Clinical trial results:
An Open Label, Single Arm, Extension Study to Evaluate the Long Term Safety of Denosumab for Prolonging Bone Metastasis-Free Survival in Men with Hormone-Refractory Prostate Cancer

Summary

EudraCT number	2010-021846-23
Trial protocol	GB CZ
Global end of trial date	21 February 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	23 July 2015

Trial information

Trial identification

Sponsor protocol code	20080585

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01824342
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info – Clinical Trials, Amgen (EUROPE) GmbH, MedinfoInternational@amgen.com
Scientific contact	IHQ Medical Info – Clinical Trials, Amgen (EUROPE) GmbH, MedinfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the safety and tolerability of denosumab administration as measured by adverse events, immunogenicity, and safety laboratory parameters in subjects who previously received denosumab or placebo in Amgen study 20050147.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations, and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Czech Republic: 12
Worldwide total number of subjects	18
EEA total number of subjects	18

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a single-arm, open-label extension (OLE) phase of a phase 3, randomized, double-blind study (Study 20050147) comparing denosumab with placebo on prolonging bone metastasis-free survival in men with hormone-refractory (androgen independent) prostate cancer.

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	Placebo/Denosumab

Arm description:

Participants who received placebo in the parent study received open-label denosumab 120 mg by subcutaneous injecton once every 4 weeks (Q4W) for up to 3 years.

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

Dosage and administration details:

120 mg administered by subcutaneous injection every 4 weeks

Arm title	Denosumab/Denosumab

Arm description:

Participants who received denosumab in the parent study received open-label denosumab 120 mg by subcutaneous injecton once every 4 weeks (Q4W) for up to 3 years.

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

Dosage and administration details:

120 mg administered by subcutaneous injection every 4 weeks

Number of subjects in period 1	Placebo/Denosumab	Denosumab/Denosumab
Started	11	7
Completed	2	2
Not completed	9	5
Physician decision	5	-
Consent withdrawn by subject	-	3
Adverse event, non-fatal	1	1
Death	2	-
Disease Progression	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/Denosumab
Reporting group description:	
Participants who received placebo in the parent study received open-label denosumab 120 mg by subcutaneous injecton once every 4 weeks (Q4W) for up to 3 years.	
Reporting group title	Denosumab/Denosumab
Reporting group description:	
Participants who received denosumab in the parent study received open-label denosumab 120 mg by subcutaneous injecton once every 4 weeks (Q4W) for up to 3 years.	

Reporting group values	Placebo/Denosumab	Denosumab/Denosumab	Total
Number of subjects	11	7	18
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	71.6	70.3	
standard deviation	± 4.3	± 7.4	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	11	7	18
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self care, unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
Grade 0	7	5	12
Grade 1	4	1	5
Grade 2	0	1	1
Grade 3	0	0	0
Grade 4	0	0	0
Race/Ethnicity			
Units: Subjects			
White or Caucasian	11	7	18
Albumin-adjusted calcium			
Units: mmol/L			
arithmetic mean	2.44	2.42	
standard deviation	± 0.1	± 0.04	-
Creatinine			
Units: µmol/L			
arithmetic mean	88.4	89.66	
standard deviation	± 14.25	± 23.63	-
Phosphorus			

Units: mmol/L			
arithmetic mean	1.09	1.01	
standard deviation	± 0.22	± 0.24	-

End points

End points reporting groups

Reporting group title	Placebo/Denosumab
Reporting group description:	
Participants who received placebo in the parent study received open-label denosumab 120 mg by subcutaneous injecton once every 4 weeks (Q4W) for up to 3 years.	
Reporting group title	Denosumab/Denosumab
Reporting group description:	
Participants who received denosumab in the parent study received open-label denosumab 120 mg by subcutaneous injecton once every 4 weeks (Q4W) for up to 3 years.	

Primary: Number of Participants With Treatment-emergent Adverse Events (AEs) and Deaths

End point title	Number of Participants With Treatment-emergent Adverse Events (AEs) and Deaths[1]
End point description:	
A serious adverse event is defined as an adverse event that meets at least one of the following serious criteria: • fatal, • life threatening, • requires in-patient hospitalization or prolongation of existing hospitalization, • results in persistent or significant disability/incapacity, • congenital anomaly/birth defect, and/or • other significant medical hazard. The adverse event severity grading scale used was the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, according to the following: Grade 1 = Mild AE; Grade 2 = Moderate AE; Grade 3 = Severe AE; Grade 4 = Life-threatening or disabling AE; Grade 5 = Death related to AE. The investigator assessed whether each adverse event was possibly related to the investigational product (IP).	
End point type	Primary
End point timeframe:	
From the first dose of open-label denosumab until 4 weeks after the last; maximum time on study was 37 months. Follow-up survival information was collected for up to 3 years after the last dose of blinded investigation product in the 20050147 study.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical reporting of the safety outcomes was entirely descriptive, with no formal statistical testing performed.

End point values	Placebo/Denosumab	Denosumab/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: participants				
Any adverse event (AE)	11	7		
Serious adverse event	7	4		
Fatal adverse event	2	0		
AE leading to study discontinuation	2	1		
AE leading to IP discontinuation	4	1		
CTCAE Grade 3, 4, or 5	6	2		
AE related to investigational product (IP)	2	3		
Serious AE related to IP	0	2		
Fatal AE related to IP	0	0		
AE related to IP leading to study discontinuation	1	1		

AE related to IP leading to IP discontinuation	1	1		
AE related to IP and CTCAE Grade 3, 4, or 5	0	1		
Deaths	4	1		
Deaths on study	2	0		
Deaths during the safety follow-up	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in Laboratory Values

End point title	Percent Change From Baseline in Laboratory Values[2]

End point description:

End point type	Primary

End point timeframe:

Baseline and Week 49

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: The statistical reporting of the safety outcomes was entirely descriptive, with no formal statistical testing performed.

End point values	Placebo/Denosumab	Denosumab/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[3]	6[4]		
Units: percent change				
arithmetic mean (standard deviation)				
Albumin-adjusted Calcium	-0.9 (± 2.5)	1.1 (± 3.1)		
Alkaline Phosphatase	-23.8 (± 21.8)	-1.6 (± 20.5)		
Creatinine	16.3 (± 31.5)	2.4 (± 5.8)		
Phosphorus	-2.6 (± 25.2)	0 (± 10.4)		

Notes:

[3] - Safety analysis set with available laboratory data at each time point.

[4] - Safety analysis set with available laboratory data at each time point.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Anti-denosumab Neutralizing Antibody Formation

End point title	Number of Participants With Anti-denosumab Neutralizing Antibody Formation[5]

End point description:

End point type	Primary

End point timeframe:

3 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical reporting of the safety outcomes was entirely descriptive, with no formal statistical testing performed.

End point values	Placebo/Denosumab	Denosumab/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[6]	7[7]		
Units: participants	0	0		

Notes:

[6] - Participants exposed to open-label denosumab with ≥ 1 antibody sample

[7] - Participants exposed to open-label denosumab with ≥ 1 antibody sample

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

End point title	Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

End point description:

A scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work); 2 = Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 = Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair; 5 = Dead.

End point type	Secondary

End point timeframe:

Baseline and Week 49

End point values	Placebo/Denosumab	Denosumab/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[8]	6[9]		
Units: participants				
4-point increase in PS	0	0		
3-point increase in PS	0	0		
2-point increase in PS	0	0		
1-point increase in PS	0	1		
No change	10	5		
1-point decrease in PS	0	0		
2-point decrease in PS	0	0		

Notes:

[8] - Safety analysis set with available data at both time points

[9] - Safety analysis set with available data at both time points

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of open-label denosumab until 4 weeks after the last; maximum time on study was 37 months. Follow-up survival information was collected for up to 3 years after the last dose of blinded investigation product in the 20050147 study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo/Denosumab 120 mg Q4W

Reporting group description:

Participants who received placebo in the parent study received open-label denosumab 120 mg by subcutaneous injecton once every 4 weeks (Q4W) for up to 3 years.

Reporting group title	Denosumab/Denosumab 120 mg Q4W

Reporting group description:

Participants who received denosumab in the parent study received open-label denosumab 120 mg by subcutaneous injecton once every 4 weeks (Q4W) for up to 3 years.

Serious adverse events	Placebo/Denosumab 120 mg Q4W	Denosumab/Denosumab 120 mg Q4W	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 11 (63.64%)	4 / 7 (57.14%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events			
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary sediment present			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchial carcinoma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant anorectal neoplasm			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic pain			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoaesthesia			

subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Medical device complication			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder neck obstruction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			

subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocturia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			

subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 11 (0.00%)	2 / 7 (28.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo/Denosumab 120 mg Q4W	Denosumab/Denosumab 120 mg Q4W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	6 / 7 (85.71%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Metastatic pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			

Tooth extraction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Device expulsion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Device leakage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Face oedema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	3 / 11 (27.27%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Malaise			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	3 / 11 (27.27%)	1 / 7 (14.29%)	
occurrences (all)	5	1	
Pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Prostatic pain			

subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Dyspnoea exertional			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Haemoptysis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hydrothorax			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Investigations			

Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	7	0	
Prostatic specific antigen increased			
subjects affected / exposed	2 / 11 (18.18%)	2 / 7 (28.57%)	
occurrences (all)	2	2	
Urinary sediment present			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Weight decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Radiation injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rib fracture			

subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	3 / 11 (27.27%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Hypoaesthesia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Muscle contractions involuntary			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Poor quality sleep			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Sciatica			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 11 (27.27%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Meniere's disease			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Vertigo			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Dry eye			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Faecal incontinence			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gingival pain			

subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Loose tooth			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Tooth disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Tooth loss			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)	1 / 7 (14.29%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Pruritus generalised			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin exfoliation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

Skin lesion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Calculus bladder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Haematuria			
subjects affected / exposed	3 / 11 (27.27%)	1 / 7 (14.29%)	
occurrences (all)	6	1	
Hypertonic bladder			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Nocturia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Renal cyst			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Renal failure chronic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Renal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Urethral haemorrhage			

subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Urethral stenosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	2 / 11 (18.18%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	4 / 11 (36.36%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Flank pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Fracture pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal pain			

subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rheumatic disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Sensation of heaviness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abscess of salivary gland			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Cellulitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Localised infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

Lower respiratory tract infection			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oral fungal infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Post procedural infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	3 / 11 (27.27%)	2 / 7 (28.57%)	
occurrences (all)	10	3	
Viral infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	3	1	
Diabetes mellitus			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Hypercholesterolaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vitamin B12 deficiency			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2012	The purpose of this amendment was to include information on a denosumab formulation of 70 mg/mL. Additional study visits were added to Schedule A to accurately reflect the 3-year open-label extension period.
22 February 2013	The purpose of this amendment was to clarify the serious adverse event reporting process and timelines and lay out in the protocol a mechanism by which to report pregnancies that occur in female partners of male subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported