Clinical trial results:
A Single-arm, Multicenter, Proof-of-concept Study of Denosumab in the Treatment of Hypercalcemia of Malignancy in Subjects with Elevated Serum Calcium Despite Recent Treatment with IV Bisphosphonates.

Summary

EudraCT number	2009-009756-21
Trial protocol	PL FR IT
Global end of trial date	21 August 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	24 July 2015

Trial information

Trial identification

Sponsor protocol code	20070315

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00896454
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, 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 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the potential for denosumab to treat hypercalcemia of malignancy that does not respond to recent treatment with Intravenous (IV) bisphosphonates by lowering corrected serum calcium (CSC) ≤ 11.5 mg/dL (2.9 mmol/L) by study day 10.

Protection of trial subjects:

This study was conducted in accordance with the current version of the Declaration of Helsinki and the FDA and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations. The study protocol, subject information, and informed consent form were reviewed and approved by the independent ethics committee (IEC) or institutional review board (IRB) for each study center. All subjects provided written informed consent after the aims, methods, and potential hazards of the study were adequately explained; the appropriate informed consent was obtained before any protocol-specific screening procedures or any investigational products were administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	33
EEA total number of subjects	10

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)	19
From 65 to 84 years	13
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First patient was enrolled on 16 November 2009 and the last patient enrolled on 02 July 2012. The primary analysis cut-off date was 13 September 2012; the last subject completed follow-up 21 August 2013.

Pre-assignment

Screening details:

Eligible subjects were adults ≥ 18 years of age who had hypercalcemia of malignancy (HCM), defined as documented histologically or cytologically confirmed cancer and a corrected serum calcium (CSC) > 12.5 mg/dL (3.1 mmol/L) despite IV bisphosphonates administered ≥ 7 days and ≤ 30 days prior to the screening CSC.

Period 1

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

Arms

Arm title	Denosumab

Arm description:

Participants received denosumab at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W) with a loading dose of 120 mg SC on study Days 8 and 15.

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:

Denosumab was administered at a dose of 120 mg SC Q4W with loading doses of 120 mg SC being administered on study days 8 and 15.

Number of subjects in period 1	Denosumab
Started	33
Completed	0
Not completed	33
Consent withdrawn by subject	1
Disease progression	5
Death	10
Other	4
Administrative reasons	1
Adverse event	9
Requirement for alternative therapy	3

Baseline characteristics

Reporting groups	
Reporting group title	Denosumab
Reporting group description:	
Participants received denosumab at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W) with a loading dose of 120 mg SC on study Days 8 and 15.	

Reporting group values	Denosumab	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60.3		
standard deviation	± 14.8	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	21	21	
Race/Ethnicity Units: Subjects			
White or Caucasian	23	23	
Black or African American	7	7	
Hispanic or Latino	1	1	
Asian	1	1	
Other	1	1	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Scale used to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self care, confined to a bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
Grade 0	1	1	
Grade 1	7	7	
Grade 2	14	14	
Grade 3	8	8	
Grade 4	3	3	
Tumor Type Units: Subjects			
Bladder	1	1	
Breast	6	6	
Head and neck	2	2	
Liver	1	1	
Neuroendocrine/carcinoid	4	4	
Non-hodgkin's	2	2	
Non-small cell lung cancer	3	3	

Ovarian	1	1	
Renal	3	3	
Small cell lung cancer	1	1	
Soft tissue sarcoma	1	1	
Unknown (primary tumor)	1	1	
Multiple myeloma	3	3	
Chronic lymphocytic leukemia	2	2	
IGG kappa multiple myeloma	1	1	
Myeloma	1	1	
Presence of metastatic disease at enrollment Units: Subjects			
Yes	30	30	
No	3	3	
Presence of bone metastatic disease at enrollment Units: Subjects			
Yes	13	13	
No	20	20	
Time from initial cancer diagnosis to enrollment Units: months			
arithmetic mean	56.9		
standard deviation	± 68.8	-	
Calcium (corrected) Units: mg/dL			
arithmetic mean	13.89		
standard deviation	± 1.27	-	

End points

End points reporting groups

Reporting group title	Denosumab

Reporting group description:

Participants received denosumab at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W) with a loading dose of 120 mg SC on study Days 8 and 15.

Primary: Percentage of Participants With a Response Within 10 Days of First Dose of Denosumab

End point title	Percentage of Participants With a Response Within 10 Days of First Dose of Denosumab[1]

End point description:

Response is defined as corrected serum calcium (CSC) ≤ 11.5 mg/dL, within 10 days after the first dose of denosumab. For all CSC values, if albumin was < 4 g/dL, the following formula was used to calculate CSC: CSC = Total serum calcium [mg/dL] + (0.8 x (4 – serum albumin [g/dL])).

The Response Analysis Subset included all participants who received at least 1 dose of denosumab and had a screening CSC (from local lab) > 12.5 mg/dL (3.1 mmol/L).

End point type	Primary

End point timeframe:

10 days

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: No formal hypothesis was tested.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	33[2]			
Units: percentage of participants				
number (confidence interval 95%)	63.6 (45.1 to 79.6)			

Notes:

[2] - Reponse analysis subset

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Response by Visit

End point title	Percentage of Participants With a Response by Visit

End point description:

Response is defined as corrected serum calcium (CSC) ≤ 11.5 mg/dL, within 10 days after the first dose of denosumab. For all CSC values, if albumin was < 4 g/dL, the following formula was used to calculate CSC: CSC = Total serum calcium [mg/dL] + (0.8 x (4 – serum albumin [g/dL])) .

End point type	Secondary

End point timeframe:

Days 2, 4, 8, 10, 15, 19, 23, 29, 36, 43, 50 and 57

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of participants				
number (confidence interval 95%)				
By Day 2	9.1 (1.9 to 24.3)			
By Day 4	24.2 (11.1 to 42.3)			
By Day 8	48.5 (30.8 to 66.5)			
By Day 10	63.6 (45.1 to 79.6)			
By Day 15	63.6 (45.1 to 79.6)			
By Day 19	69.7 (51.3 to 84.4)			
By Day 23	69.7 (51.3 to 84.4)			
By Day 29	69.7 (51.3 to 84.4)			
By Day 36	69.7 (51.3 to 84.4)			
By Day 43	69.7 (51.3 to 84.4)			
By Day 50	69.7 (51.3 to 84.4)			
By Day 57	69.7 (51.3 to 84.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Complete Response by Visit

End point title	Percentage of Participants With a Complete Response by Visit

End point description:

Response is defined as corrected serum calcium (CSC) ≤ 10.8 mg/dL (2.7 mmol/L). For all CSC values, if albumin was < 4 g/dL, the following formula was used to calculate CSC: CSC = Total serum calcium [mg/dL] + (0.8 x (4 – serum albumin [g/dL])).

End point type	Secondary

End point timeframe:

Days 2, 4, 8, 10, 15, 19, 23, 29, 36, 43, 50 and 57

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	33[3]			
Units: percentage of participants				
number (confidence interval 95%)				
By Day 2	3 (0.1 to 15.8)			
By Day 4	15.2 (5.1 to 31.9)			
By Day 8	27.3 (13.3 to 45.5)			
By Day 10	36.4 (20.4 to 54.9)			
By Day 15	45.5 (28.1 to 63.6)			
By Day 19	45.5 (28.1 to 63.6)			
By Day 23	51.5 (33.5 to 69.2)			
By Day 29	51.5 (33.5 to 69.2)			
By Day 36	60.6 (42.1 to 77.1)			
By Day 43	63.6 (45.1 to 79.6)			
By Day 50	63.6 (45.1 to 79.6)			
By Day 57	63.6 (45.1 to 79.6)			

Notes:

[3] - Response Analysis Subset

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to Response was defined as the time period from study Day 1 to the first time post-baseline corrected serum calcium (CSC) ≤ 11.5 mg/dL. Participants were censored on the last CSC assessment day if no response was observed. If there was no post-baseline CSC assessment, time to response was censored on study Day 1.
Time to response was analyzed using Kaplan–Meier methods. The confidence interval was calculated using bootstrap method.

End point type	Secondary

End point timeframe:

From Day 1 until the end of study date or primary data cutoff date (13 September 2012), whichever occured first; median time on study was 1.8 months.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	33[4]			
Units: days				
median (confidence interval 95%)	9 (5 to 19)			

Notes:

[4] - Response Analysis Subset

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Response

End point title	Time to Complete Response

End point description:

Time to complete response was defined as the time period from study Day 1 to the first time post-baseline corrected serum calcium (CSC) was ≤ 10.8 mg/dL (2.7 mmol/L). Participants were censored on the last CSC assessment day if no complete response was observed. If there was no post-baseline CSC assessment, time to complete response was censored on study Day 1. Time to complete response was analyzed using Kaplan–Meier methods. The confidence interval is calculated using bootstrap method.

End point type	Secondary

End point timeframe:

From Day 1 until the end of study date or primary data cutoff date (13 September 2012), whichever occured first; median time on study was 1.8 months.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	33[5]			
Units: days				
median (confidence interval 95%)	23 (11 to 43)			

Notes:

[5] - Response Analysis Subset

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response is defined as the number of days from the first day of corrected serum calcium ≤ 11.5 mg/dL (2.9 millimoles/L) to the last day of corrected serum calcium ≤ 11.5 mg/dL. Participants were censored on the last CSC assessment day if their CSC level never reached > 11.5 mg/dL after the first response. If a participant had no CSC assessment after the first response, duration of response was set to zero and censored. Duration of response was summarized for participants who achieved a response using the Kaplan-Meier method. "99999" indicates values were not estimable due to the low number of events.

End point type	Secondary

End point timeframe:

From Day 1 until the end of study date or primary data cutoff date (13 September 2012), whichever

occured first; median time on study was 1.8 months.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	23[6]			
Units: days				
median (confidence interval 95%)	104 (9 to 99999)			

Notes:

[6] - Participants with a response in the Response Analysis Subset

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Response

End point title	Duration of Complete Response

End point description:

Duration of complete response is defined as the number of days from the first day of of corrected serum calcium ≤ 10.8 mg/dL (2.7 millimoles/L) to the last day of corrected serum calcium ≤ 10.8 mg/dL. Participants were censored on the last CSC assessment day if their CSC level never reached > 10.8 mg/dL after the complete response. If a participant had no CSC assessment after the complete response, duration of complete response was set to zero and censored. Duration of complete response was summarized for participants who achieved a complete response using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From Day 1 until the end of study date or primary data cutoff date (13 September 2012), whichever occured first; median time on study was 1.8 months.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	21[7]			
Units: days				
median (confidence interval 95%)	34 (1 to 134)			

Notes:

[7] - Participants with a complete response in the Response Analysis Subset

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Relapse/Nonresponse of Hypercalcemia of Malignancy

End point title	Time to Relapse/Nonresponse of Hypercalcemia of Malignancy

End point description:

Time to relapse/nonresponse was defined as the number of days from study Day 1 until the last day of CSC ≤ 11.5 mg/dL for all particiipants with relapse after the first response. Participants were censored on the last CSC assessment day if their CSC level never reached > 11.5 mg/dL after first response. For

participants who never achieved response, time to relapse/nonresponse was set to zero. Otherwise, if there was no post-baseline CSC assessment, time to relapse/nonresponse was censored on study Day 1. Time to relapse/nonresponse was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From Day 1 until the end of study date or primary data cutoff date (13 September 2012), whichever occured first; median time on study was 1.8 months.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	33[8]			
Units: days				
median (confidence interval 95%)	19 (5 to 114)			

Notes:

[8] - Response Analysis Subset

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Corrected Serum Calcium

End point title	Change From Baseline in Corrected Serum Calcium

End point description:

The Efficacy Analysis Subset included all participants who received at least 1 dose of denosumab. n = the number of participants who had non-missing data at Baseline and the time point of interest.

End point type	Secondary

End point timeframe:

Baseline and Days 2, 4, 8, 10, 15, 19, 23, 29, 36, 43, 50 and 57

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	33[9]			
Units: mmol/L				
median (inter-quartile range (Q1-Q3))				
Change from Baseline to Day 2 (n = 32)	-0.13 (-0.31 to 0.09)			
Change from Baseline to Day 4 (n = 32)	-0.25 (-0.44 to -0.14)			
Change form Baseline to Day 8 (n = 27)	-0.43 (-0.73 to -0.2)			
Change from Baseline to Day 10 (n = 28)	-0.54 (-0.77 to -0.25)			
Change from Baseline to Day 15 (n = 24)	-0.51 (-0.89 to -0.15)			
Change from Baseline to Day 19 (n = 22)	-0.64 (-0.8 to -0.3)			
Change from Baseline to Day 23 (n = 21)	-0.6 (-0.85 to -0.4)			

Change from Baseline to Day 29 (n = 22)	-0.53 (-0.75 to -0.3)			
Change from Baseline to Day 36 (n = 20)	-0.61 (-0.84 to -0.15)			
Change from Baseline to Day 43 (n = 19)	-0.75 (-0.98 to -0.1)			
Change from Baseline to Day 50 (n = 15)	-0.83 (-1.03 to -0.2)			
Change from Baseline to Day 57 (n = 17)	-0.73 (-1.03 to -0.25)			

Notes:

[9] - Efficacy Analysis Subset

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were followed for up to 6 months after last dose for serious adverse events. Median time on study was 1.8 months, maximum was 23 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Denosumab

Reporting group description:

Participants received denosumab at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W) with a loading dose of 120 mg SC on study Days 8 and 15.

Serious adverse events	Denosumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 33 (90.91%)		
number of deaths (all causes)	31		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Breast cancer			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Breast cancer metastatic			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 3		
Chronic lymphocytic leukaemia			

subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Diffuse large B-cell lymphoma				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal stromal tumour				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Head and neck cancer				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Hepatic cancer				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lung neoplasm malignant				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Non-small cell lung cancer				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Ovarian cancer				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Plasma cell myeloma				

subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Renal cell carcinoma				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Hypotension				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Hypoxia				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Urine output decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Tachycardia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Lethargy			
subjects affected / exposed	1 / 33 (3.03%)		
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	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal obstruction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Renal failure acute			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal tubular necrosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
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 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Denosumab		
Total subjects affected by non-serious adverse events subjects affected / exposed	26 / 33 (78.79%)		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2 6 / 33 (18.18%) 9 8 / 33 (24.24%) 12 4 / 33 (12.12%) 5		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 6 2 / 33 (6.06%) 2 7 / 33 (21.21%) 10		

Epistaxis subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Pleural effusion subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5		
Pulmonary oedema subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Insomnia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Investigations Haemoglobin decreased subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 14		
Weight decreased subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Nervous system disorders Depressed level of consciousness			

subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	12		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	7		
Febrile neutropenia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	6		
Constipation			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	9		
Dry mouth			

subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	10 / 33 (30.30%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Rash pruritic			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Musculoskeletal pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Myalgia			

subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	9		
Fluid overload			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	6		
Hyperkalaemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	6		
Hypomagnesaemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypophosphataemia			

subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2010	The primary reason for this amendment was to delete the exclusion of a prior history or current evidence of ONJ, and related factors. Subjects who qualified for this protocol, ie, HCM that is relapsed or refractory to bisphosphonate treatment, could have been previously treated with long-term bisphosphonates for their underlying malignancy, which has been shown to be associated with ONJ. HCM is a serious and potentially life-threatening condition that requires immediate treatment. Excluding bisphosphonate-refractory subjects with prior or current ONJ or related factors would deny them treatment with another anti-resorptive agent that could potentially reduce their serum calcium levels. Additional changes included the following: -deleted the exclusion criterion of previous treatment with denosumab -modified the contraceptive exclusion criteria -clarified that screening chemistry and pregnancy testing was to be performed at a local laboratory -changed the criteria for denosumab discontinuation, such that after 4 doses of denosumab or by study day 57, denosumab could be discontinued if CSC ≥ 12.5 mg/dL instead of ≥ 11.6 mg/dL -modified the informed consent to be consistent with the protocol and updated safety information -made minor wording changes and clarifications
05 May 2011	-Modified the eligibility criteria and informed consent to include 2 methods of highly effective contraception during treatment and for 7 months after the last dose of denosumab -Modified the prestudy window for treatment with other therapeutic agents for hypercalcemia such that the determination for evaluating the expected potentially effective therapeutic window of these agents was at the discretion of the physician -Made minor revisions to definitions of subsets, objectives, and endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported