

**Clinical trial results:****A Randomized, Multicenter, Open-label, Parallel Group Study in Postmenopausal Women With Osteoporosis to Evaluate the Noninferiority of Subject-administered Romosozumab via Autoinjector/Pen vs Healthcare Provider-administered Romosozumab via Prefilled Syringe****Summary**

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2017-003512-40  |
| Trial protocol           | GB PL           |
| Global end of trial date | 08 January 2020 |

**Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 21 November 2020 |
| First version publication date | 21 November 2020 |

**Trial information****Trial identification**

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20150120 |
|-----------------------|----------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03432533 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Amgen Inc.   |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States,                                |
| Public contact               | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH,<br>MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH,<br>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                       | 08 January 2020 |
| Is this the analysis of the primary completion data? | No              |

|                                  |                 |
|----------------------------------|-----------------|
| Global end of trial reached?     | Yes             |
| Global end of trial date         | 08 January 2020 |
| Was the trial ended prematurely? | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the noninferiority of a 6-month treatment with romosozumab 210 mg administered subcutaneously (SC) once monthly (QM) in postmenopausal women with osteoporosis either by subject self-administration with autoinjector (AI)/pen or by healthcare provider (HCP) administration with prefilled syringe (PFS).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations/guidelines. 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                          | 06 February 2018 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 95  |
| Country: Number of subjects enrolled | United Kingdom: 32 |
| Country: Number of subjects enrolled | Poland: 156        |
| Worldwide total number of subjects   | 283                |
| EEA total number of subjects         | 188                |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 74 |

|                     |     |
|---------------------|-----|
| From 65 to 84 years | 197 |
| 85 years and over   | 12  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 36 centers in Poland, United Kingdom, and United States.

### Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio.

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | Romosozumab 210 mg QM: PFS |
|------------------|----------------------------|

Arm description:

During the open-label treatment period, participants received 210 mg romosozumab subcutaneously (SC) once a month (QM) by health care provider (HCP) administration with pre-filled syringe (PFS).

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | romosozumab                                  |
| Investigational medicinal product code | AMG785                                       |
| Other name                             | Evenity                                      |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subconjunctival use, Subcutaneous use        |

Dosage and administration details:

210 mg romosozumab SC QM by HCP administration with 2 PFS

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Romosozumab 210 mg QM: AI/Pen |
|------------------|-------------------------------|

Arm description:

During the open-label treatment period, participants received 210 mg romosozumab SC QM by self-administration with autoinjector (AI)/pen.

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | romosozumab                              |
| Investigational medicinal product code | AMG785                                   |
| Other name                             | Evenity                                  |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

210 mg romosozumab SC QM by self-administration with 2 AI/Pens

| <b>Number of subjects in period 1</b> | Romosozumab 210<br>mg QM: PFS | Romosozumab 210<br>mg QM: AI/Pen |
|---------------------------------------|-------------------------------|----------------------------------|
| Started                               | 141                           | 142                              |
| Completed 6-Month Treatment Period    | 136                           | 137                              |
| Completed                             | 126                           | 131                              |
| Not completed                         | 15                            | 11                               |
| Consent withdrawn by subject          | 14                            | 9                                |
| Lost to follow-up                     | 1                             | 2                                |

## Baseline characteristics

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Romosozumab 210 mg QM: PFS |
|-----------------------|----------------------------|

Reporting group description:

During the open-label treatment period, participants received 210 mg romosozumab subcutaneously (SC) once a month (QM) by health care provider (HCP) administration with pre-filled syringe (PFS).

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Romosozumab 210 mg QM: AI/Pen |
|-----------------------|-------------------------------|

Reporting group description:

During the open-label treatment period, participants received 210 mg romosozumab SC QM by self-administration with autoinjector (AI)/pen.

| Reporting group values | Romosozumab 210 mg QM: PFS | Romosozumab 210 mg QM: AI/Pen | Total |
|------------------------|----------------------------|-------------------------------|-------|
| Number of subjects     | 141                        | 142                           | 283   |
| Age categorical        |                            |                               |       |
| Units: Subjects        |                            |                               |       |

|   |       |       |     |
|---|-------|-------|-----|
| Age Continuous  |       |       |     |
| Units: years  |       |       |     |
| arithmetic mean   | 70.3  | 69.5  |     |
| standard deviation  | ± 7.1 | ± 8.4 | -   |
| Sex: Female, Male   |       |       |     |
| Units:  |       |       |     |
| Female  | 141   | 142   | 283 |
| Male  | 0     | 0     | 0   |
| Ethnicity (NIH/OMB)   |       |       |     |
| Units: Subjects   |       |       |     |
| Hispanic or Latino  | 3     | 1     | 4   |
| Not Hispanic or Latino  | 138   | 141   | 279 |
| Unknown or Not Reported   | 0     | 0     | 0   |
| Participants With Pre-Existing Anti-Romosozumab Antibodies  |       |       |     |
| Number of participants with pre-existing antibodies, including those who were binding antibody positive and those who were neutralizing antibody positive at or before baseline (BL). |       |       |     |
| Units: Subjects   |       |       |     |
| Binding Antibody Positive at or Before BL   | 3     | 0     | 3   |
| Neutralizing Antibody Positive at or Before BL  | 0     | 0     | 0   |
| Binding Antibody Negative at or Before BL   | 138   | 142   | 280 |
| Race (NIH/OMB)  |       |       |     |
| Units: Subjects   |       |       |     |
| American Indian or Alaska Native  | 0     | 0     | 0   |
| Asian   | 1     | 1     | 2   |
| Native Hawaiian or Other Pacific Islander   | 0     | 0     | 0   |
| Black or African American   | 1     | 1     | 2   |
| White   | 139   | 140   | 279 |
| More than one race  | 0     | 0     | 0   |
| Unknown or Not Reported   | 0     | 0     | 0   |

|   |        |        |   |
|---|--------|--------|---|
| Lumbar Spine Bone Mineral Density (BMD) T-Score   |        |        |   |
| The T-score is the BMD at the site when compared to that of a healthy thirty-year-old of the same sex. Lower scores (more negative) mean lower bone density. Normal is a T-score of –1.0 or higher; Osteopenia is defined as between –1.0 and –2.5, meaning below-normal bone density without full osteoporosis; Osteoporosis is defined as –2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman. |        |        |   |
| Units: T-score  |        |        |   |
| arithmetic mean   | -2.69  | -2.85  |   |
| standard deviation  | ± 1.03 | ± 1.00 | - |
| Total Hip BMD T-Score   |        |        |   |
| The T-score is the BMD at the site when compared to that of a healthy thirty-year-old of the same sex. Lower scores (more negative) mean lower bone density. Normal is a T-score of –1.0 or higher; Osteopenia is defined as between –1.0 and –2.5, meaning below-normal bone density without full osteoporosis; Osteoporosis is defined as –2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman. |        |        |   |
| Units: T-score  |        |        |   |
| arithmetic mean   | -2.29  | -2.30  |   |
| standard deviation  | ± 0.73 | ± 0.77 | - |
| Femoral Neck BMD T-Score  |        |        |   |
| The T-score is the BMD at the site when compared to that of a healthy thirty-year-old of the same sex. Lower scores (more negative) mean lower bone density. Normal is a T-score of –1.0 or higher; Osteopenia is defined as between –1.0 and –2.5, meaning below-normal bone density without full osteoporosis; Osteoporosis is defined as –2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman. |        |        |   |
| Units: T-score  |        |        |   |
| arithmetic mean   | -2.54  | -2.49  |   |
| standard deviation  | ± 0.63 | ± 0.65 | - |

## End points

### End points reporting groups

|  |                               |
|--|-------------------------------|
| Reporting group title  | Romosozumab 210 mg QM: PFS    |
| Reporting group description:<br>During the open-label treatment period, participants received 210 mg romosozumab subcutaneously (SC) once a month (QM) by health care provider (HCP) administration with pre-filled syringe (PFS). |                               |
| Reporting group title  | Romosozumab 210 mg QM: AI/Pen |
| Reporting group description:<br>During the open-label treatment period, participants received 210 mg romosozumab SC QM by self-administration with autoinjector (AI)/pen.  |                               |

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

|  |   |
|--|---|
| End point title  | Percent Change From Baseline in Lumbar Spine BMD at Month 6 |
| End point description:<br>Percent change from baseline in BMD at the lumbar spine as measured by dual-energy x-ray absorptiometry (DXA). |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline, Month 6  |   |

| End point values                    | Romosozumab 210 mg QM: PFS | Romosozumab 210 mg QM: AI/Pen |  |  |
|-------------------------------------|----------------------------|-------------------------------|--|--|
| Subject group type                  | Reporting group            | Reporting group               |  |  |
| Number of subjects analysed         | 135                        | 134                           |  |  |
| Units: percent change               |                            |                               |  |  |
| least squares mean (standard error) | 9.2 ( $\pm$ 0.4)           | 9.0 ( $\pm$ 0.5)              |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Statistical Analysis 1                                     |
| Comparison groups                       | Romosozumab 210 mg QM: PFS v Romosozumab 210 mg QM: AI/Pen |
| Number of subjects included in analysis | 269  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.84   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS Mean Difference   |
| Point estimate                          | -0.1   |



|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -1.3                       |
| upper limit          | 1                          |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.6                        |

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

|   |  |
|---|--|
| End point title   | Percent Change From Baseline in Total Hip BMD at Month 6 |
| End point description:<br>Percent change from baseline in BMD for total hip as measured by DXA. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline, Month 6   |  |

| End point values                    | Romosozumab<br>210 mg QM:<br>PFS | Romosozumab<br>210 mg QM:<br>AI/Pen |  |  |
|-------------------------------------|----------------------------------|-------------------------------------|--|--|
| Subject group type                  | Reporting group                  | Reporting group                     |  |  |
| Number of subjects analysed         | 135                              | 134                                 |  |  |
| Units: percent change               |                                  |                                     |  |  |
| least squares mean (standard error) | 3.7 ( $\pm$ 0.6)                 | 3.6 ( $\pm$ 0.3)                    |  |  |

### Statistical analyses

No statistical analyses for this end point

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

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in Femoral Neck BMD at Month 6 |
| End point description:<br>Percent change from baseline in BMD at femoral neck as measured by DXA. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline, Month 6   |   |

| End point values                    | Romosozumab<br>210 mg QM:<br>PFS | Romosozumab<br>210 mg QM:<br>AI/Pen |  |  |
|-------------------------------------|----------------------------------|-------------------------------------|--|--|
| Subject group type                  | Reporting group                  | Reporting group                     |  |  |
| Number of subjects analysed         | 135                              | 134                                 |  |  |
| Units: percent change               |                                  |                                     |  |  |
| least squares mean (standard error) | 3.4 (± 0.7)                      | 3.6 (± 0.5)                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Device-Related AEs, Discontinuations Due to AEs, and Deaths

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Device-Related AEs, Discontinuations Due to AEs, and Deaths |
|-----------------|---|

End point description:

AE: any untoward medical occurrence irrespective of a causal relationship with the study treatment.  
SAE: any untoward medical occurrence that meets at least 1 of the following criteria: results in death; is immediately life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is a medically important serious event. Adverse device effect: any AE related to the use of a combination product or medical device. TEAEs are those AEs occurring after first dose of study drug.

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

End point timeframe:

up to Month 9 (-7/+3 days)

| End point values                                  | Romosozumab<br>210 mg QM:<br>PFS | Romosozumab<br>210 mg QM:<br>AI/Pen |  |  |
|---|----------------------------------|-------------------------------------|--|--|
| Subject group type                                | Reporting group                  | Reporting group                     |  |  |
| Number of subjects analysed                       | 141                              | 142                                 |  |  |
| Units: participants                               |                                  |                                     |  |  |
| TEAEs: All  | 94                               | 96                                  |  |  |
| TEAEs: SAEs                                       | 7                                | 4                                   |  |  |
| TEAEs: Leading to Study Drug Discontinuation (DC) | 7                                | 15                                  |  |  |
| TEAEs: Fatal                                      | 0                                | 0                                   |  |  |
| Treatment-Related (TR) TEAEs: All                 | 38                               | 59                                  |  |  |
| TR TEAEs: SAEs                                    | 0                                | 0                                   |  |  |
| TR TEAEs: Leading to Study Drug DC                | 6                                | 10                                  |  |  |
| TR TEAEs: Fatal                                   | 0                                | 0                                   |  |  |
| Device-Related (DR) TEAEs: All                    | 18                               | 30                                  |  |  |
| DR TEAEs: SAEs                                    | 0                                | 0                                   |  |  |
| DR TEAEs: Leading to Study Drug DC                | 0                                | 5                                   |  |  |
| DR TEAEs: Fatal                                   | 0                                | 0                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Developing Anti-Romosozumab Antibodies

|                 |   |
|-----------------|---|
| End point title | Number of Participants Developing Anti-Romosozumab Antibodies |
|-----------------|---|

End point description:

Participants with a negative or no result at baseline (BL) developing anti-romosozumab antibodies postbaseline, including those who were binding antibody-positive or neutralizing antibody-positive postbaseline. 'Transient' positive results are those with a negative result at the participant's last time point tested within the study period.

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

End point timeframe:

up to Month 9 (-7/+3 days)

| End point values                                    | Romosozumab<br>210 mg QM:<br>PFS | Romosozumab<br>210 mg QM:<br>AI/Pen |  |  |
|---|----------------------------------|-------------------------------------|--|--|
| Subject group type                                  | Reporting group                  | Reporting group                     |  |  |
| Number of subjects analysed                         | 139                              | 142                                 |  |  |
| Units: participants                                 |                                  |                                     |  |  |
| Binding Antibody Positive Post-BL                   | 21                               | 22                                  |  |  |
| Transient Binding Antibody Positive<br>Post-BL      | 6                                | 3                                   |  |  |
| Neutralizing Antibody Positive Post-BL              | 5                                | 4                                   |  |  |
| Transient Neutralizing Antibody Positive<br>Post-BL | 0                                | 2                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

up to Month 9 (-7/+3 days)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Romosozumab 210 mg SC QM by PFS |
|-----------------------|---------------------------------|

Reporting group description:

During the open-label treatment period, participants received 210 mg romosozumab subcutaneously (SC) once a month (QM) by health care provider (HCP) administration with pre-filled syringe (PFS).

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Romosozumab 210 mg SC QM by AI/Pen |
|-----------------------|------------------------------------|

Reporting group description:

During the open-label treatment period, participants received 210 mg romosozumab SC QM by self-administration with autoinjector (AI)/pen.

| Serious adverse events  | Romosozumab 210 mg SC QM by PFS | Romosozumab 210 mg SC QM by AI/Pen |  |
|---|---------------------------------|------------------------------------|--|
| Total subjects affected by serious adverse events                   |                                 |                                    |  |
| subjects affected / exposed   | 7 / 141 (4.96%)                 | 4 / 142 (2.82%)                    |  |
| number of deaths (all causes)                                       | 0                               | 0                                  |  |
| number of deaths resulting from adverse events                      |                                 |                                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                 |                                    |  |
| Basal cell carcinoma  |                                 |                                    |  |
| subjects affected / exposed   | 1 / 141 (0.71%)                 | 0 / 142 (0.00%)                    |  |
| occurrences causally related to treatment / all                     | 0 / 1                           | 0 / 0                              |  |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                              |  |
| Glioblastoma  |                                 |                                    |  |
| subjects affected / exposed   | 1 / 141 (0.71%)                 | 0 / 142 (0.00%)                    |  |
| occurrences causally related to treatment / all                     | 0 / 1                           | 0 / 0                              |  |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                              |  |
| Injury, poisoning and procedural complications                      |                                 |                                    |  |
| Forearm fracture  |                                 |                                    |  |
| subjects affected / exposed   | 1 / 141 (0.71%)                 | 0 / 142 (0.00%)                    |  |
| occurrences causally related to treatment / all                     | 0 / 1                           | 0 / 0                              |  |
| deaths causally related to treatment / all                          | 0 / 0                           | 0 / 0                              |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound   |                 |                 |  |
| subjects affected / exposed                     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 1 / 142 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Anaphylactic reaction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Colitis ischaemic                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 0 / 142 (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                     |                 |                 |  |
| Cellulitis                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                                   | Romosozumab 210 mg SC QM by PFS | Romosozumab 210 mg SC QM by AI/Pen |  |
|---|---------------------------------|------------------------------------|--|
| Total subjects affected by non-serious adverse events               |                                 |                                    |  |
| subjects affected / exposed   | 92 / 141 (65.25%)               | 95 / 142 (66.90%)                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                 |                                    |  |
| Lipoma  |                                 |                                    |  |
| subjects affected / exposed   | 0 / 141 (0.00%)                 | 1 / 142 (0.70%)                    |  |
| occurrences (all)   | 0                               | 1                                  |  |
| Meningioma  |                                 |                                    |  |
| subjects affected / exposed   | 1 / 141 (0.71%)                 | 0 / 142 (0.00%)                    |  |
| occurrences (all)   | 1                               | 0                                  |  |
| Seborrhoeic keratosis   |                                 |                                    |  |
| subjects affected / exposed   | 0 / 141 (0.00%)                 | 1 / 142 (0.70%)                    |  |
| occurrences (all)   | 0                               | 1                                  |  |
| Vascular disorders  |                                 |                                    |  |
| Haematoma   |                                 |                                    |  |
| subjects affected / exposed   | 1 / 141 (0.71%)                 | 0 / 142 (0.00%)                    |  |
| occurrences (all)   | 1                               | 0                                  |  |
| Hot flush   |                                 |                                    |  |
| subjects affected / exposed   | 2 / 141 (1.42%)                 | 1 / 142 (0.70%)                    |  |
| occurrences (all)   | 2                               | 1                                  |  |
| Hypertension  |                                 |                                    |  |

|  |                   |                   |  |
|--|-------------------|-------------------|--|
| subjects affected / exposed                          | 3 / 141 (2.13%)   | 1 / 142 (0.70%)   |  |
| occurrences (all)                                    | 3                 | 1                 |  |
| Hypotension  |                   |                   |  |
| subjects affected / exposed                          | 0 / 141 (0.00%)   | 1 / 142 (0.70%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Peripheral arterial occlusive disease                |                   |                   |  |
| subjects affected / exposed                          | 0 / 141 (0.00%)   | 1 / 142 (0.70%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Vasculitis   |                   |                   |  |
| subjects affected / exposed                          | 1 / 141 (0.71%)   | 0 / 142 (0.00%)   |  |
| occurrences (all)                                    | 1                 | 0                 |  |
| General disorders and administration site conditions |                   |                   |  |
| Injection site erythema                              |                   |                   |  |
| subjects affected / exposed                          | 25 / 141 (17.73%) | 35 / 142 (24.65%) |  |
| occurrences (all)                                    | 49                | 69                |  |
| Injection site pain                                  |                   |                   |  |
| subjects affected / exposed                          | 14 / 141 (9.93%)  | 21 / 142 (14.79%) |  |
| occurrences (all)                                    | 20                | 34                |  |
| Injection site swelling                              |                   |                   |  |
| subjects affected / exposed                          | 11 / 141 (7.80%)  | 23 / 142 (16.20%) |  |
| occurrences (all)                                    | 13                | 43                |  |
| Asthenia   |                   |                   |  |
| subjects affected / exposed                          | 0 / 141 (0.00%)   | 1 / 142 (0.70%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Chest pain   |                   |                   |  |
| subjects affected / exposed                          | 0 / 141 (0.00%)   | 1 / 142 (0.70%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Chills   |                   |                   |  |
| subjects affected / exposed                          | 0 / 141 (0.00%)   | 1 / 142 (0.70%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Cyst   |                   |                   |  |
| subjects affected / exposed                          | 0 / 141 (0.00%)   | 1 / 142 (0.70%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Exercise tolerance decreased                         |                   |                   |  |

|                                 |                 |                 |
|---------------------------------|-----------------|-----------------|
| subjects affected / exposed     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)               | 0               | 1               |
| Fatigue                         |                 |                 |
| subjects affected / exposed     | 1 / 141 (0.71%) | 2 / 142 (1.41%) |
| occurrences (all)               | 1               | 4               |
| Influenza like illness          |                 |                 |
| subjects affected / exposed     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)               | 1               | 0               |
| Injection site bruising         |                 |                 |
| subjects affected / exposed     | 1 / 141 (0.71%) | 5 / 142 (3.52%) |
| occurrences (all)               | 2               | 7               |
| Injection site discolouration   |                 |                 |
| subjects affected / exposed     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)               | 0               | 1               |
| Injection site extravasation    |                 |                 |
| subjects affected / exposed     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)               | 1               | 0               |
| Injection site haemorrhage      |                 |                 |
| subjects affected / exposed     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)               | 0               | 1               |
| Injection site hypersensitivity |                 |                 |
| subjects affected / exposed     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)               | 0               | 1               |
| Injection site hypertrophy      |                 |                 |
| subjects affected / exposed     | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)               | 1               | 1               |
| Injection site induration       |                 |                 |
| subjects affected / exposed     | 2 / 141 (1.42%) | 2 / 142 (1.41%) |
| occurrences (all)               | 7               | 2               |
| Injection site irritation       |                 |                 |
| subjects affected / exposed     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)               | 1               | 0               |
| Injection site nodule           |                 |                 |
| subjects affected / exposed     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)               | 0               | 1               |
| Injection site oedema           |                 |                 |



|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 141 (1.42%) | 4 / 142 (2.82%) |
| occurrences (all)           | 2               | 7               |
| Injection site pruritus     |                 |                 |
| subjects affected / exposed | 6 / 141 (4.26%) | 7 / 142 (4.93%) |
| occurrences (all)           | 8               | 15              |
| Injection site rash         |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 2 / 142 (1.41%) |
| occurrences (all)           | 0               | 2               |
| Injection site reaction     |                 |                 |
| subjects affected / exposed | 3 / 141 (2.13%) | 2 / 142 (1.41%) |
| occurrences (all)           | 4               | 3               |
| Injection site urticaria    |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 2 / 142 (1.41%) |
| occurrences (all)           | 0               | 2               |
| Injection site warmth       |                 |                 |
| subjects affected / exposed | 2 / 141 (1.42%) | 3 / 142 (2.11%) |
| occurrences (all)           | 2               | 6               |
| Malaise                     |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 1               |
| Mass                        |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 2               |
| Non-cardiac chest pain      |                 |                 |
| subjects affected / exposed | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)           | 1               | 1               |
| Oedema peripheral           |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 1               |
| Pain                        |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 2               |
| Peripheral swelling         |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 1               |
| Pyrexia                     |                 |                 |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Reproductive system and breast disorders<br>Breast cyst<br>subjects affected / exposed<br>occurrences (all)  | 0 / 141 (0.00%)<br>0 | 2 / 142 (1.41%)<br>2 |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 0 / 141 (0.00%)<br>0 | 3 / 142 (2.11%)<br>3 |  |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>2 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 141 (0.71%)<br>1 | 1 / 142 (0.70%)<br>1 |  |
| Pulmonary fibrosis<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)  | 3 / 141 (2.13%)<br>3 | 0 / 142 (0.00%)<br>0 |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 141 (0.71%)<br>1 | 1 / 142 (0.70%)<br>1 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 141 (2.13%)<br>3 | 2 / 142 (1.41%)<br>2 |  |
| Investigations   |                      |                      |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 2 / 141 (1.42%)<br>2 | 0 / 142 (0.00%)<br>0 |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Blood urea increased<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Chest X-ray abnormal<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Injury, poisoning and procedural complications   |                      |                      |  |
| Anaemia postoperative<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Bone contusion<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Cataract operation complication<br>subjects affected / exposed<br>occurrences (all)        | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                              | 3 / 141 (2.13%)<br>4 | 1 / 142 (0.70%)<br>1 |  |
| Epicondylitis  |                      |                      |  |

|                              |                 |                 |
|------------------------------|-----------------|-----------------|
| subjects affected / exposed  | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)            | 0               | 1               |
| Facial bones fracture        |                 |                 |
| subjects affected / exposed  | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)            | 1               | 1               |
| Fall                         |                 |                 |
| subjects affected / exposed  | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Femur fracture               |                 |                 |
| subjects affected / exposed  | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)            | 0               | 1               |
| Fibula fracture              |                 |                 |
| subjects affected / exposed  | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Foot fracture                |                 |                 |
| subjects affected / exposed  | 2 / 141 (1.42%) | 2 / 142 (1.41%) |
| occurrences (all)            | 2               | 2               |
| Hand fracture                |                 |                 |
| subjects affected / exposed  | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Humerus fracture             |                 |                 |
| subjects affected / exposed  | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)            | 1               | 1               |
| Post procedural complication |                 |                 |
| subjects affected / exposed  | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)            | 0               | 1               |
| Post-traumatic pain          |                 |                 |
| subjects affected / exposed  | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Procedural pain              |                 |                 |
| subjects affected / exposed  | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)            | 0               | 1               |
| Radius fracture              |                 |                 |
| subjects affected / exposed  | 2 / 141 (1.42%) | 0 / 142 (0.00%) |
| occurrences (all)            | 2               | 0               |
| Spinal column injury         |                 |                 |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Tooth injury                |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Cardiac disorders           |                 |                 |  |
| Bundle branch block right   |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Myocardial ischaemia        |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Palpitations                |                 |                 |  |
| subjects affected / exposed | 2 / 141 (1.42%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Ventricular pre-excitation  |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Nervous system disorders    |                 |                 |  |
| Headache                    |                 |                 |  |
| subjects affected / exposed | 3 / 141 (2.13%) | 9 / 142 (6.34%) |  |
| occurrences (all)           | 4               | 13              |  |
| Dementia                    |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Dizziness                   |                 |                 |  |
| subjects affected / exposed | 2 / 141 (1.42%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 2               | 1               |  |
| Paraesthesia                |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Post herpetic neuralgia     |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Sciatica                    |                 |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 141 (0.71%)<br>1 | 1 / 142 (0.70%)<br>1 |  |
| Transient ischaemic attack<br>subjects affected / exposed<br>occurrences (all)       | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Blood and lymphatic system disorders   |                      |                      |  |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                       | 4 / 141 (2.84%)<br>4 | 0 / 142 (0.00%)<br>0 |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 141 (1.42%)<br>2 | 2 / 142 (1.41%)<br>2 |  |
| Normocytic anaemia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>2 |  |
| Ear and labyrinth disorders  |                      |                      |  |
| Ear congestion<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Eye disorders  |                      |                      |  |
| Age-related macular degeneration<br>subjects affected / exposed<br>occurrences (all) | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Blepharitis<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Cataract   |                      |                      |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Dry eye                     |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Entropion                   |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Macular degeneration        |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Ocular hyperaemia           |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Swelling of eyelid          |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Vision blurred              |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Visual impairment           |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Gastrointestinal disorders  |                 |                 |  |
| Abdominal distension        |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Abdominal pain              |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 2 / 142 (1.41%) |  |
| occurrences (all)           | 1               | 2               |  |
| Abdominal pain lower        |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Abdominal pain upper        |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 3 / 142 (2.11%) |  |
| occurrences (all)           | 0               | 3               |  |

|                                  |                 |                 |
|----------------------------------|-----------------|-----------------|
| Colitis                          |                 |                 |
| subjects affected / exposed      | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                | 0               | 1               |
| Constipation                     |                 |                 |
| subjects affected / exposed      | 1 / 141 (0.71%) | 2 / 142 (1.41%) |
| occurrences (all)                | 1               | 2               |
| Dental cyst                      |                 |                 |
| subjects affected / exposed      | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Diaphragmatic hernia             |                 |                 |
| subjects affected / exposed      | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                | 0               | 1               |
| Diarrhoea                        |                 |                 |
| subjects affected / exposed      | 5 / 141 (3.55%) | 1 / 142 (0.70%) |
| occurrences (all)                | 5               | 1               |
| Diverticulum intestinal          |                 |                 |
| subjects affected / exposed      | 0 / 141 (0.00%) | 2 / 142 (1.41%) |
| occurrences (all)                | 0               | 2               |
| Dry mouth                        |                 |                 |
| subjects affected / exposed      | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                | 0               | 1               |
| Gastritis                        |                 |                 |
| subjects affected / exposed      | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                | 0               | 1               |
| Gastrooesophageal reflux disease |                 |                 |
| subjects affected / exposed      | 1 / 141 (0.71%) | 2 / 142 (1.41%) |
| occurrences (all)                | 1               | 2               |
| Gingival pain                    |                 |                 |
| subjects affected / exposed      | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                | 0               | 1               |
| Hiatus hernia                    |                 |                 |
| subjects affected / exposed      | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                | 0               | 1               |
| Irritable bowel syndrome         |                 |                 |
| subjects affected / exposed      | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                | 0               | 1               |



|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Large intestine polyp<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 141 (1.42%)<br>2 | 2 / 142 (1.41%)<br>2 |  |
| Oesophageal ulcer<br>subjects affected / exposed<br>occurrences (all)   | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Oral mucosal blistering<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>2 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)   | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 0 / 141 (0.00%)<br>0 | 2 / 142 (1.41%)<br>2 |  |
| Hepatobiliary disorders<br>Hypertransaminasaemia<br>subjects affected / exposed<br>occurrences (all)          | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders<br>Decubitus ulcer<br>subjects affected / exposed<br>occurrences (all) | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Dermal cyst<br>subjects affected / exposed<br>occurrences (all)   | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Dermatitis allergic   |                      |                      |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)   | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)   | 1 / 141 (0.71%)<br>1 | 1 / 142 (0.70%)<br>3 |  |
| Pruritus generalised<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 4 / 141 (2.84%)<br>4 | 1 / 142 (0.70%)<br>1 |  |
| Rash pruritic<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Swelling face<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Renal and urinary disorders<br>Micturition urgency<br>subjects affected / exposed<br>occurrences (all) | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Renal cyst<br>subjects affected / exposed<br>occurrences (all)   | 1 / 141 (0.71%)<br>1 | 0 / 142 (0.00%)<br>0 |  |
| Renal failure<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 141 (0.00%)<br>0 | 1 / 142 (0.70%)<br>1 |  |
| Endocrine disorders<br>Hypothyroidism  |                      |                      |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 141 (1.42%) | 0 / 142 (0.00%) |  |
| occurrences (all)                               | 2               | 0               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 7 / 141 (4.96%) | 9 / 142 (6.34%) |  |
| occurrences (all)                               | 8               | 12              |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 141 (1.42%) | 3 / 142 (2.11%) |  |
| occurrences (all)                               | 2               | 4               |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 141 (2.13%) | 1 / 142 (0.70%) |  |
| occurrences (all)                               | 3               | 1               |  |
| Bursitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Muscle spasms                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 2 / 142 (1.41%) |  |
| occurrences (all)                               | 1               | 2               |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Musculoskeletal stiffness                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Myalgia   |                 |                 |  |
| subjects affected / exposed                     | 2 / 141 (1.42%) | 1 / 142 (0.70%) |  |
| occurrences (all)                               | 2               | 1               |  |
| Neck pain                                       |                 |                 |  |

|                                   |                   |                  |  |
|-----------------------------------|-------------------|------------------|--|
| subjects affected / exposed       | 1 / 141 (0.71%)   | 0 / 142 (0.00%)  |  |
| occurrences (all)                 | 1                 | 0                |  |
| Nodal osteoarthritis              |                   |                  |  |
| subjects affected / exposed       | 0 / 141 (0.00%)   | 1 / 142 (0.70%)  |  |
| occurrences (all)                 | 0                 | 1                |  |
| Osteoarthritis                    |                   |                  |  |
| subjects affected / exposed       | 1 / 141 (0.71%)   | 0 / 142 (0.00%)  |  |
| occurrences (all)                 | 1                 | 0                |  |
| Pain in extremity                 |                   |                  |  |
| subjects affected / exposed       | 4 / 141 (2.84%)   | 3 / 142 (2.11%)  |  |
| occurrences (all)                 | 4                 | 5                |  |
| Plantar fasciitis                 |                   |                  |  |
| subjects affected / exposed       | 2 / 141 (1.42%)   | 0 / 142 (0.00%)  |  |
| occurrences (all)                 | 2                 | 0                |  |
| Rheumatoid arthritis              |                   |                  |  |
| subjects affected / exposed       | 1 / 141 (0.71%)   | 0 / 142 (0.00%)  |  |
| occurrences (all)                 | 1                 | 0                |  |
| Spinal osteoarthritis             |                   |                  |  |
| subjects affected / exposed       | 2 / 141 (1.42%)   | 1 / 142 (0.70%)  |  |
| occurrences (all)                 | 2                 | 1                |  |
| Spinal pain                       |                   |                  |  |
| subjects affected / exposed       | 0 / 141 (0.00%)   | 1 / 142 (0.70%)  |  |
| occurrences (all)                 | 0                 | 1                |  |
| Spondylitis                       |                   |                  |  |
| subjects affected / exposed       | 0 / 141 (0.00%)   | 1 / 142 (0.70%)  |  |
| occurrences (all)                 | 0                 | 1                |  |
| Infections and infestations       |                   |                  |  |
| Nasopharyngitis                   |                   |                  |  |
| subjects affected / exposed       | 15 / 141 (10.64%) | 10 / 142 (7.04%) |  |
| occurrences (all)                 | 16                | 10               |  |
| Upper respiratory tract infection |                   |                  |  |
| subjects affected / exposed       | 2 / 141 (1.42%)   | 8 / 142 (5.63%)  |  |
| occurrences (all)                 | 2                 | 8                |  |
| Bacterial vulvovaginitis          |                   |                  |  |
| subjects affected / exposed       | 1 / 141 (0.71%)   | 0 / 142 (0.00%)  |  |
| occurrences (all)                 | 1                 | 0                |  |

|                                   |                 |                 |
|-----------------------------------|-----------------|-----------------|
| Bronchitis                        |                 |                 |
| subjects affected / exposed       | 4 / 141 (2.84%) | 6 / 142 (4.23%) |
| occurrences (all)                 | 4               | 8               |
| Cystitis                          |                 |                 |
| subjects affected / exposed       | 3 / 141 (2.13%) | 0 / 142 (0.00%) |
| occurrences (all)                 | 3               | 0               |
| Ear infection                     |                 |                 |
| subjects affected / exposed       | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                 | 0               | 1               |
| Furuncle                          |                 |                 |
| subjects affected / exposed       | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Gastroenteritis                   |                 |                 |
| subjects affected / exposed       | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)                 | 1               | 1               |
| Genital herpes                    |                 |                 |
| subjects affected / exposed       | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)                 | 0               | 1               |
| Herpes virus infection            |                 |                 |
| subjects affected / exposed       | 0 / 141 (0.00%) | 2 / 142 (1.41%) |
| occurrences (all)                 | 0               | 2               |
| Herpes zoster                     |                 |                 |
| subjects affected / exposed       | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)                 | 1               | 1               |
| Hordeolum                         |                 |                 |
| subjects affected / exposed       | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)                 | 1               | 1               |
| Influenza                         |                 |                 |
| subjects affected / exposed       | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Laryngitis                        |                 |                 |
| subjects affected / exposed       | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)                 | 1               | 1               |
| Lower respiratory tract infection |                 |                 |
| subjects affected / exposed       | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)                 | 1               | 0               |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| Lung abscess                |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 1               |
| Oral herpes                 |                 |                 |
| subjects affected / exposed | 2 / 141 (1.42%) | 1 / 142 (0.70%) |
| occurrences (all)           | 2               | 1               |
| Pharyngitis                 |                 |                 |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Pharyngitis streptococcal   |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 1               |
| Pneumonia                   |                 |                 |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Respiratory tract infection |                 |                 |
| subjects affected / exposed | 2 / 141 (1.42%) | 2 / 142 (1.41%) |
| occurrences (all)           | 2               | 2               |
| Rhinitis                    |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 1               |
| Sinusitis                   |                 |                 |
| subjects affected / exposed | 2 / 141 (1.42%) | 1 / 142 (0.70%) |
| occurrences (all)           | 2               | 1               |
| Tonsillitis                 |                 |                 |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Tooth infection             |                 |                 |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Tooth abscess               |                 |                 |
| subjects affected / exposed | 1 / 141 (0.71%) | 1 / 142 (0.70%) |
| occurrences (all)           | 1               | 1               |
| Urethritis                  |                 |                 |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |
| occurrences (all)           | 0               | 1               |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Urinary tract infection                 |                 |                 |  |
| subjects affected / exposed             | 4 / 141 (2.84%) | 4 / 142 (2.82%) |  |
| occurrences (all)                       | 4               | 4               |  |
| Urinary tract infection bacterial       |                 |                 |  |
| subjects affected / exposed             | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Viral infection                         |                 |                 |  |
| subjects affected / exposed             | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Viral labyrinthitis                     |                 |                 |  |
| subjects affected / exposed             | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Viral upper respiratory tract infection |                 |                 |  |
| subjects affected / exposed             | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Metabolism and nutrition disorders      |                 |                 |  |
| Dehydration                             |                 |                 |  |
| subjects affected / exposed             | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Glucose tolerance impaired              |                 |                 |  |
| subjects affected / exposed             | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Hyperglycaemia                          |                 |                 |  |
| subjects affected / exposed             | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Hyperlipidaemia                         |                 |                 |  |
| subjects affected / exposed             | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Hypoalbuminaemia                        |                 |                 |  |
| subjects affected / exposed             | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Hypocalcaemia                           |                 |                 |  |
| subjects affected / exposed             | 1 / 141 (0.71%) | 1 / 142 (0.70%) |  |
| occurrences (all)                       | 1               | 1               |  |
| Hypokalaemia                            |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 141 (0.71%) | 2 / 142 (1.41%) |  |
| occurrences (all)           | 1               | 2               |  |
| Hyponatraemia               |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Malnutrition                |                 |                 |  |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) |  |
| occurrences (all)           | 0               | 1               |  |
| Type 2 diabetes mellitus    |                 |                 |  |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 142 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported