



## Clinical trial results: Open-Label Access Protocol of Denosumab for Subjects with Advanced Cancer

### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2011-002114-36                |
| Trial protocol           | HU CZ AT FR ES PL BE LV LT IT |
| Global end of trial date | 10 August 2018                |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 17 August 2019 |
| First version publication date | 17 August 2019 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20110113 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01419717 |
| 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                       | 10 August 2018 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 10 August 2018 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to facilitate the access of denosumab until denosumab was approved and available for sale for subjects with advanced cancer who had participated in a denosumab phase 3 study.

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 were submitted to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for written approval before recruitment of subjects into the study and shipment of Amgen investigational product.

Before a subject's participation in the clinical study, the investigator was responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products were administered.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 22 November 2011 |
| 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 | Russian Federation: 13 |
| Country: Number of subjects enrolled | Poland: 12             |
| Country: Number of subjects enrolled | Latvia: 8              |
| Country: Number of subjects enrolled | Lithuania: 8           |
| Country: Number of subjects enrolled | Spain: 6               |
| Country: Number of subjects enrolled | Israel: 6              |
| Country: Number of subjects enrolled | Ukraine: 5             |
| Country: Number of subjects enrolled | France: 5              |
| Country: Number of subjects enrolled | Czech Republic: 5      |
| Country: Number of subjects enrolled | Austria: 4             |
| Country: Number of subjects enrolled | Italy: 4               |
| Country: Number of subjects enrolled | Belgium: 3             |
| Country: Number of subjects enrolled | Hungary: 3             |
| Country: Number of subjects enrolled | Brazil: 16             |

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Argentina: 8    |
| Country: Number of subjects enrolled | Peru: 6         |
| Country: Number of subjects enrolled | Panama: 1       |
| Country: Number of subjects enrolled | Japan: 15       |
| Country: Number of subjects enrolled | South Africa: 1 |
| Worldwide total number of subjects   | 129             |
| EEA total number of subjects         | 58              |

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)                      | 60 |
| From 65 to 84 years                       | 64 |
| 85 years and over                         | 5  |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 65 centers in Europe, Latin America, Japan, and South Africa. Participants were enrolled from 22 November 2011 to 27 October 2014.

### Pre-assignment

Screening details:

Adults with advanced cancer who had been previously enrolled in an Amgen denosumab phase 3 study and had participated in the open-label extension portion of that study were eligible to enroll in this study.

### Period 1

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

### Arms

|           |           |
|-----------|-----------|
| Arm title | Denosumab |
|-----------|-----------|

Arm description:

Participants were offered 120 milligrams of denosumab injected subcutaneously every 4 weeks until denosumab was approved and available for sale.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Denosumab              |
| Investigational medicinal product code | AMG 162                |
| Other name                             | Xgeva                  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Administered by subcutaneous injection once every 4 weeks (Q4W) at a dose of 120 mg.

| Number of subjects in period 1 | Denosumab |
|--------------------------------|-----------|
| Started                        | 129       |
| Received Denosumab             | 128       |
| Completed                      | 4         |
| Not completed                  | 125       |
| Adverse event, serious fatal   | 17        |
| Consent withdrawn by subject   | 10        |
| Adverse event, non-fatal       | 19        |
| Other                          | 4         |
| Administrative Decision        | 1         |
| Lost to follow-up              | 2         |
| Protocol-specified Criteria    | 62        |
| Disease Progression            | 9         |

|               |   |
|---------------|---|
| Noncompliance | 1 |
|---------------|---|

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Participants were offered 120 milligrams of denosumab injected subcutaneously every 4 weeks until denosumab was approved and available for sale.

| Reporting group values     | Denosumab | Total |  |
|----------------------------|-----------|-------|--|
| Number of subjects         | 129       | 129   |  |
| Age, Customized            |           |       |  |
| Units: Subjects            |           |       |  |
| 18 - 64 years              | 60        | 60    |  |
| 65 - 74 years              | 36        | 36    |  |
| 75 - 84 years              | 28        | 28    |  |
| ≥ 85 years                 | 5         | 5     |  |
| Age Continuous             |           |       |  |
| Units: years               |           |       |  |
| arithmetic mean            | 65.74     |       |  |
| standard deviation         | ± 11.48   | -     |  |
| Sex: Female, Male          |           |       |  |
| Units: Subjects            |           |       |  |
| Female                     | 97        | 97    |  |
| Male                       | 32        | 32    |  |
| Race/Ethnicity, Customized |           |       |  |
| Units: Subjects            |           |       |  |
| White                      | 103       | 103   |  |
| Asian                      | 15        | 15    |  |
| Black or African American  | 6         | 6     |  |
| Other                      | 4         | 4     |  |
| Unknown                    | 1         | 1     |  |
| Ethnicity (NIH/OMB)        |           |       |  |
| Units: Subjects            |           |       |  |
| Hispanic or Latino         | 28        | 28    |  |
| Not Hispanic or Latino     | 101       | 101   |  |
| Unknown or Not Reported    | 0         | 0     |  |

## End points

### End points reporting groups

|                                                                                                                                                  |           |
|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Reporting group title                                                                                                                            | Denosumab |
| Reporting group description:                                                                                                                     |           |
| Participants were offered 120 milligrams of denosumab injected subcutaneously every 4 weeks until denosumab was approved and available for sale. |           |

### Primary: Number of Participants with Adverse Events

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Number of Participants with Adverse Events <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                           |
| An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial participant. The event does not necessarily have a causal relationship with study treatment. Each AE was graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, where<br>Grade 1 = Mild AE<br>Grade 2 = Moderate AE<br>Grade 3 = Severe AE<br>Grade 4 = Life-threatening or disabling AE<br>Grade 5 = Death related to AE.<br>Treatment-related adverse events (TRAEs) includes events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product. |                                                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Primary                                                   |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                           |
| From first dose of denosumab in Study 20110113 to end of study. Median (minimum, maximum) time on study was 13.93 (0.0, 74.7) months.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                           |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis in this study was entirely descriptive; no formal statistical hypothesis was tested or estimated.

| End point values                             | Denosumab          |  |  |  |
|----------------------------------------------|--------------------|--|--|--|
| Subject group type                           | Reporting group    |  |  |  |
| Number of subjects analysed                  | 128 <sup>[2]</sup> |  |  |  |
| Units: participants                          |                    |  |  |  |
| All adverse events                           | 98                 |  |  |  |
| Serious adverse events                       | 45                 |  |  |  |
| AE leading to discontinuation of denosumab   | 28                 |  |  |  |
| AE leading to discontinuation from study     | 22                 |  |  |  |
| Fatal adverse events                         | 18                 |  |  |  |
| AE grade 3, 4, or 5                          | 46                 |  |  |  |
| Treatment-related adverse event              | 26                 |  |  |  |
| Treatment-related serious adverse event      | 10                 |  |  |  |
| TRAE leading to discontinuation of denosumab | 18                 |  |  |  |
| TRAE leading to discontinuation from study   | 16                 |  |  |  |
| Treatment-related fatal adverse events       | 0                  |  |  |  |
| Treatment-related AE grade 3, 4, or 5        | 8                  |  |  |  |

Notes:

[2] - Participants who received at least 1 dose of denosumab in study 20110113.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Anti-denosumab Binding Antibodies

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Number of Participants with Anti-denosumab Binding Antibodies |
|-----------------|---------------------------------------------------------------|

End point description:

A blood sample was collected at the end of study visit for the measurement of anti-denosumab binding antibodies.

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

End point timeframe:

Assessed at end of study; the median (minimum, maximum) time on study for all enrolled participants was 13.9 (0.0, 74.7) months.

|                             |                   |  |  |  |
|-----------------------------|-------------------|--|--|--|
| <b>End point values</b>     | Denosumab         |  |  |  |
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 86 <sup>[3]</sup> |  |  |  |
| Units: participants         | 0                 |  |  |  |

Notes:

[3] - Participants who received at least 1 dose of denosumab and with at least 1 antibody result.

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of denosumab in Study 20110113 to end of study. Median (minimum, maximum) time on study was 13.93 (0.0, 74.7) months

Adverse event reporting additional description:

Participants who received at least one dose of denosumab.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants received 120 milligrams of denosumab injected subcutaneously every 4 weeks until denosumab was approved and available for sale.

| Serious adverse events                                              | Denosumab         |  |  |
|---------------------------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed                                         | 45 / 128 (35.16%) |  |  |
| number of deaths (all causes)                                       | 18                |  |  |
| number of deaths resulting from adverse events                      |                   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Breast cancer                                                       |                   |  |  |
| subjects affected / exposed                                         | 2 / 128 (1.56%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 2             |  |  |
| deaths causally related to treatment / all                          | 0 / 2             |  |  |
| Cardiac myxoma                                                      |                   |  |  |
| subjects affected / exposed                                         | 1 / 128 (0.78%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Metastases to liver                                                 |                   |  |  |
| subjects affected / exposed                                         | 1 / 128 (0.78%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 1             |  |  |
| Neoplasm malignant                                                  |                   |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                          | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Prostate cancer                                      |                 |  |  |
| subjects affected / exposed                          | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 2           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia                                             |                 |  |  |
| subjects affected / exposed                          | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 3           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Disease progression                                  |                 |  |  |
| subjects affected / exposed                          | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 2           |  |  |
| General physical health deterioration                |                 |  |  |
| subjects affected / exposed                          | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 2           |  |  |
| Respiratory, thoracic and mediastinal disorders      |                 |  |  |
| Acute pulmonary oedema                               |                 |  |  |
| subjects affected / exposed                          | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Dyspnoea                                             |                 |  |  |
| subjects affected / exposed                          | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pleural effusion                                     |                 |  |  |
| subjects affected / exposed                          | 3 / 128 (2.34%) |  |  |
| occurrences causally related to treatment / all      | 0 / 4           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Pleurisy                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Fall                                            |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femur fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Arrhythmia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac arrest                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cardiac failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cardiopulmonary failure                         |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Nervous system disorders                        |                 |  |  |
| Hemiparesis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Paraplegia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Radiculopathy                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vertebrobasilar insufficiency                   |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Anaemia                                         |                 |  |  |
| subjects affected / exposed                     | 3 / 128 (2.34%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Febrile neutropenia                             |                 |  |  |
| subjects affected / exposed                     | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ascites                                         |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal obstruction                          |                 |  |  |
| subjects affected / exposed                     | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Melaena                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea                                          |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting                                        |                 |  |  |
| subjects affected / exposed                     | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholecystitis acute                             |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Jaundice                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue           |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| disorders                                       |                 |  |  |
| Muscle spasms                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Muscular weakness                               |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteonecrosis of jaw                            |                 |  |  |
| subjects affected / exposed                     | 7 / 128 (5.47%) |  |  |
| occurrences causally related to treatment / all | 7 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Abscess jaw                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cellulitis                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myelitis                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteomyelitis                                   |                 |  |  |
| subjects affected / exposed                     | 3 / 128 (2.34%) |  |  |
| occurrences causally related to treatment / all | 2 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 4 / 128 (3.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Pulpitis dental                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Septic shock                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Upper respiratory tract infection               |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Cachexia                                        |                 |  |  |
| subjects affected / exposed                     | 2 / 128 (1.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Hypoglycaemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 128 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Denosumab         |  |  |
|-------------------------------------------------------|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 66 / 128 (51.56%) |  |  |
| Blood and lymphatic system disorders                  |                   |  |  |
| Anaemia                                               |                   |  |  |
| subjects affected / exposed                           | 8 / 128 (6.25%)   |  |  |
| occurrences (all)                                     | 11                |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Asthenia                                              |                   |  |  |
| subjects affected / exposed                           | 15 / 128 (11.72%) |  |  |
| occurrences (all)                                     | 18                |  |  |

|                                                                          |                         |  |  |
|--------------------------------------------------------------------------|-------------------------|--|--|
| Fatigue<br>subjects affected / exposed<br>occurrences (all)              | 12 / 128 (9.38%)<br>18  |  |  |
| Gastrointestinal disorders                                               |                         |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 9 / 128 (7.03%)<br>10   |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 11 / 128 (8.59%)<br>17  |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 15 / 128 (11.72%)<br>23 |  |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)            | 9 / 128 (7.03%)<br>11   |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 11 / 128 (8.59%)<br>16  |  |  |
| Respiratory, thoracic and mediastinal disorders                          |                         |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)             | 7 / 128 (5.47%)<br>12   |  |  |
| Musculoskeletal and connective tissue disorders                          |                         |  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 15 / 128 (11.72%)<br>26 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 16 / 128 (12.50%)<br>18 |  |  |
| Osteonecrosis of jaw<br>subjects affected / exposed<br>occurrences (all) | 8 / 128 (6.25%)<br>8    |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)    | 13 / 128 (10.16%)<br>14 |  |  |



|                                                                                                              |                         |  |  |
|--------------------------------------------------------------------------------------------------------------|-------------------------|--|--|
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 14 / 128 (10.94%)<br>14 |  |  |
|--------------------------------------------------------------------------------------------------------------|-------------------------|--|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                     |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 22 February 2013 | Summary of changes: <ul style="list-style-type: none"><li>• Clarify that serious adverse events must be reported within 24 hours</li><li>• Clarify how serious adverse events reported to Amgen will be reported to regulators and investigators</li><li>• Provide lactation notification worksheet in the protocol</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported