95 %                                                                          |
| sides                                   | 2-sided                                                                       |
| lower limit                             | 2                                                                             |
| upper limit                             | 3.9                                                                           |

Notes:

[5] - Non-inferiority was shown if the lower bound of the two-sided 95% CI for the difference between the least-squares means (denosumab minus risedronate) was higher than the prespecified non-inferiority margin of -1.1 percentage points for the glucocorticoid-initiating subpopulation.

[6] - One-sided p-value based on the prespecified noninferiority margin for lumbar spine of -1.1%.

|                                   |                                             |
|-----------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b> | GC-C Subpopulation Non-inferiority Analysis |
|-----------------------------------|---------------------------------------------|

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.

The glucocorticoid-continuing subpopulation was analyzed using an ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use (< 12 months vs ≥ 12 months).

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing |
| Number of subjects included in analysis | 420                                                                           |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           | non-inferiority <sup>[7]</sup>                                                |
| P-value                                 | < 0.001 <sup>[8]</sup>                                                        |
| Method                                  | ANCOVA                                                                        |
| Parameter estimate                      | LS Mean Difference                                                            |
| Point estimate                          | 2.2                                                                           |
| Confidence interval                     |                                                                               |
| level                                   | 95 %                                                                          |
| sides                                   | 2-sided                                                                       |
| lower limit                             | 1.4                                                                           |
| upper limit                             | 3                                                                             |

Notes:

[7] - Non-inferiority was shown if the lower bound of the two-sided 95% CI for the difference between the least-squares means (denosumab minus risedronate) was higher than the prespecified non-inferiority margin of -0.7 percentage points for the glucocorticoid-continuing subpopulation.

[8] - One-sided p-value based on the prespecified noninferiority margins for lumbar spine of -0.7%.

## **Secondary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 (Superiority Analysis)**

|                 |                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 (Superiority Analysis) |
|-----------------|------------------------------------------------------------------------------------------------------|

|                                                                                                  |           |
|--------------------------------------------------------------------------------------------------|-----------|
| End point description:                                                                           |           |
| Bone mineral density at the lumbar spine was measured by dual-energy x-ray absorptiometry (DXA). |           |
| End point type                                                                                   | Secondary |
| End point timeframe:                                                                             |           |
| Baseline and month 12                                                                            |           |

| End point values                             | Risedronate:<br>Glucocorticoid-<br>initiating | Denosumab:<br>Glucocorticoid-<br>initiating | Risedronate:<br>Glucocorticoid-<br>continuing | Denosumab:<br>Glucocorticoid-<br>continuing |
|----------------------------------------------|-----------------------------------------------|---------------------------------------------|-----------------------------------------------|---------------------------------------------|
| Subject group type                           | Reporting group                               | Reporting group                             | Reporting group                               | Reporting group                             |
| Number of subjects analysed                  | 126 <sup>[9]</sup>                            | 119 <sup>[10]</sup>                         | 211 <sup>[11]</sup>                           | 209 <sup>[12]</sup>                         |
| Units: percent change                        |                                               |                                             |                                               |                                             |
| least squares mean (confidence interval 95%) | 0.8 (0.2 to 1.5)                              | 3.8 (3.1 to 4.5)                            | 2.3 (1.7 to 2.9)                              | 4.4 (3.8 to 5.0)                            |

Notes:

[9] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[10] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[11] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[12] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

## Statistical analyses

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | GC-I Subpopulation Superiority Analysis |
|-----------------------------------|-----------------------------------------|

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.

The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. LS Mean difference was calculated as Denosumab - Risedronate.

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating |
| Number of subjects included in analysis | 245                                                                           |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           | superiority                                                                   |
| P-value                                 | < 0.001 <sup>[13]</sup>                                                       |
| Method                                  | ANCOVA                                                                        |
| Parameter estimate                      | LS Mean Difference                                                            |
| Point estimate                          | 2.9                                                                           |
| Confidence interval                     |                                                                               |
| level                                   | 95 %                                                                          |
| sides                                   | 2-sided                                                                       |
| lower limit                             | 2                                                                             |
| upper limit                             | 3.9                                                                           |

Notes:

[13] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | GC-C Subpopulation Superiority Analysis |
|-----------------------------------|-----------------------------------------|

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level. The glucocorticoid-continuing subpopulation was analyzed using an

ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use. LS Mean difference = Denosumab - Risedronate.

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing |
| Number of subjects included in analysis | 420                                                                           |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           | superiority                                                                   |
| P-value                                 | < 0.001 <sup>[14]</sup>                                                       |
| Method                                  | ANCOVA                                                                        |
| Parameter estimate                      | LS Mean Difference                                                            |
| Point estimate                          | 2.2                                                                           |
| Confidence interval                     |                                                                               |
| level                                   | 95 %                                                                          |
| sides                                   | 2-sided                                                                       |
| lower limit                             | 1.4                                                                           |
| upper limit                             | 3                                                                             |

Notes:

[14] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

## Secondary: Percent Change From Baseline in Total Hip Bone Mineral Density at Month 12

|                        |                                                                                               |
|------------------------|-----------------------------------------------------------------------------------------------|
| End point title        | Percent Change From Baseline in Total Hip Bone Mineral Density at Month 12                    |
| End point description: | Bone mineral density at the total hip was measured by dual-energy x-ray absorptiometry (DXA). |
| End point type         | Secondary                                                                                     |
| End point timeframe:   | Baseline and month 12                                                                         |

| End point values                             | Risedronate: Glucocorticoid-initiating | Denosumab: Glucocorticoid-initiating | Risedronate: Glucocorticoid-continuing | Denosumab: Glucocorticoid-continuing |
|----------------------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|
| Subject group type                           | Reporting group                        | Reporting group                      | Reporting group                        | Reporting group                      |
| Number of subjects analysed                  | 128 <sup>[15]</sup>                    | 119 <sup>[16]</sup>                  | 215 <sup>[17]</sup>                    | 217 <sup>[18]</sup>                  |
| Units: percent change                        |                                        |                                      |                                        |                                      |
| least squares mean (confidence interval 95%) | 0.2 (-0.2 to 0.7)                      | 1.7 (1.2 to 2.2)                     | 0.6 (0.2 to 1.0)                       | 2.1 (1.7 to 2.5)                     |

Notes:

[15] - Randomized participants with a baseline and month 12 measurement for the total hip BMD.

[16] - Randomized participants with a baseline and month 12 measurement for the total hip BMD.

[17] - Randomized participants with a baseline and month 12 measurement for the total hip BMD.

[18] - Randomized participants with a baseline and month 12 measurement for the total hip BMD.

## Statistical analyses

|                                   |                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title        | GC-I Subpopulation Superiority Analysis                                                                                                                                                                                                                                                                                                |
| Statistical analysis description: | Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.<br>The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for |

treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. LS mean difference = Denosumab - Risedronate.

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating |
| Number of subjects included in analysis | 247                                                                           |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           | superiority                                                                   |
| P-value                                 | < 0.001 <sup>[19]</sup>                                                       |
| Method                                  | ANCOVA                                                                        |
| Parameter estimate                      | LS Mean Difference                                                            |
| Point estimate                          | 1.5                                                                           |
| Confidence interval                     |                                                                               |
| level                                   | 95 %                                                                          |
| sides                                   | 2-sided                                                                       |
| lower limit                             | 0.8                                                                           |
| upper limit                             | 2.1                                                                           |

Notes:

[19] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | GC-C Subpopulation Superiority Analysis |
|-----------------------------------|-----------------------------------------|

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level. The glucocorticoid-continuing subpopulation was analyzed using an ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use. LS Mean difference = Denosumab - Risedronate.

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing |
| Number of subjects included in analysis | 432                                                                           |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           | superiority                                                                   |
| P-value                                 | < 0.001 <sup>[20]</sup>                                                       |
| Method                                  | ANCOVA                                                                        |
| Parameter estimate                      | LS Mean Difference                                                            |
| Point estimate                          | 1.5                                                                           |
| Confidence interval                     |                                                                               |
| level                                   | 95 %                                                                          |
| sides                                   | 2-sided                                                                       |
| lower limit                             | 1                                                                             |
| upper limit                             | 2.1                                                                           |

Notes:

[20] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

## Secondary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 24

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 24 |
|-----------------|-------------------------------------------------------------------------------|

End point description:

Bone mineral density at the lumbar spine was measured by dual-energy x-ray absorptiometry (DXA).

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

End point timeframe:

Baseline and month 24

| End point values                             | Risedronate:<br>Glucocorticoid-<br>initiating | Denosumab:<br>Glucocorticoid-<br>initiating | Risedronate:<br>Glucocorticoid-<br>continuing | Denosumab:<br>Glucocorticoid-<br>continuing |
|----------------------------------------------|-----------------------------------------------|---------------------------------------------|-----------------------------------------------|---------------------------------------------|
| Subject group type                           | Reporting group                               | Reporting group                             | Reporting group                               | Reporting group                             |
| Number of subjects analysed                  | 113 <sup>[21]</sup>                           | 107 <sup>[22]</sup>                         | 174 <sup>[23]</sup>                           | 183 <sup>[24]</sup>                         |
| Units: percent change                        |                                               |                                             |                                               |                                             |
| least squares mean (confidence interval 95%) | 1.7 (0.8 to 2.7)                              | 6.2 (5.3 to 7.2)                            | 3.2 (2.3 to 4.1)                              | 6.4 (5.5 to 7.2)                            |

Notes:

[21] - Randomized participants with a baseline and month 24 measurement for the lumbar spine BMD.

[22] - Randomized participants with a baseline and month 24 measurement for the lumbar spine BMD.

[23] - Randomized participants with a baseline and month 24 measurement for the lumbar spine BMD.

[24] - Randomized participants with a baseline and month 24 measurement for the lumbar spine BMD.

## Statistical analyses

| Statistical analysis title | GC-I Subpopulation Superiority Analysis |
|----------------------------|-----------------------------------------|
|----------------------------|-----------------------------------------|

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.

The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. LS mean difference = Denosumab - Risedronate.

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating |
| Number of subjects included in analysis | 220                                                                           |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           | superiority                                                                   |
| P-value                                 | < 0.001 <sup>[25]</sup>                                                       |
| Method                                  | ANCOVA                                                                        |
| Parameter estimate                      | LS Mean Difference                                                            |
| Point estimate                          | 4.5                                                                           |
| Confidence interval                     |                                                                               |
| level                                   | 95 %                                                                          |
| sides                                   | 2-sided                                                                       |
| lower limit                             | 3.2                                                                           |
| upper limit                             | 5.8                                                                           |

Notes:

[25] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

| Statistical analysis title | GC-C Subpopulation Superiority Analysis |
|----------------------------|-----------------------------------------|
|----------------------------|-----------------------------------------|

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level. The glucocorticoid-continuing subpopulation was analyzed using an ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use. LS Mean difference = Denosumab - Risedronate.

|                   |                                                                               |
|-------------------|-------------------------------------------------------------------------------|
| Comparison groups | Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing |
|-------------------|-------------------------------------------------------------------------------|

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 357                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.001 <sup>[26]</sup> |
| Method                                  | ANCOVA                  |
| Parameter estimate                      | LS Mean Difference      |
| Point estimate                          | 3.2                     |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 2                       |
| upper limit                             | 4.3                     |

Notes:

[26] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

## Secondary: Percent Change From Baseline in Total Hip Bone Mineral Density at Month 24

|                        |                                                                                               |
|------------------------|-----------------------------------------------------------------------------------------------|
| End point title        | Percent Change From Baseline in Total Hip Bone Mineral Density at Month 24                    |
| End point description: | Bone mineral density at the total hip was measured by dual-energy x-ray absorptiometry (DXA). |
| End point type         | Secondary                                                                                     |
| End point timeframe:   | Baseline and month 24                                                                         |

| End point values                             | Risedronate: Glucocorticoid-initiating | Denosumab: Glucocorticoid-initiating | Risedronate: Glucocorticoid-continuing | Denosumab: Glucocorticoid-continuing |
|----------------------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|
| Subject group type                           | Reporting group                        | Reporting group                      | Reporting group                        | Reporting group                      |
| Number of subjects analysed                  | 111 <sup>[27]</sup>                    | 104 <sup>[28]</sup>                  | 176 <sup>[29]</sup>                    | 181 <sup>[30]</sup>                  |
| Units: percent change                        |                                        |                                      |                                        |                                      |
| least squares mean (confidence interval 95%) | -0.0 (-0.6 to 0.6)                     | 3.1 (2.4 to 3.7)                     | 0.5 (-0.1 to 1.0)                      | 2.9 (2.4 to 3.5)                     |

Notes:

[27] - Randomized participants with a baseline and month 24 measurement for the total hip BMD.

[28] - Randomized participants with a baseline and month 24 measurement for the total hip BMD.

[29] - Randomized participants with a baseline and month 24 measurement for the total hip BMD.

[30] - Randomized participants with a baseline and month 24 measurement for the total hip BMD.

## Statistical analyses

|                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title        | CG-I Subpopulation Superiority Analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Statistical analysis description: | Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.<br>The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. LS mean difference = Denosumab - Risedronate. |
| Comparison groups                 | Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating                                                                                                                                                                                                                                                                                                                                                                                                              |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 215                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.001 <sup>[31]</sup> |
| Method                                  | ANCOVA                  |
| Parameter estimate                      | LS Mean Difference      |
| Point estimate                          | 3.1                     |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 2.2                     |
| upper limit                             | 3.9                     |

Notes:

[31] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | GC-C Subpopulation Superiority Analysis |
|-----------------------------------|-----------------------------------------|

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level. The glucocorticoid-continuing subpopulation was analyzed using an ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use. LS Mean difference = Denosumab - Risedronate.

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing |
| Number of subjects included in analysis | 357                                                                           |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           | superiority                                                                   |
| P-value                                 | < 0.001 <sup>[32]</sup>                                                       |
| Method                                  | ANCOVA                                                                        |
| Parameter estimate                      | LS Mean Difference                                                            |
| Point estimate                          | 2.5                                                                           |
| Confidence interval                     |                                                                               |
| level                                   | 95 %                                                                          |
| sides                                   | 2-sided                                                                       |
| lower limit                             | 1.7                                                                           |
| upper limit                             | 3.2                                                                           |

Notes:

[32] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 Months

Adverse event reporting additional description:

One participant was randomized to risedronate but received denosumab in error; this participant was included in the denosumab group for safety analyses.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Denosumab |
|-----------------------|-----------|

Reporting group description:

Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Risedronate |
|-----------------------|-------------|

Reporting group description:

Participants received 5 mg risedronate orally once a day for 24 months and placebo to denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18.

| Serious adverse events                                              | Denosumab         | Risedronate       |  |
|---------------------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed                                         | 92 / 394 (23.35%) | 98 / 385 (25.45%) |  |
| number of deaths (all causes)                                       | 13                | 9                 |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Basal cell carcinoma                                                |                   |                   |  |
| subjects affected / exposed                                         | 1 / 394 (0.25%)   | 0 / 385 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Breast cancer                                                       |                   |                   |  |
| subjects affected / exposed                                         | 0 / 394 (0.00%)   | 1 / 385 (0.26%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Colon cancer                                                        |                   |                   |  |
| subjects affected / exposed                                         | 0 / 394 (0.00%)   | 1 / 385 (0.26%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |

|                                                                 |                 |                 |  |
|-----------------------------------------------------------------|-----------------|-----------------|--|
| Gastrointestinal stromal tumour<br>subjects affected / exposed  | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Invasive ductal breast carcinoma<br>subjects affected / exposed | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Lung neoplasm<br>subjects affected / exposed                    | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Metastases to liver<br>subjects affected / exposed              | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Metastases to lung<br>subjects affected / exposed               | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Metastatic neoplasm<br>subjects affected / exposed              | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 1           | 0 / 0           |  |
| Neoplasm<br>subjects affected / exposed                         | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 2           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 1           | 0 / 0           |  |
| Prostate cancer<br>subjects affected / exposed                  | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Prostatic adenoma                                               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal cancer metastatic                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterine leiomyoma                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic stenosis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Capillary leak syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemodynamic instability                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Temporal arteritis                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombosis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vasculitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Cataract operation                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colectomy                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileostomy                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Knee arthroplasty                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung neoplasm surgery                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphadenectomy                                 |                 |                 |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Sigmoidectomy                                        |                 |                 |  |
| subjects affected / exposed                          | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Spinal decompression                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 394 (0.25%) | 0 / 385 (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 |                 |                 |  |
| Asthenia                                             |                 |                 |  |
| subjects affected / exposed                          | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death                                                |                 |                 |  |
| subjects affected / exposed                          | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1           |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pyrexia                                              |                 |                 |  |
| subjects affected / exposed                          | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Immune system disorders                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Eosinophilic granulomatosis with polyangiitis   |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Food allergy                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Cervix haematoma uterine                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystocele                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Menorrhagia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian cyst                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Alveolitis allergic                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Asthma                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopneumopathy                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 3 / 385 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic respiratory failure                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Organising pneumonia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |

|                                                       |                 |                 |  |
|-------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                           | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                                    |                 |                 |  |
| subjects affected / exposed                           | 0 / 394 (0.00%) | 5 / 385 (1.30%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 5           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 1           |  |
| Pulmonary fibrosis                                    |                 |                 |  |
| subjects affected / exposed                           | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Vocal cord polyp                                      |                 |                 |  |
| subjects affected / exposed                           | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                                 |                 |                 |  |
| Anxiety                                               |                 |                 |  |
| subjects affected / exposed                           | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Behaviour disorder due to a general medical condition |                 |                 |  |
| subjects affected / exposed                           | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Confusional state                                     |                 |                 |  |
| subjects affected / exposed                           | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Delirium                                              |                 |                 |  |
| subjects affected / exposed                           | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Investigations                                        |                 |                 |  |

|                                                                 |                 |                 |  |
|-----------------------------------------------------------------|-----------------|-----------------|--|
| Blood creatinine increased<br>subjects affected / exposed       | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Blood pressure increased<br>subjects affected / exposed         | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 2           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 1           |  |
| White blood cell count increased<br>subjects affected / exposed | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications               |                 |                 |  |
| Acetabulum fracture<br>subjects affected / exposed              | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Chest injury<br>subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Fall<br>subjects affected / exposed                             | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture<br>subjects affected / exposed            | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 2           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Femur fracture<br>subjects affected / exposed                   | 3 / 394 (0.76%) | 0 / 385 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 3           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Fibula fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| 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                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ligament rupture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Limb injury                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar vertebral fracture                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meniscus injury                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multiple injuries                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Patella fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax traumatic                          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pubis fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radius fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (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                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxicity to various agents                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Traumatic haemothorax                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Congenital megaureter                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic valve sclerosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Aortic valve stenosis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (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                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 394 (0.76%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiopulmonary failure                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mitral valve disease                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (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                        |                 |                 |  |
| Ataxia                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 394 (0.76%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cervicobrachial syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hemiparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydrocephalus                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multiple sclerosis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paresis                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parkinson's disease                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica                                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 394 (0.76%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Cataract                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Glaucoma                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| 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 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis ulcerative                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum intestinal                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum intestinal haemorrhagic            |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspepsia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphagia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterovesical fistula                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erosive oesophagitis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia strangulated                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Large intestinal ulcer                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar hernia                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal ulcer                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peptic ulcer                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subileus                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Vomiting                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct stone                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Biliary dyskinesia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis chronic                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Dermatomyositis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pruritus generalised                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lupus nephritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Ankylosing spondylitis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 3 / 385 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bursitis                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Exposed bone in jaw                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc degeneration                |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar spinal stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mixed connective tissue disease                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscle haemorrhage                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neck pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 5 / 385 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polymyalgia rheumatica                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rheumatoid arthritis                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sjogren's syndrome                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Synovitis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertebral foraminal stenosis                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (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                     |                 |                 |  |
| Abdominal abscess                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess limb                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis infective                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium colitis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic fever                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Helicobacter gastritis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymph node tuberculosis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphangitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Necrotising fasciitis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonsillar abscess                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 7 / 394 (1.78%) | 8 / 385 (2.08%) |  |
| occurrences causally related to treatment / all | 0 / 8           | 1 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia bacterial                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural infection                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 2 / 385 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Serratia infection                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinusitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection bacterial               |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection bacterial                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 394 (0.51%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 394 (0.25%) | 0 / 385 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ketosis                                         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periarthritis calcarea                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 394 (0.00%) | 1 / 385 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Denosumab         | Risedronate       |  |
|-------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 77 / 394 (19.54%) | 76 / 385 (19.74%) |  |
| Vascular disorders                                    |                   |                   |  |
| Hypertension                                          |                   |                   |  |
| subjects affected / exposed                           | 21 / 394 (5.33%)  | 15 / 385 (3.90%)  |  |
| occurrences (all)                                     | 23                | 18                |  |
| Musculoskeletal and connective tissue disorders       |                   |                   |  |
| Arthralgia                                            |                   |                   |  |
| subjects affected / exposed                           | 23 / 394 (5.84%)  | 33 / 385 (8.57%)  |  |
| occurrences (all)                                     | 26                | 44                |  |
| Back pain                                             |                   |                   |  |
| subjects affected / exposed                           | 24 / 394 (6.09%)  | 21 / 385 (5.45%)  |  |
| occurrences (all)                                     | 24                | 22                |  |
| Infections and infestations                           |                   |                   |  |
| Viral upper respiratory tract infection               |                   |                   |  |
| subjects affected / exposed                           | 20 / 394 (5.08%)  | 19 / 385 (4.94%)  |  |
| occurrences (all)                                     | 21                | 24                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06 December 2011 | <ul style="list-style-type: none"><li>• Exploratory objectives clarified: HR-pQCT data to be collected in a subset of subjects only, and PK/BTM samples are only to be collected in subjects participating in the PK/BTM substudy</li><li>• Added statement that subjects in the transiliac bone biopsy substudy are to receive tetracycline or tetracycline derivative prior to the bone biopsy procedure</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 15 February 2012 | <ul style="list-style-type: none"><li>• Entry criteria clarified:<ul style="list-style-type: none"><li>- Subjects less than 50 years old and without an osteoporotic fracture will not be eligible to enroll.</li><li>- Subjects initiating biologics within 4 weeks prior to screening will not be eligible to enroll; however, administration of biologic medications will not be proscribed during the study</li><li>- Subjects with a history of infection immediately prior to screening will not be eligible to enroll.</li></ul></li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 29 June 2012     | <ul style="list-style-type: none"><li>• Entry criteria clarified:<ul style="list-style-type: none"><li>- GC-C subjects <math>\geq 50</math> years of age are required to have a BMD value equivalent to a T-score <math>\leq -2.0</math> at the lumbar spine, total hip, or femoral neck; or a BMD value equivalent to a T-score <math>\leq -1.0</math> at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture.</li><li>- Subjects administering <math>&gt; 1</math> biologic agent for the treatment of underlying inflammatory disease to be excluded</li><li>- Subjects with a history of Addison's disease to be excluded</li><li>- Clarified the existing exclusion criterion of recent tooth extraction or dental surgery</li></ul></li><li>• Secondary objectives were separated with respect to lumbar spine and total hip.</li><li>• Information on choice of noninferiority margins was updated.</li><li>• Clarified that safety analyses would be done in the combined subpopulations</li><li>• Added information regarding a DRT</li><li>• Added criteria for permanent withholding of denosumab and risedronate due to serious infection</li><li>• Added urine dipstick pregnancy tests at day 10 and months 6, 12, and 18, and clarified that any female subject who becomes pregnant should permanently discontinue investigational product</li></ul> |
| 22 February 2013 | <ul style="list-style-type: none"><li>• Incorporated updated procedures of reporting adverse events and serious adverse events to IRB/IECs and regulatory authorities</li><li>• Replaced the DRT with a DMC for ongoing monitoring of study data</li><li>• Clarified that the noninferiority comparison will only be performed for the primary efficacy endpoint within each subpopulation</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 30 June 2016     | <ul style="list-style-type: none"><li>• Bone biopsy assessment added at 24 months for the bone biopsy substudy to bring the number of evaluable specimens closer to the protocol-indicated number (due to difficulties in recruitment to the substudy and some collected specimens being unevaluable)</li><li>• Noted that analysis of HR-pQCT data will be performed at the end of the study (month 24)</li><li>• Updated safety language</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported