Clinical trial results:
A Randomized Double-blind Study to Evaluate the Safety and Efficacy of Denosumab Compared With Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates

Summary

EudraCT number	2012-001821-28
Trial protocol	BE DE ES DK PL
Global end of trial date	09 January 2015

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	08 July 2016

Trial information

Trial identification

Sponsor protocol code	20110153

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01732770
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thoudand 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	09 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will compare the effectiveness of denosumab treatment every 6 months with once yearly zoledronic acid treatment on bone mineral density (BMD) at various skeletal sites.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
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	07 November 2012
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	Denmark: 208
Country: Number of subjects enrolled	Poland: 157
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	Belgium: 42
Country: Number of subjects enrolled	Canada: 83
Country: Number of subjects enrolled	United States: 73
Country: Number of subjects enrolled	Australia: 26
Worldwide total number of subjects	643
EEA total number of subjects	461

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)	190
From 65 to 84 years	434
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 37 centers in Belgium, Denmark, Poland, Spain, Canada, United States of America, and Australia. The first participant enrolled on 07 November 2012 and the last participant enrolled on 15 January 2014.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 allocation ratio to receive either denosumab or zoledronic acid. Randomization was stratified by screening serum type I collagen C-telopeptide (sCTX) values (< 0.3 ng/mL, 0.3 to 0.5 ng/mL).

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledronic Acid 5 mg Q12M

Arm description:

Participants received zoledronic acid 5 mg by intravenous infusion once every 12 months (Q12M) on Day 1 and placebo to denosumab by subcutaneous injection on Day 1 and at Month 6.

Arm type	Active comparator
Investigational medicinal product name	Zoledronic Acid
Investigational medicinal product code	
Other name	Zometa
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as an intravenous infusion, 5 mg in 100 mL of normal saline.

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

Dosage and administration details:

Administered by 1 mL subcutaneous injection

Arm title	Denosumab 60 mg Q6M

Arm description:

Participants received denosumab 60 mg subcutaneous injection once every 6 months (Q6M) for 12 months and placebo to zoledronic acid by intravenous infusion on Day 1.

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: Administered by subcutaneous injection , 60 mg in 1 mL	
Investigational medicinal product name	Placebo to Zoledronic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion, 100 mL of normal saline.

Number of subjects in period 1	Zoledronic Acid 5 mg Q12M	Denosumab 60 mg Q6M
Started	322	321
Received Study Treatment	320	320
Completed	312	313
Not completed	10	8
Consent withdrawn by subject	5	3
Decision by Sponsor	2	2
Death	1	-
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Zoledronic Acid 5 mg Q12M
Reporting group description:	
Participants received zoledronic acid 5 mg by intravenous infusion once every 12 months (Q12M) on Day 1 and placebo to denosumab by subcutaneous injection on Day 1 and at Month 6.	
Reporting group title	Denosumab 60 mg Q6M
Reporting group description:	
Participants received denosumab 60 mg subcutaneous injection once every 6 months (Q6M) for 12 months and placebo to zoledronic acid by intravenous infusion on Day 1.	

Reporting group values	Zoledronic Acid 5 mg Q12M	Denosumab 60 mg Q6M	Total
Number of subjects	322	321	643
Age categorical Units: Subjects			
< 65 years	89	101	190
≥ 65 years	233	220	453
Age Continuous Units: years			
arithmetic mean	69.5	68.5	
standard deviation	± 7.7	± 7.1	-
Gender, Male/Female Units: participants			
Female	322	321	643
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	314	309	623
Asian	4	5	9
Other	2	4	6
Native Hawaiian or Other Pacific Islander	1	2	3
Black or African American	0	1	1
Multiple	1	0	1
Screening serum CTX Units: Subjects			
< 0.3 ng/mL	242	239	481
≥ 0.3 ng/mL	78	82	160
Missing	2	0	2
Lumbar Spine Bone Mineral Density (BMD) T-score			
BMD was measured using dual-energy x-ray absorptiometry (DXA) of the lumbar spine. The T-score is a comparison of a person's bone density with that of a healthy 30-year-old of the same sex. Lower scores (more negative) mean lower bone density: A T-score of -2.5 or lower qualifies as osteoporosis and a T-score of -1.0 to -2.5 signifies osteopenia, meaning below-normal bone density without full osteoporosis.			
Units: T-score			
arithmetic mean	-2.64	-2.74	
standard deviation	± 0.86	± 0.83	-
Total Hip BMD T-score Units: T-score			

arithmetic mean	-1.93	-1.93	
standard deviation	± 0.8	± 0.74	-
Femoral Neck BMD T-score Units: T-score			
arithmetic mean	-2.17	-2.17	
standard deviation	± 0.68	± 0.66	-
Prior Oral Bisphosphonate Duration Units: years			
arithmetic mean	6.35	6.21	
standard deviation	± 3.68	± 3.84	-
Body Mass Index (BMI) Units: kg/m²			
arithmetic mean	24.31	24.27	
standard deviation	± 4.18	± 3.99	-

End points

End points reporting groups

Reporting group title	Zoledronic Acid 5 mg Q12M
Reporting group description:	
Participants received zoledronic acid 5 mg by intravenous infusion once every 12 months (Q12M) on Day 1 and placebo to denosumab by subcutaneous injection on Day 1 and at Month 6.	
Reporting group title	Denosumab 60 mg Q6M
Reporting group description:	
Participants received denosumab 60 mg subcutaneous injection once every 6 months (Q6M) for 12 months and placebo to zoledronic acid by intravenous infusion on Day 1.	

Primary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 - Non-inferiority Analysis

End point title	Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 - Non-inferiority Analysis
End point description:	
Bone mineral density (BMD) of the lumbar spine was measured by dual-energy x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging facility. This endpoint was analyzed in the primary efficacy analysis set which includes all randomized participants who have a baseline BMD measurement and at least one postbaseline BMD measurement. Any postbaseline BMD value obtained at the early termination visit was carried forward as the month 12 value (ie, last observation carried forward [LOCF]).	
End point type	Primary
End point timeframe:	
Baseline and Month 12	

End point values	Zoledronic Acid 5 mg Q12M	Denosumab 60 mg Q6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	314		
Units: percent change				
least squares mean (confidence interval 95%)	1.1 (0.7 to 1.5)	3.2 (2.8 to 3.6)		

Statistical analyses

Statistical analysis title	Primary Analysis of in Lumbar Spine BMD
Statistical analysis description:	
A step-down sequential testing procedure was used in order to maintain the overall type I error rate at 5% for the tests of primary and secondary BMD endpoints. For the non-inferiority analysis the 1-sided significance level was 2.5%. Treatment difference = denosumab – zoledronic acid.	
Comparison groups	Zoledronic Acid 5 mg Q12M v Denosumab 60 mg Q6M

Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	2.6

Notes:

[1] - The lower bound of the 2-sided 95% confidence interval (CI) of (denosumab – zoledronic acid) was compared with the non-inferiority margin of -0.46% for assessing non-inferiority.
[2] - The model included treatment, screening sCTX, baseline BMD, DXA machine type (Hologic or Lunar), and baseline BMD-by-machine type interaction.

Secondary: Percent Change From Baseline in Total Hip BMD at Month 12 - Non-inferiority Analysis

End point title	Percent Change From Baseline in Total Hip BMD at Month 12 - Non-inferiority Analysis

End point description:

BMD of the hip was measured by DXA. DXA scans were analyzed by a central imaging facility.

Analyzed in the primary efficacy analysis set; any postbaseline BMD value obtained at the early termination visit was carried forward as the month 12 value (ie, LOCF).

End point type	Secondary

End point timeframe:

Baseline and Month 12

End point values	Zoledronic Acid 5 mg Q12M	Denosumab 60 mg Q6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	311		
Units: percent change				
least squares mean (confidence interval 95%)	0.6 (0.3 to 0.8)	1.9 (1.7 to 2.2)		

Statistical analyses

Statistical analysis title	Primary Analysis of Total Hip BMD

Statistical analysis description:

A step-down sequential testing procedure was used in order to maintain the overall type I error rate at 5% for the tests of primary and secondary BMD endpoints. For the non-inferiority analysis the 1-sided significance level was 2.5%. Treatment difference = denosumab – zoledronic acid.

Comparison groups	Zoledronic Acid 5 mg Q12M v Denosumab 60 mg Q6M

Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.7

Notes:

[3] - The lower bound of the 2-sided 95% CI) of (denosumab – zoledronic acid) was compared with the non-inferiority margin of -0.51% for assessing non-inferiority.
[4] - The model included treatment, screening sCTX, baseline BMD, DXA machine type (Hologic or Lunar), and baseline BMD-by-machine type interaction.

Secondary: Percent Change From Baseline in Lumbar Spine BMD at Month 12 - Superiority Analysis

End point title	Percent Change From Baseline in Lumbar Spine BMD at Month 12 - Superiority Analysis

End point description:

Analysis was performed in the primary efficacy analysis set; any postbaseline BMD value obtained at the early termination visit was carried forward as the month 12 value (ie, LOCF).

End point type	Secondary

End point timeframe:

Baseline and Month 12

End point values	Zoledronic Acid 5 mg Q12M	Denosumab 60 mg Q6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	314		
Units: percent change				
least squares mean (confidence interval 95%)	1.1 (0.7 to 1.5)	3.2 (2.8 to 3.6)		

Statistical analyses

Statistical analysis title	Secondary Analysis of Lumbar Spine BMD

Statistical analysis description:

A step-down sequential testing procedure was used in order to maintain the overall type I error rate at 5% for the tests of primary and secondary BMD endpoints. For the superiority analysis the 2-sided significance level was 5%. Treatment difference = denosumab – zoledronic acid.

Comparison groups	Zoledronic Acid 5 mg Q12M v Denosumab 60 mg Q6M

Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	2.6

Notes:

[5] - The model included treatment, screening sCTX, baseline BMD, DXA machine type (Hologic or Lunar), and baseline BMD-by-machine type interaction.

Secondary: Percent Change From Baseline in Total Hip BMD at Month 12 - Superiority Analysis

End point title	Percent Change From Baseline in Total Hip BMD at Month 12 - Superiority Analysis

End point description:

Analysis was performed in the primary efficacy analysis set; any postbaseline BMD value obtained at the early termination visit was carried forward as the month 12 value (ie, LOCF).

End point type	Secondary

End point timeframe:

Baseline and Month 12

End point values	Zoledronic Acid 5 mg Q12M	Denosumab 60 mg Q6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	311		
Units: percent change				
least squares mean (confidence interval 95%)	0.6 (0.3 to 0.8)	1.9 (1.7 to 2.2)		

Statistical analyses

Statistical analysis title	Secondary Analysis of Total Hip BMD

Statistical analysis description:

A step-down sequential testing procedure was used in order to maintain the overall type I error rate at 5% for the tests of primary and secondary BMD endpoints. For the superiority analysis the 2-sided significance level was 5%. Treatment difference = denosumab – zoledronic acid.

Comparison groups	Zoledronic Acid 5 mg Q12M v Denosumab 60 mg Q6M

Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	Treatment Difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.7

Notes:

[6] - The model included treatment, screening sCTX, baseline BMD, DXA machine type (Hologic or Lunar), and baseline BMD-by-machine type interaction.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 Months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Denosumab 60 mg Q6M
Reporting group description:	
Participants received denosumab 60 mg subcutaneous injection once every 6 months (Q6M) for 12 months and placebo to zoledronic acid by intravenous infusion on Day 1.	
Reporting group title	Zoledronic Acid 5 mg Q12M
Reporting group description:	
Participants received zoledronic acid 5 mg by intravenous infusion once every 12 months (Q12M) on Day 1 and placebo to denosumab by subcutaneous injection on Day 1 and at Month 6.	

Serious adverse events	Denosumab 60 mg Q6M	Zoledronic Acid 5 mg Q12M	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 320 (7.81%)	29 / 320 (9.06%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer female			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage I			

subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleomorphic adenoma			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			

subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Tendon operation			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee operation			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein operation			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (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			
Drug interaction			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectocele			

subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 320 (0.63%)	2 / 320 (0.63%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (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 / 320 (0.31%)	0 / 320 (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			

Cerebral thrombosis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 320 (0.63%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Inguinal hernia			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
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 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 320 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 320 (0.31%)	2 / 320 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Denosumab 60 mg Q6M	Zoledronic Acid 5 mg Q12M	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 320 (4.69%)	22 / 320 (6.88%)	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 320 (4.69%)	22 / 320 (6.88%)	
occurrences (all)	18	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported