



Clinical trial results:

An Open label, Multi center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone

Summary

| | |
|--------------------------|-------------------------------------------|
| EudraCT number | 2008-001606-16 |
| Trial protocol | NL DE AT FR ES GB PL IT SE Outside EU/EEA |
| Global end of trial date | 17 May 2018 |

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20062004 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00680992 |
| 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, 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) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000145-PIP01-07 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 17 May 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 17 May 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety profile of denosumab in participants with giant cell tumor of bone (GCTB).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation Good Clinical Practice, Declaration of Helsinki, and applicable national or regional regulations/guidelines.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment | 09 September 2008 |
| 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: 144 |
| Country: Number of subjects enrolled | France: 75 |
| Country: Number of subjects enrolled | Australia: 41 |
| Country: Number of subjects enrolled | Austria: 10 |
| Country: Number of subjects enrolled | Canada: 22 |
| Country: Number of subjects enrolled | Germany: 26 |
| Country: Number of subjects enrolled | Italy: 83 |
| Country: Number of subjects enrolled | Netherlands: 26 |
| Country: Number of subjects enrolled | Poland: 39 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | Sweden: 18 |
| Country: Number of subjects enrolled | United Kingdom: 24 |
| Worldwide total number of subjects | 532 |
| EEA total number of subjects | 325 |

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) | 28 |
| Adults (18-64 years) | 481 |
| From 65 to 84 years | 23 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Adults and skeletally mature adolescents (≥ 12 years of age) were enrolled in this open-label single-arm study. The study was conducted at 30 centers in North America, Europe, and Australia from 09 Sep 2008 to study completion on 17 May 2018. The planned study duration for each participant was at least 60 months (following protocol amendment 7).

Pre-assignment

Screening details:

3 participants from study 20040215 (NCT00396279) were enrolled directly into safety follow-up phase without retreatment. They were excluded from all defined analysis sets and results are reported for the 532 participants enrolled into the treatment phase. Non-completion reasons are summarized for the on-study period (ie, initial treatment phase).

Period 1

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

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1 (Denosumab 120 mg Q4W) |

Arm description:

Participants with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases) were enrolled into cohort 1.

| | |
|----------------------------------------|------------------------------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Denosumab |
| Investigational medicinal product code | AMG 162 |
| Other name | Immunoglobulin G2 human monoclonal antibody to RANK ligand |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The dosing schedule was 120 milligrams (mg) subcutaneously (SC) every 4 weeks (Q4W) with a loading dose of 120 mg on study days 8 and 15. Denosumab was supplied as a sterile, clear, colorless to slightly yellow, preservative-free liquid in single-use 3.0 milliliter (mL) glass vials containing a deliverable dose of 1.7 mL.

| | |
|------------------|---------------------------------|
| Arm title | Cohort 2 (Denosumab 120 mg Q4W) |
|------------------|---------------------------------|

Arm description:

Participants with surgically salvageable disease whose planned initial on-study surgery was associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy) were enrolled into cohort 2.

| | |
|----------------------------------------|------------------------------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Denosumab |
| Investigational medicinal product code | AMG 162 |
| Other name | Immunoglobulin G2 human monoclonal antibody to RANK ligand |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The dosing schedule was 120 mg SC Q4W with a loading dose of 120 mg on study days 8 and 15. Denosumab was supplied as a sterile, clear, colorless to slightly yellow, preservative-free liquid in single-use 3.0 mL glass vials containing a deliverable dose of 1.7 mL.

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| Arm title | Cohort 3 (Denosumab 120 mg Q4W) |
| Arm description: Participants who participated in study 20040215 and were eligible to enroll in the current study (20062004) for continuation of treatment were enrolled into cohort 3. | |
| Arm type | Experimental |
| Investigational medicinal product name | Denosumab |
| Investigational medicinal product code | AMG 162 |
| Other name | Immunoglobulin G2 human monoclonal antibody to RANK ligand |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The dosing schedule was 120 mg SC Q4W. Denosumab was supplied as a sterile, clear, colorless to slightly yellow, preservative-free liquid in single-use 3.0 mL glass vials containing a deliverable dose of 1.7 mL.

| Number of subjects in period 1 | Cohort 1 (Denosumab 120 mg Q4W) | Cohort 2 (Denosumab 120 mg Q4W) | Cohort 3 (Denosumab 120 mg Q4W) |
|---------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Started | 268 | 252 | 12 |
| Safety analysis set | 265 | 249 | 12 |
| Efficacy analysis set | 260 | 242 | 11 |
| Completed | 0 | 0 | 0 |
| Not completed | 268 | 252 | 12 |
| Administrative Decision | 83 | 42 | 5 |
| Disease Progression | 21 | 9 | - |
| Consent withdrawn by subject | 33 | 11 | 1 |
| Complete Resection (as per protocol) | 25 | 121 | - |
| Ineligibility Determined | - | 1 | - |
| Adverse event, non-fatal | 21 | 19 | 1 |
| Other | 19 | 14 | 1 |
| Death | 5 | 1 | - |
| End of Trial | 32 | 12 | 3 |
| Pregnancy | 5 | - | 1 |
| Lost to follow-up | 12 | 14 | - |
| Requirement for Alternative Therapy | 8 | 2 | - |
| Noncompliance | 4 | 6 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title | Cohort 1 (Denosumab 120 mg Q4W) |
| Reporting group description: Participants with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases) were enrolled into cohort 1. | |
| Reporting group title | Cohort 2 (Denosumab 120 mg Q4W) |
| Reporting group description: Participants with surgically salvageable disease whose planned initial on-study surgery was associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy) were enrolled into cohort 2. | |
| Reporting group title | Cohort 3 (Denosumab 120 mg Q4W) |
| Reporting group description: Participants who participated in study 20040215 and were eligible to enroll in the current study (20062004) for continuation of treatment were enrolled into cohort 3. | |

| Reporting group values | Cohort 1 (Denosumab 120 mg Q4W) | Cohort 2 (Denosumab 120 mg Q4W) | Cohort 3 (Denosumab 120 mg Q4W) |
|-------------------------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Number of subjects | 268 | 252 | 12 |
| Age Categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 14 | 14 | 0 |
| Adults (18-64 years) | 238 | 231 | 12 |
| From 65-84 years | 16 | 7 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 36.4 | 35.1 | 36.1 |
| standard deviation | ± 14.6 | ± 13.5 | ± 14.9 |
| Gender Categorical Units: Subjects | | | |
| Female | 154 | 142 | 5 |
| Male | 114 | 110 | 7 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White or Caucasian | 221 | 208 | 11 |
| Black or African American | 18 | 12 | 0 |
| Hispanic or Latino | 13 | 13 | 1 |
| Asian | 11 | 14 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 0 |
| Other | 5 | 4 | 0 |
| GCTB Disease Type | | | |

| | | | |
|------------------------|-----|-----|----|
| Units: Subjects | | | |
| Primary resectable | 0 | 167 | 0 |
| Primary unresectable | 93 | 0 | 2 |
| Recurrent resectable | 0 | 85 | 0 |
| Recurrent unresectable | 175 | 0 | 10 |

| | | | |
|-------------------------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 532 | | |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 28 | | |
| Adults (18-64 years) | 481 | | |
| From 65-84 years | 23 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 301 | | |
| Male | 231 | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White or Caucasian | 440 | | |
| Black or African American | 30 | | |
| Hispanic or Latino | 27 | | |
| Asian | 25 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |
| Other | 9 | | |
| GCTB Disease Type | | | |
| Units: Subjects | | | |
| Primary resectable | 167 | | |
| Primary unresectable | 95 | | |
| Recurrent resectable | 85 | | |
| Recurrent unresectable | 185 | | |

End points

End points reporting groups

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Reporting group title | Cohort 1 (Denosumab 120 mg Q4W) |
| Reporting group description: Participants with surgically unsalvageable disease (eg, sacral, spinal GCTB, or multiple lesions including pulmonary metastases) were enrolled into cohort 1. | |
| Reporting group title | Cohort 2 (Denosumab 120 mg Q4W) |
| Reporting group description: Participants with surgically salvageable disease whose planned initial on-study surgery was associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy) were enrolled into cohort 2. | |
| Reporting group title | Cohort 3 (Denosumab 120 mg Q4W) |
| Reporting group description: Participants who participated in study 20040215 and were eligible to enroll in the current study (20062004) for continuation of treatment were enrolled into cohort 3. | |
| Subject analysis set title | Adolescent PK Subset (Denosumab 120 mg Q4W) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Adolescent participants enrolled in the pharmacokinetic (PK) substudy who received at least 1 dose of denosumab with baseline PK measurement and at least 1 post-baseline PK measurement were included in the adolescent PK analysis set. Participants received denosumab 120 mg SC Q4W, starting on study day 1, with loading doses of 120 mg SC on days 8 and 15 in the first month of treatment for those enrolled in cohorts 1 or 2. | |
| Subject analysis set title | Adult PK Subset (Denosumab 120 mg Q4W) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Adult participants enrolled in the PK substudy who received at least 1 dose of denosumab with baseline PK measurement and at least 1 post-baseline PK measurement were included in the adult PK analysis set. Participants received denosumab 120 mg SC Q4W, starting on study day 1, with loading doses of 120 mg SC on days 8 and 15 in the first month of treatment for those enrolled in cohorts 1 or 2. | |

Primary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs)

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent Adverse Events (TEAEs) ^[1] |
| End point description: AE: any untoward medical occurrence in clinical trial participant. Serious AE: AE that is fatal, life threatening, requires in-patient hospitalization/prolongation of existing hospitalization, results in persistent or significant disability/incapacity, congenital anomaly/birth defect or other significant medical hazard. Severity of AEs assessed according to Common Terminology Criteria for Adverse Events (CTCAE, v3.0) based on guideline: Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening or disabling; Grade 5: Death related to AE. Investigator assessed AEs for relatedness to study drug. Results presented for treatment-emergent events (TEAEs) (i.e. all AEs from first dose in initial treatment phase to end of initial treatment phase [or for participants entering retreatment, from first dose in initial treatment phase until end of retreatment phase]). Safety analysis set included all enrolled participants who received at least 1 dose of denosumab on the study. | |
| End point type | Primary |
| End point timeframe: From first dose of study drug up to last study visit for treatment-emergent period (until data cut-off for study completion; a maximum of approximately 111 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: Only descriptive analyses were performed as planned.

| End point values | Cohort 1 (Denosumab 120 mg Q4W) | Cohort 2 (Denosumab 120 mg Q4W) | Cohort 3 (Denosumab 120 mg Q4W) | |
|-------------------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 265 | 249 | 12 | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Any TEAE | 260 | 231 | 12 | |
| Serious TEAE | 98 | 39 | 5 | |
| Fatal TEAE | 8 | 3 | 0 | |
| TEAE leading to treatment phase discontinuation | 27 | 24 | 1 | |
| TEAE leading to study drug discontinuation | 27 | 23 | 1 | |
| CTCAE Grade 3, 4, or 5 | 121 | 59 | 6 | |
| Any TEAE related to study drug | 184 | 136 | 9 | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Experienced the Maximum Toxicity Grade (CTCAE Grade ≥ 3) in the Indicated Clinical Chemistry Parameters

| | |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants who Experienced the Maximum Toxicity Grade (CTCAE Grade ≥ 3) in the Indicated Clinical Chemistry Parameters ^[2] |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Serum samples for clinical chemistry were collected on study day 1 (baseline), day 15, week 5 and each study visit Q4W thereafter until last study visit for the on-study period (ie, until end of initial treatment phase). The parameters included albumin, calcium (albumin-adjusted), creatinine, magnesium and phosphate. Results are presented for number of participants who experienced the maximum toxicity grade for each of these clinical parameters. The maximum toxicity grade experienced by each participant was based on CTCAE, v3.0, and are summarized for Grade 3 and 4. Increases and decreases in relationship to the normal parameter ranges are indicated as 'Above' and 'Below' respectively. Safety analysis set included all enrolled participants who received at least 1 dose of denosumab on the study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (day 1) up to last study visit for initial treatment phase (median duration approximately 30 months up to a maximum of approximately 109 months).

Notes:

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

Justification: Only descriptive analyses were performed as planned.

| End point values | Cohort 1 (Denosumab 120 mg Q4W) | Cohort 2 (Denosumab 120 mg Q4W) | Cohort 3 (Denosumab 120 mg Q4W) | |
|-----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 265 | 249 | 12 | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Calcium corrected Grade 3 (Above) | 0 | 1 | 0 | |
| Calcium corrected Grade 4 (Above) | 1 | 1 | 0 | |
| Calcium corrected Grade 3 (Below) | 1 | 0 | 0 | |

| | | | | |
|-----------------------------------|----|----|---|--|
| Calcium corrected Grade 4 (Below) | 2 | 0 | 0 | |
| Phosphate Grade 3 (Below) | 60 | 41 | 4 | |
| Magnesium Grade 3 (Above) | 4 | 5 | 2 | |
| Magnesium Grade 3 (Below) | 1 | 0 | 0 | |
| Creatinine Grade 3 (Above) | 0 | 1 | 0 | |
| Albumin Grade 3 (Below) | 1 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression or Recurrence During the On-Study Period for Cohort 1, Presented as Kaplan-Meier Estimates of Probability

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to Disease Progression or Recurrence During the On-Study Period for Cohort 1, Presented as Kaplan-Meier Estimates of Probability ^[3] |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Time to disease progression or recurrence during the on-study period defined as time interval (in days) from date of first dose of study drug to date of earliest Progressive Disease (PD) during initial treatment phase. PD defined as response of progressive disease, locally recurrent disease or relapse as captured in Disease Status page of Case Report Form. If a participant had not had PD by end of initial treatment phase, time to disease progression or recurrence were censored at her/his end of initial treatment phase date. Median time to disease progression or recurrence for participants in cohort 1 was not reached so Kaplan-Meier estimates for probability (expressed as a percentage) of participants in cohort 1 to have disease progression or recurrence at months 6, 12, 24, 36 and 60 are presented. Efficacy analysis set included all enrolled participants who were eligible for the study and who received at least 1 dose of denosumab on the study. Analysis performed on cohort 1 only.

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

End point timeframe:

From first dose of study drug up to the end of the initial treatment phase (median duration approximately 30 months up to a maximum of approximately 109 months).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The secondary endpoint for time to disease progression applied to cohort 1 only.

| End point values | Cohort 1 (Denosumab 120 mg Q4W) | | | |
|----------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 260 | | | |
| Units: Percent probability | | | | |
| number (confidence interval 95%) | | | | |
| Month 6 | 1.9 (0.3 to 3.6) | | | |
| Month 12 | 4.3 (1.8 to 6.8) | | | |
| Month 24 | 6.1 (3.1 to 9.0) | | | |
| Month 36 | 8.2 (4.6 to 11.8) | | | |
| Month 60 | 11.7 (7.1 to 16.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants without any On-Study Surgery at Month 6 for Cohort 2

| | |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants without any On-Study Surgery at Month 6 for Cohort 2 ^[4] |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

The percentage of participants without any surgery at month 6 was equivalent to the number of participants without any surgery by month 6 divided by the number of cohort 2 participants who had an opportunity to complete 6 months of treatment, expressed as a percentage. Efficacy analysis set included all enrolled participants who were eligible for the study and who received at least 1 dose of denosumab on the study. Analysis performed on cohort 2 only for those who had the opportunity to be on-study for at least 6 months.

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

End point timeframe:

At month 6.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The secondary endpoint for proportion of participants without any surgery at month 6 applied to cohort 2 only.

| | | | | |
|-----------------------------------|---------------------------------------|--|--|--|
| End point values | Cohort 2 (Denosumab 120 mg Q4W) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 238 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 92.0 (87.8 to 95.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Serum Denosumab Trough Concentrations

| | |
|-----------------|--------------------------------------------|
| End point title | Mean Serum Denosumab Trough Concentrations |
|-----------------|--------------------------------------------|

End point description:

Blood samples for determination of serum denosumab concentration levels were obtained from participants included in the PK substudy at baseline (prior to administration of study drug on day 1) and at scheduled time points during the study up to week 25. Analysis was performed on the PK analysis set. Only participants with available data at each indicated time point were included in the analysis.

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

End point timeframe:

Blood samples were collected at baseline (day 1), days 8 and 15 and weeks 5, 9, 13 and 25.

| End point values | Adolescent PK Subset (Denosumab 120 mg Q4W) | Adult PK Subset (Denosumab 120 mg Q4W) | | |
|--------------------------------------|------------------------------------------------|-------------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 10 | 15 | | |
| Units: nanograms / milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n=10, n=15) | 0.0 (± 0.0) | 0.0 (± 0.0) | | |
| Day 8 (n=9, n=14) | 11800 (± 4130) | 12000 (± 4300) | | |
| Day 15 (n=9, n=13) | 21800 (± 5620) | 24200 (± 9050) | | |
| Week 5 (n=9, n=14) | 30400 (± 6150) | 33500 (± 8970) | | |
| Week 9 (n=9, n=15) | 25100 (± 6450) | 30000 (± 10300) | | |
| Week 13 (n=7, n=12) | 22300 (± 6840) | 29100 (± 10000) | | |
| Week 17 (n=7, n=13) | 23600 (± 4370) | 28300 (± 11600) | | |
| Week 25 (n=8, n=11) | 22400 (± 6690) | 25400 (± 10800) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until last study visit; a maximum of approximately 113 months. The planned study duration for each participant was at least 60 months (following protocol amendment 7).

Adverse event reporting additional description:

Data are presented for the entire study duration and include AEs occurring during the treatment-emergent period (comprising both the initial treatment phase and retreatment phase) and AEs occurring after the treatment-emergent period (ie, during the safety follow-up phase).

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|------------------------------------|
| Reporting group title | Denosumab 120 mg Q4W (All Cohorts) |
|-----------------------|------------------------------------|

Reporting group description:

All participants received denosumab 120 mg SC Q4W, starting on study day 1, with loading doses of 120 mg SC on days 8 and 15 in the first month of treatment for those enrolled in cohorts 1 or 2.

| Serious adverse events | Denosumab 120 mg Q4W (All Cohorts) | | |
|---------------------------------------------------------------------|------------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 176 / 526 (33.46%) | | |
| number of deaths (all causes) | 26 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone giant cell tumour | | | |
| subjects affected / exposed | 19 / 526 (3.61%) | | |
| occurrences causally related to treatment / all | 2 / 21 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| Bone neoplasm | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone sarcoma | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer stage I | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ganglioneuroma | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to lung | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Myeloproliferative neoplasm | | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neoplasm | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuroendocrine tumour | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oncologic complication | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oesophageal adenocarcinoma | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteosarcoma | | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pelvic neoplasm | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal cancer | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Rhabdomyosarcoma | | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Sarcoma | | | |
| subjects affected / exposed | 5 / 526 (0.95%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Second primary malignancy | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Spindle cell sarcoma | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thyroid cancer metastatic | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour pain | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Circulatory collapse | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vasculitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Bone lesion excision | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leg amputation | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal operation | | | |

| | | | |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Disease recurrence | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hernia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Impaired healing | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucosal inflammation | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial haemorrhage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pharyngeal fistula | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| Lung disorder | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device failure | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| Device loosening | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atypical femur fracture | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| Fracture displacement | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gun shot wound | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Joint dislocation | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lumbar vertebral fracture | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meniscus injury | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Overdose | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Post procedural fistula | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative respiratory failure | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Procedural haemorrhage | | | | |

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|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pubis fracture | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Radiation myelopathy | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal compression fracture | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stress fracture | | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thoracic vertebral fracture | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tibia fracture | | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper limb fracture | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vena cava injury | | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound dehiscence | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|--------------------------------------------------------------|-----------------|--|--|
| Supraventricular tachycardia subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cauda equina syndrome subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Central nervous system lesion subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Facial neuralgia subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lethargy subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nerve compression | | | |

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|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| 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 | 8 / 526 (1.52%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |

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|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis | | | |

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|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastritis | | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestine perforation | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Melaena | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatic failure | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peptic ulcer | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis psoriasiform | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| 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 | 3 / 526 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder prolapse | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| Renal colic | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethral fistula | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urge incontinence | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxic nodular goitre | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 5 / 526 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 526 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| Bone pain | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Exposed bone in jaw | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral disc protrusion | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lumbar spinal stenosis | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscular weakness | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal pain | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myositis | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteitis | | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | | |
| occurrences causally related to treatment / all | 2 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteonecrosis | | | | |

| | | | |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed | 4 / 526 (0.76%) | | |
| occurrences causally related to treatment / all | 5 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 25 / 526 (4.75%) | | |
| occurrences causally related to treatment / all | 27 / 27 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudarthrosis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal wall infection | | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abscess | | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abscess jaw | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 4 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abscess neck | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abscess oral | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Appendicitis | | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arthritis infective | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspergillus infection | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacteraemia | | | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacteroides bacteraemia | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Catheter site infection | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bone abscess | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related infection | | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected cyst | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected skin ulcer | | | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious colitis | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscle abscess | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Orchitis | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteomyelitis | | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | | | |
| occurrences causally related to treatment / all | 6 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteomyelitis bacterial | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonsillar abscess | | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis | | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrotal abscess | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal osteomyelitis | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcutaneous abscess | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 526 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 2 / 526 (0.38%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 4 / 526 (0.76%) | | |
| occurrences causally related to treatment / all | 6 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 526 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Denosumab 120 mg Q4W (All Cohorts) | | |
|-------------------------------------------------------|------------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 480 / 526 (91.25%) | | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 30 / 526 (5.70%) | | |
| occurrences (all) | 69 | | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 39 / 526 (7.41%) | | |
| occurrences (all) | 49 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 34 / 526 (6.46%) | | |
| occurrences (all) | 46 | | |
| Headache | | | |
| subjects affected / exposed | 134 / 526 (25.48%) | | |
| occurrences (all) | 300 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 38 / 526 (7.22%) | | |
| occurrences (all) | 46 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 48 / 526 (9.13%) | | |
| occurrences (all) | 59 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 30 / 526 (5.70%) | | |
| occurrences (all) | 67 | | |
| General disorders and administration site conditions | | | |

| | | | |
|-----------------------------|--------------------|--|--|
| Fatigue | | | |
| subjects affected / exposed | 142 / 526 (27.00%) | | |
| occurrences (all) | 266 | | |
| Asthenia | | | |
| subjects affected / exposed | 48 / 526 (9.13%) | | |
| occurrences (all) | 65 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 27 / 526 (5.13%) | | |
| occurrences (all) | 28 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 46 / 526 (8.75%) | | |
| occurrences (all) | 60 | | |
| Pyrexia | | | |
| subjects affected / exposed | 47 / 526 (8.94%) | | |
| occurrences (all) | 72 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 49 / 526 (9.32%) | | |
| occurrences (all) | 80 | | |
| Constipation | | | |
| subjects affected / exposed | 60 / 526 (11.41%) | | |
| occurrences (all) | 71 | | |
| Dental caries | | | |
| subjects affected / exposed | 32 / 526 (6.08%) | | |
| occurrences (all) | 41 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 60 / 526 (11.41%) | | |
| occurrences (all) | 93 | | |
| Nausea | | | |
| subjects affected / exposed | 122 / 526 (23.19%) | | |
| occurrences (all) | 172 | | |
| Toothache | | | |
| subjects affected / exposed | 68 / 526 (12.93%) | | |
| occurrences (all) | 86 | | |
| Vomiting | | | |

| | | | |
|-------------------------------------------------|--------------------|--|--|
| subjects affected / exposed | 66 / 526 (12.55%) | | |
| occurrences (all) | 114 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 54 / 526 (10.27%) | | |
| occurrences (all) | 63 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 36 / 526 (6.84%) | | |
| occurrences (all) | 49 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 33 / 526 (6.27%) | | |
| occurrences (all) | 36 | | |
| Rash | | | |
| subjects affected / exposed | 45 / 526 (8.56%) | | |
| occurrences (all) | 57 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 29 / 526 (5.51%) | | |
| occurrences (all) | 37 | | |
| Depression | | | |
| subjects affected / exposed | 31 / 526 (5.89%) | | |
| occurrences (all) | 35 | | |
| Insomnia | | | |
| subjects affected / exposed | 45 / 526 (8.56%) | | |
| occurrences (all) | 53 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 41 / 526 (7.79%) | | |
| occurrences (all) | 47 | | |
| Back pain | | | |
| subjects affected / exposed | 154 / 526 (29.28%) | | |
| occurrences (all) | 263 | | |
| Arthralgia | | | |
| subjects affected / exposed | 192 / 526 (36.50%) | | |
| occurrences (all) | 325 | | |

| | | | |
|------------------------------------|--------------------|--|--|
| Muscle spasms | | | |
| subjects affected / exposed | 37 / 526 (7.03%) | | |
| occurrences (all) | 53 | | |
| Joint swelling | | | |
| subjects affected / exposed | 28 / 526 (5.32%) | | |
| occurrences (all) | 31 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 70 / 526 (13.31%) | | |
| occurrences (all) | 102 | | |
| Myalgia | | | |
| subjects affected / exposed | 42 / 526 (7.98%) | | |
| occurrences (all) | 51 | | |
| Neck pain | | | |
| subjects affected / exposed | 29 / 526 (5.51%) | | |
| occurrences (all) | 43 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 146 / 526 (27.76%) | | |
| occurrences (all) | 237 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 40 / 526 (7.60%) | | |
| occurrences (all) | 50 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 28 / 526 (5.32%) | | |
| occurrences (all) | 35 | | |
| Influenza | | | |
| subjects affected / exposed | 44 / 526 (8.37%) | | |
| occurrences (all) | 73 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 76 / 526 (14.45%) | | |
| occurrences (all) | 184 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 48 / 526 (9.13%) | | |
| occurrences (all) | 72 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| Hypercalcaemia | | | |
| subjects affected / exposed | 29 / 526 (5.51%) | | |
| occurrences (all) | 47 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 36 / 526 (6.84%) | | |
| occurrences (all) | 48 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 66 / 526 (12.55%) | | |
| occurrences (all) | 121 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12 December 2008 | <ul style="list-style-type: none">• Key inclusion criteria updated to include skeletally mature adolescents ≥ 12 years of age and clarify that skeletally mature adolescents must weigh at least 45 kilograms.• Key exclusion criteria updated to exclude women of child bearing potential who are evidently pregnant or breastfeeding and participants enrolled in or who have not yet completed at least 30 days since ending other investigational device or drug study(s), or participants receiving other investigational agents.• Sample size was clarified to include approximately 100 participants and the supporting sample size considerations were detailed.• The safety follow-up phase of the study was extended from 6 months for up to 12 months after the end of the study date. |
| 11 January 2010 | <ul style="list-style-type: none">• Study sample size increased from 100 participants to approximately 250 participants.• Secondary objective and endpoint clarified to include participants who do not require any surgery.• Eligibility criteria excluding women of childbearing potential who are evidently pregnant or breastfeeding was updated.• Exploratory endpoints were added to the protocol.• Addition of interim analysis corresponding with the increased sample size. |
| 14 May 2010 | <ul style="list-style-type: none">• Protocol updated to allow enrollment of participants from Amgen Study 20040215.• The exploratory objectives and endpoints were updated to include the proportion of participants who are able to undergo a less morbid surgical procedure compared with the planned surgical procedure at baseline for cohort 2 and disease status changes over time for all participants. |
| 15 November 2010 | <ul style="list-style-type: none">• Study sample size increased from 250 participants to 375 participants.• Secondary endpoints clarified.• Analysis of safety data from the safety follow-up clarified in Section 10.6.3 of the protocol. |
| 05 May 2011 | <ul style="list-style-type: none">• Exclusion criteria modified for contraception to include 2 methods of highly effective contraception during treatment and for 7 months after the end of treatment.• Criteria for a participant to receive retreatment were clarified.• The frequency of interim analysis was modified. |
| 30 August 2011 | <ul style="list-style-type: none">• Study sample size increased from approximately 375 participants to approximately 500 participants. |
| 15 May 2013 | <ul style="list-style-type: none">• Protocol amended to include PK analyses for an additional approximately 20 participants, approximately 10 adolescents and 10 adults.• The end of the clinical trial defined as when participants enrolled through November 2012 (before Amendment 7) complete a minimum of 60 months on study, or until death or lost to follow-up, whichever comes first.• Objectives, endpoints, sample collection and analyses were added consistent with the PK subset.• Clarification that participants who rolled over from Study 20040215 will follow the Study 20062004 schedule under Amendment 7.• End of treatment visit and safety follow-up visits clarified.• Added oral examinations for all participants and provided additional guidance regarding investigational product dosing and oral/dental procedures.• Safety reporting timelines clarified.• Added updated pregnancy and lactation reporting section, with additional instructions regarding counseling women of childbearing potential on the risks of pregnancy while receiving denosumab and discussing methods to decrease the risk. |

| | |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 September 2015 | <ul style="list-style-type: none"> • Updated safety follow-up period information and listed AEs of interest to align the protocol language with postmarketing data collection requirements, and to increase compliance with long-term follow-up data requirements. • Removed interim analysis 4 as it was not a regulatory requirement, and no study report was expected from this interim analysis per regulatory requirements. • Updated medical history section for clarification and aligned with other sections of the protocol. • Modified the dose escalation and stopping rules section to clarify that the planned dose may be given up to 7 days before the scheduled visit, as long as there are 21 days between doses. • Updated calcium and vitamin D information to match XGEVA product information. • Updated Protocol Synopsis, Investigational Product Dosage and Administration sections with text regarding supplementation of all participants with calcium and vitamin D. • Updated the number of birth control methods and amount of washout time required between the end of treatment and pregnancy or breastfeeding to align with the informed consent and current safety information. • Pregnancy reporting was changed from the Pregnancy Surveillance Program to Amgen Global Patient Safety as per current Amgen standard. |
| 15 December 2017 | <ul style="list-style-type: none"> • Added guidance about monitoring participants for hypercalcemia upon discontinuation or interruption of denosumab, including: <ul style="list-style-type: none"> ◦ Clarification added to AEs of Interest. ◦ Language for calcium and vitamin D supplementation. • Updated End of Study language to clarify definitions of the 'End of Treatment', End of Safety Follow-up Phase, and 'End of Study' visits. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported