Clinical trial results:
A Double-blind, Placebo-controlled Study to Evaluate New or Worsening Lens Opacifications in Subjects With Non-metastatic Prostate Cancer Receiving Denosumab for Bone Loss due to Androgen-Deprivation Therapy

Summary

EudraCT number	2009-012076-26
Trial protocol	FR CZ PL LV GR SK BG HU SI
Global end of trial date	12 May 2016

Results information

Result version number	v1 (current)
This version publication date	13 May 2017
First version publication date	13 May 2017

Trial information

Trial identification

Sponsor protocol code	20080560

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00925600
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	12 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a phase 3, randomized, double-blind, placebo-controlled study to evaluate new or worsening lens opacifications in subjects with non-metastatic prostate cancer receiving denosumab for bone loss due to androgen deprivation therapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and other regulations as applicable.
The study protocol and all amendments, subject information, and informed consent form were reviewed and approved by the respective independent ethics committee or institutional review board for each study center before Amgen’s recruitment of subjects into the study and shipment of investigational product.
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	30 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Canada: 77
Country: Number of subjects enrolled	Czech Republic: 72
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Greece: 33
Country: Number of subjects enrolled	Hungary: 134
Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Latvia: 14
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	New Zealand: 22
Country: Number of subjects enrolled	Poland: 65
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Slovakia: 79
Country: Number of subjects enrolled	Slovenia: 3

Country: Number of subjects enrolled	South Africa: 49
Country: Number of subjects enrolled	Ukraine: 22
Country: Number of subjects enrolled	United States: 112
Worldwide total number of subjects	769
EEA total number of subjects	416

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)	139
From 65 to 84 years	618
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 125 centers in 18 countries: Australia, Bulgaria, Canada, the Czech Republic, France, Greece, Hungary, India, Latvia, Mexico, New Zealand, Poland, Russia, Slovakia, Slovenia, South Africa, Ukraine, and the United States.
The first participant enrolled on 30 November 2009 and the last participant enrolled on 04 May 2015.

Pre-assignment

Screening details:

Participants were randomly assigned to receive denosumab or placebo in a 1:1 allocation ratio. Randomization was stratified on the basis of screening Lens Opacities Classification System (LOCS) III status (< 3.0 at all sites versus ≥ 3.0 at any site); age group (< 75, ≥ 75 years), and patient-reported history of cataract (yes/no).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomized to receive placebo administered by subcutaneous injection on Day 1 and at Month 6.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Prefilled syringe for subcutaneous (SC) injection

Arm title	Denosumab

Arm description:

Participants randomized to receive denosumab 60 mg administered by subcutaneous injection on Day 1 and at Month 6.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	AMG 162
Other name	Prolia®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Prefilled syringe for subcutaneous (SC) injection administered at a dose of 60 mg

Number of subjects in period 1	Placebo	Denosumab
Started	386	383
Received Treatment	383	382
Completed	354	355
Not completed	32	28
Consent withdrawn by subject	16	14
Ineligibility Determined	2	-
Protocol Deviation	-	1
Death	4	3
Other	3	1
Administrative Decision	1	1
Adverse event	1	2
Lost to follow-up	2	2
Requirement for Alternative Therapy	-	1
Disease Progression	1	3
Noncompliance	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive placebo administered by subcutaneous injection on Day 1 and at Month 6.	
Reporting group title	Denosumab
Reporting group description:	
Participants randomized to receive denosumab 60 mg administered by subcutaneous injection on Day 1 and at Month 6.	

Reporting group values	Placebo	Denosumab	Total
Number of subjects	386	383	769
Age Categorical Units: Subjects			
18 - 64 years	73	66	139
65 - 74 years	189	194	383
75 - 84 years	119	116	235
≥ 85 years	5	7	12
Age Continuous Units: years			
arithmetic mean	71	71.1	
standard deviation	± 7	± 7.2	-
Gender, Male/Female Units: Subjects			
Female	0	0	0
Male	386	383	769
Race/Ethnicity, Customized Units: Subjects			
White	359	346	705
Black (or African American)	12	11	23
Hispanic/Latino	1	9	10
Other	7	8	15
Asian	7	7	14
Japanese	0	1	1
Native Hawaiian or Other Pacific Islander	0	1	1
Presence of Cataract(s)			
From baseline medical history			
Units: Subjects			
Yes	59	63	122
No	327	320	647
Presence of Diabetes Units: Subjects			
Yes	70	61	131
No	316	322	638
Received Androgen-deprivation Therapy (ADT) Units: Subjects			

Yes	350	353	703
No	36	30	66
Orchiectomy (Surgical Castration) Units: Subjects			
Yes	58	51	109
No	328	332	660
Screening Lens Opacities Classification System (LOCS) III Status			
The Lens Opacities Classification System III (LOCS III) is a slit lamp based opacification grading method. Photographs of slit lamp cross-sections of the lens are used as references for grading nuclear opalescence (NO) and nuclear color (NC), and photographs of the lens seen by retroillumination are used as references for grading cortical (C) and posterior subcapsular (P) cataract. Opacification severity is graded on a decimal scale, scores can range from 0.1 to 6.9 for NO and NC and from 0.1 to 5.9 for C and P. For each opacification type the higher grading scores indicate greater severity.			
Units: Subjects			
< 3.0 at all sites [P, C, and NO]	299	299	598
≥ 3.0 at any of these sites	87	84	171
Participant-reported History of Cataract			
Participant-reported history of cataracts was a study stratification factor.			
Units: Subjects			
Yes	35	35	70
No	351	348	699

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive placebo administered by subcutaneous injection on Day 1 and at Month 6.	
Reporting group title	Denosumab
Reporting group description:	
Participants randomized to receive denosumab 60 mg administered by subcutaneous injection on Day 1 and at Month 6.	
Subject analysis set title	Placebo - Left Eye
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo subcutaneous injection on Day 1 and at Month 6.	
Subject analysis set title	Placebo - Right Eye
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo subcutaneous injection on Day 1 and at Month 6.	
Subject analysis set title	Denosumab - Left Eye
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received denosumab 60 mg administered by subcutaneous injection on Day 1 and at Month 6.	
Subject analysis set title	Denosumab - Right Eye
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received denosumab 60 mg administered by subcutaneous injection on Day 1 and at Month 6.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo administered by subcutaneous injection on Day 1 and at Month 6. The safety analysis set includes all enrolled subjects who received at least one dose of study drug. Subjects were analyzed according to their actual treatment received.	
Subject analysis set title	Denosumab
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received denosumab 60 mg administered by subcutaneous injection on Day 1 and/or at Month 6. The safety analysis set includes all enrolled subjects who received at least one dose of study drug. Subjects were analyzed according to their actual treatment received. This group includes three participants randomized to the placebo group who received at least 1 dose of denosumab in error.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants in the Lens Opacification Analysis Set received placebo administered by subcutaneous injection on Day 1 and at Month 6. The lens opacification analysis set, for the primary endpoint, includes all randomized subjects who received at least one dose of study drug, had an evaluable baseline LOCS III assessment, and at least one evaluable post-baseline LOCS III assessment at the corresponding lens site. Subjects in the lens opacification analysis set were analyzed according to their actual treatment received.	
Subject analysis set title	Denosumab
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants in the Lens Opacification Analysis Set received denosumab 60 mg administered by subcutaneous injection on Day 1 and at Month 6.
The lens opacification analysis set, for the primary endpoint, includes all randomized subjects who received at least one dose of study drug, had an evaluable baseline LOCS III assessment, and at least one evaluable post-baseline LOCS III assessment at the corresponding lens site. Subjects in the lens opacification analysis set were analyzed according to their actual treatment received. This group includes three participants randomized to the placebo group who received at least 1 dose of denosumab in error.

Primary: Percentage of Participants with Lens Opacification Event Development or Progression by Month 12

End point title	Percentage of Participants with Lens Opacification Event Development or Progression by Month 12

End point description:

The Lens Opacities Classification System III (LOCS III) is a slit lamp based opacification grading method. Photographs of slit lamp cross-sections of the lens are used as references for grading nuclear opalescence (NO) and nuclear color (NC), and photographs of the lens seen by retroillumination are used as references for grading cortical (C) and posterior subcapsular (P) cataract. Opacification severity is graded on a decimal scale, scores can range from 0.1 to 6.9 for NO and NC and from 0.1 to 5.9 for C and P. Higher grading scores indicate greater severity. Lens opacification event development or progression was based on a change of ≥ 1.0 in P, ≥ 1.0 in C, or ≥ 0.7 in NO in the LOCS III score from baseline.
The analysis was conducted in the lens opacification analysis set, which includes participants who received at least 1 dose of study drug, had an evaluable baseline LOCS III assessment, and at least 1 evaluable post-baseline LOCS III assessment at the corresponding lens site.

End point type	Primary

End point timeframe:

12 months

End point values	Placebo	Denosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	374	379		
Units: percentage of participants				
number (not applicable)	33.2	33.5		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The primary endpoint was summarized with the point estimate of absolute risk difference (difference in incidence rates, denosumab minus placebo) and the corresponding 95% confidence interval using the Mantel-Haenszel method adjusting for the stratification factors: baseline LOCS III status (< 3.0 at all sites [P, C, and NO] vs. ≥ 3.0 at any of these sites), age group (< 75, ≥ 75 years), and patient-reported history of cataract (yes/no).

Comparison groups	Placebo v Denosumab

Number of subjects included in analysis	753
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0026
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	7.2
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[1] - Non-inferiority was demonstrated if the upper bound of the 97.5% one-sided confidence interval, or equivalently upper bound of two-sided 95% confidence interval was less than the pre-specified non-inferiority bound of 10%.

Other pre-specified: Percentage of Participant with Lens Opacification Event Development or Progression by Month 12 Based on a Change of ≥ 1.5 in P, ≥ 1.5 in C, or ≥ 1.5 in NO in the LOCS III score

End point title	Percentage of Participant with Lens Opacification Event Development or Progression by Month 12 Based on a Change of ≥ 1.5 in P, ≥ 1.5 in C, or ≥ 1.5 in NO in the LOCS III score

End point description:

LOCS III is a slit lamp based opacification grading method. Photographs of slit lamp cross-sections of the lens are used as references for grading nuclear opalescence (NO) and nuclear color (NC), and photographs of the lens seen by retroillumination are used as references for grading cortical (C) and posterior subcapsular (P) cataract. Opacification severity is graded on a decimal scale, scores can range from 0.1 to 6.9 for NO and NC and from 0.1 to 5.9 for C and P. For each opacification type the higher grading scores indicate greater severity. Lens opacification event development or progression by month 12 was based on a change ≥ 1.5 in P, ≥ 1.5 in C, or ≥ 1.5 in NO in the LOCS III score from baseline. The analysis was conducted in the lens opacification analysis set which includes all randomized subjects who received at least 1 dose of study drug, an evaluable baseline LOCS III assessment, and at least 1 evaluable post-baseline LOCS III assessment at the corresponding lens site.

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Placebo	Denosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	374	379		
Units: percentage of participants				
number (not applicable)	10.7	8.4		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The point estimate of absolute risk difference (difference in incidence rates, denosumab minus placebo) and the corresponding 95% confidence interval was constructed using the Mantel-Haenszel method adjusting for the stratification factors: baseline LOCS III status (< 3.0 at all sites [P, C, and NO] vs. ≥ 3.0 at any of these sites), age group (< 75, ≥ 75 years), and patient-reported history of cataract (yes/no).

Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	753
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	2.1

Other pre-specified: Percentage of Participants with Lens Opacification Event Development or Progression by Month 6

End point title	Percentage of Participants with Lens Opacification Event Development or Progression by Month 6

End point description:

LOCS III is a slit lamp based opacification grading method. Photographs of slit lamp cross-sections of the lens are used as references for grading nuclear opalescence (NO) and nuclear color (NC), and photographs of the lens seen by retroillumination are used as references for grading cortical (C) and posterior subcapsular (P) cataract. Opacification severity is graded on a decimal scale, scores range from 0.1 to 6.9 for NO and NC and from 0.1 to 5.9 for C and P; higher grading scores indicate greater severity. Lens opacification event development or progression by month 6 was based on a change of ≥ 1.0 in P, ≥ 1.0 in C, or ≥ 0.7 in NO in the LOCS III score from baseline.
The analysis was conducted in the lens opacification analysis set which includes all randomized subjects who received at least 1 dose of study drug, had an evaluable baseline LOCS III assessment and at least 1 evaluable post-baseline LOCS III assessment at the corresponding lens site at or before month 6.

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Placebo	Denosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	374	379		
Units: percentage of participants				
number (not applicable)	19.3	19		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The point estimate of absolute risk difference (difference in incidence rates, denosumab minus placebo) and the corresponding 95% confidence interval was constructed using the Mantel-Haenszel method adjusting for the stratification factors: baseline LOCS III status (< 3.0 at all sites [P, C, and NO] vs. ≥ 3.0 at any of these sites), age group (< 75, ≥ 75 years), and patient-reported history of cataract (yes/no).

Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	753
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	5.3
Variability estimate	Standard error of the mean
Dispersion value	2.9

Other pre-specified: Percentage of Participants with Confirmed Lens Opacification Event Development or Progression by Month 12

End point title	Percentage of Participants with Confirmed Lens Opacification Event Development or Progression by Month 12

End point description:

The Lens Opacities Classification System III (LOCS III) is a slit lamp based opacification grading method. Photographs of slit lamp cross-sections of the lens are used as references for grading nuclear opalescence (NO) and nuclear color (NC), and photographs of the lens seen by retroillumination are used as references for grading cortical (C) and posterior subcapsular (P) cataract. Opacification severity is graded on a decimal scale, scores can range from 0.1 to 6.9 for NO and NC and from 0.1 to 5.9 for C and P. Higher scores indicate greater severity. Lens opacification event development or progression was based on a change of ≥ 1.0 in P, ≥ 1.0 in C, or ≥ 0.7 in NO in the LOCS III score from baseline. Confirmed lens opacification event development or progression was defined as 2 directly subsequent events at the same location (P, C, NO).
The analysis was conducted in the lens opacification analysis set with at least 2 post-baseline LOCS III measurements by month 12.

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Placebo	Denosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	361	367		
Units: percentage of participants				
number (not applicable)	18.3	16.1		

Statistical analyses

Statistical analysis title	Risk Difference

Statistical analysis description:

The point estimate of absolute risk difference (difference in incidence rates, denosumab minus placebo) and the corresponding 95% confidence interval was constructed using the Mantel-Haenszel method adjusting for the stratification factors: baseline LOCS III status (< 3.0 at all sites [P, C, and NO] vs. ≥ 3.0 at any of these sites), age group (< 75, ≥ 75 years), and patient-reported history of cataract (yes/no).

Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	2.8

Other pre-specified: Percentage of Participants with a Decrease from Baseline in Best Corrected Visual Acuity (BCVA) of ≥ 10 Letters

End point title	Percentage of Participants with a Decrease from Baseline in Best Corrected Visual Acuity (BCVA) of ≥ 10 Letters

End point description:

The best corrected visual acuity (BCVA) is the best vision one can achieve with correction (such as eye glasses) as measured on an eye chart. BCVA was assessed by a trained ophthalmologist using the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart at 4 meters. The modified University of Crete ETDRS chart was used in Ukraine, Greece, Russia and Bulgaria, which do not use the Roman alphabet. The 2000 series revised ETDRS chart was used to assess the change in all other countries. The letter score was calculated based on the number of letters that were correctly identified; higher letter scores correspond to better visual acuity.
This analysis was conducted in the lens opacification analysis set with evaluable assessments at both baseline and the time point of interest in the same eye.

End point type	Other pre-specified

End point timeframe:

Baseline and Months 3, 6, 9 and 12

End point values	Placebo	Denosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	374	379		
Units: percentage of participants				
number (not applicable)				
Month 3 (n = 372, 375)	5.4	6.1		
Month 6 (n = 355, 357)	4.2	6.4		
Month 9 (n = 350, 346)	4.6	6.6		
Month 12 (n = 343, 342)	5.2	7.3		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Refraction Needed to Achieve BCVA

End point title	Change from Baseline in Refraction Needed to Achieve BCVA

End point description:

Refraction error was measured using a phoropter. The change from baseline in spherical refraction error needed to achieve BCVA is reported.
The analysis was conducted in the lens opacification analysis set with evaluable assessments at both baseline and the time point of interest in the same eye; n = the number of evaluable eyes in the lens opacification analysis set at the corresponding time point.

End point type	Other pre-specified

End point timeframe:

Baseline and months 3, 6, 9, and 12

End point values	Placebo - Left Eye	Placebo - Right Eye	Denosumab - Left Eye	Denosumab - Right Eye
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	374	374	379	379
Units: diopters				
arithmetic mean (standard deviation)				
Month 3 (n = 362, 358, 358, 359)	0.01 (± 0.6)	0.01 (± 0.49)	0.05 (± 0.73)	0.04 (± 0.51)
Month 6 (n = 347, 343, 341, 344)	-0.01 (± 0.8)	0.06 (± 0.7)	0.06 (± 0.9)	0.04 (± 0.59)
Month 9 (n = 341, 339, 332, 332)	0 (± 0.84)	0.01 (± 0.73)	0.04 (± 0.75)	0.01 (± 0.62)
Month 12 (n = 336, 334, 328, 329)	-0.03 (± 0.7)	-0.04 (± 0.59)	0.03 (± 0.77)	0 (± 0.48)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

Adverse events (AEs) were assessed for severity by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) severity grading scale, version 3.0, where Grade 1 = Mild AE, Grade 2 = Moderate AE, Grade 3 = Severe AE, Grade 4 =Life-threatening AE and Grade 5 = Death due to AE. Treatment-related AEs (TRAEs) include only events for which the investigator indicated there was a reasonable possibility they may have been caused by the study drug.
This analysis was conducted in all enrolled participants who received at least one dose of study drug. Three participants randomized to the placebo group received at least 1 dose of denosumab in error, and are included in the denosumab group for safety.

End point type	Other pre-specified

End point timeframe:
12 months

End point values	Placebo	Denosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	380	385[2]		
Units: participants				
Any adverse event	193	191		
Serious adverse events	52	42		
AE leading to discontinuation of study drug	5	7		
AE leading to discontinuation from study	2	4		
Fatal adverse events	4	3		
AE grade 3, 4, or 5	53	46		
Treatment-related adverse events	19	21		
Serious treatment-related adverse events	1	2		
TRAE leading to discontinuation of study drug	1	3		
TRAE leading to discontinuation from study	0	1		
Fatal treatment-related adverse events	0	0		
TRAE grade 3, 4, or 5	2	2		

Notes:
[2] - Includes 3 participants who received denosumab in error

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 Months

Adverse event reporting additional description:

Analysis includes all enrolled participants who received at least one dose of study drug. Three participants randomized to the placebo group received at least 1 dose of denosumab in error, and are included in the denosumab group for safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Denosumab

Reporting group description:

Participants who received denosumab 60 mg administered by subcutaneous injection on Day 1 and/or at Month 6.

Reporting group title	Placebo

Reporting group description:

Participants received placebo administered by subcutaneous injection on Day 1 and at Month 6.

Serious adverse events	Denosumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 385 (10.91%)	52 / 380 (13.68%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			

subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pseudoangina			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (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			
Acute respiratory failure			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 385 (0.52%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cystitis radiation			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stricture postoperative			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 385 (0.52%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac fibrillation			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 385 (0.26%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 385 (0.26%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	3 / 385 (0.78%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia paroxysmal			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 385 (0.26%)	4 / 380 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 385 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalomalacia			

subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia megaloblastic			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Optic nerve disorder			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 385 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Inguinal hernia			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			

subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal stenosis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 385 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress urinary incontinence			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 385 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Connective tissue inflammation			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 385 (0.52%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (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			
Appendicitis perforated			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 385 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 385 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pyelonephritis acute			
subjects affected / exposed	1 / 385 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 385 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Denosumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 385 (31.43%)	107 / 380 (28.16%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	7 / 385 (1.82%)	7 / 380 (1.84%)	
occurrences (all)	7	7	
Hypertension			
subjects affected / exposed	8 / 385 (2.08%)	16 / 380 (4.21%)	
occurrences (all)	8	17	
Hypotension			
subjects affected / exposed	1 / 385 (0.26%)	5 / 380 (1.32%)	
occurrences (all)	1	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 385 (1.56%)	2 / 380 (0.53%)	
occurrences (all)	6	2	
Oedema peripheral			
subjects affected / exposed	7 / 385 (1.82%)	1 / 380 (0.26%)	
occurrences (all)	8	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 385 (1.04%)	6 / 380 (1.58%)	
occurrences (all)	4	7	
Dyspnoea			
subjects affected / exposed	4 / 385 (1.04%)	3 / 380 (0.79%)	
occurrences (all)	4	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 385 (1.56%)	3 / 380 (0.79%)	
occurrences (all)	6	3	
Investigations			
Prostatic specific antigen increased			

subjects affected / exposed	4 / 385 (1.04%)	0 / 380 (0.00%)	
occurrences (all)	4	0	
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 385 (0.00%)	4 / 380 (1.05%)	
occurrences (all)	0	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 385 (1.04%)	3 / 380 (0.79%)	
occurrences (all)	4	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 385 (1.56%)	4 / 380 (1.05%)	
occurrences (all)	6	4	
Headache			
subjects affected / exposed	6 / 385 (1.56%)	3 / 380 (0.79%)	
occurrences (all)	7	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 385 (0.52%)	4 / 380 (1.05%)	
occurrences (all)	2	4	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	6 / 385 (1.56%)	0 / 380 (0.00%)	
occurrences (all)	7	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	5 / 385 (1.30%)	2 / 380 (0.53%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 385 (2.08%)	16 / 380 (4.21%)	
occurrences (all)	8	17	
Diarrhoea			
subjects affected / exposed	2 / 385 (0.52%)	6 / 380 (1.58%)	
occurrences (all)	3	6	
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	5 / 385 (1.30%)	4 / 380 (1.05%)	
occurrences (all)	5	4	
Haematuria			
subjects affected / exposed	3 / 385 (0.78%)	4 / 380 (1.05%)	
occurrences (all)	3	5	
Pollakiuria			
subjects affected / exposed	7 / 385 (1.82%)	6 / 380 (1.58%)	
occurrences (all)	7	6	
Urinary incontinence			
subjects affected / exposed	1 / 385 (0.26%)	4 / 380 (1.05%)	
occurrences (all)	1	4	
Urinary retention			
subjects affected / exposed	2 / 385 (0.52%)	4 / 380 (1.05%)	
occurrences (all)	2	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 385 (3.12%)	10 / 380 (2.63%)	
occurrences (all)	12	10	
Back pain			
subjects affected / exposed	11 / 385 (2.86%)	10 / 380 (2.63%)	
occurrences (all)	11	10	
Musculoskeletal pain			
subjects affected / exposed	3 / 385 (0.78%)	5 / 380 (1.32%)	
occurrences (all)	3	5	
Myalgia			
subjects affected / exposed	5 / 385 (1.30%)	2 / 380 (0.53%)	
occurrences (all)	5	2	
Osteoarthritis			
subjects affected / exposed	7 / 385 (1.82%)	2 / 380 (0.53%)	
occurrences (all)	8	2	
Pain in extremity			
subjects affected / exposed	6 / 385 (1.56%)	10 / 380 (2.63%)	
occurrences (all)	6	12	
Infections and infestations			

Bronchitis			
subjects affected / exposed	6 / 385 (1.56%)	4 / 380 (1.05%)	
occurrences (all)	6	4	
Nasopharyngitis			
subjects affected / exposed	10 / 385 (2.60%)	7 / 380 (1.84%)	
occurrences (all)	11	7	
Sinusitis			
subjects affected / exposed	4 / 385 (1.04%)	3 / 380 (0.79%)	
occurrences (all)	4	4	
Upper respiratory tract infection			
subjects affected / exposed	5 / 385 (1.30%)	6 / 380 (1.58%)	
occurrences (all)	7	8	
Urinary tract infection			
subjects affected / exposed	5 / 385 (1.30%)	5 / 380 (1.32%)	
occurrences (all)	6	8	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	5 / 385 (1.30%)	5 / 380 (1.32%)	
occurrences (all)	5	5	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 385 (0.26%)	4 / 380 (1.05%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2009	• changed the laboratory analyses from local laboratories to a central laboratory. • added testosterone and prostate-specific antigen as analytes at specific time points during treatment. • increased the potential number of sites from 100 to 120, and modified the regions in which the study may be conducted. • clarified the pupil dilation criteria and the contraceptive language in the exclusion criteria. • clarified the description of the eye examination (adding Nuclear Color), and masking of the examiner to previous scores. • updated the schedule of assessments to reflect changes in the protocol.
10 January 2012	• investigational product would be supplied in prefilled syringes. • clarified screening examinations to be used for eligibility and stratification. • clarified that eye examination exclusion criterion applied to both eyes. • added additional sites and countries. • extended the enrollment duration. • clarified the provision of calcium and vitamin D supplements. • updated the protocol glossary.
25 June 2013	• clarified in the objectives and endpoints descriptions that the Lens Opacities Classification System III system evaluated "lens opacifications"; changed "cataract" to "lens opacifications." • deleted eligibility criteria that required male patients who were receiving a large molecule such as denosumab to use any form of Contraception. • revised safety reporting language. • added implementation of periodic reviews by an external data monitoring committee.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported