



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
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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)
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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]
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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
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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]
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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
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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]
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Denosumab 120 mg Q4W (All Cohorts)
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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				

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			

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			

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			

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 occurrences (all)	37 / 526 (7.03%) 53		
Joint swelling subjects affected / exposed occurrences (all)	28 / 526 (5.32%) 31		
Musculoskeletal pain subjects affected / exposed occurrences (all)	70 / 526 (13.31%) 102		
Myalgia subjects affected / exposed occurrences (all)	42 / 526 (7.98%) 51		
Neck pain subjects affected / exposed occurrences (all)	29 / 526 (5.51%) 43		
Pain in extremity subjects affected / exposed occurrences (all)	146 / 526 (27.76%) 237		
Pain in jaw subjects affected / exposed occurrences (all)	40 / 526 (7.60%) 50		
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	28 / 526 (5.32%) 35		
Influenza subjects affected / exposed occurrences (all)	44 / 526 (8.37%) 73		
Nasopharyngitis subjects affected / exposed occurrences (all)	76 / 526 (14.45%) 184		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	48 / 526 (9.13%) 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	• 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	• 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	• 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	• 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	• 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	• Study sample size increased from approximately 375 participants to approximately 500 participants.
15 May 2013	• 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	• 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	• Added guidance about monitoring participants for hypercalcemia upon discontinuation or interruption of denosumab, including: ◦ 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