Clinical trial results:
Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy and Safety of Denosumab Compared With Risedronate in Glucocorticoid-treated Individuals

Summary

EudraCT number	2010-024393-19
Trial protocol	BE HU NL CZ ES PL DE DK FR
Global end of trial date	29 June 2017

Results information

Result version number	v1 (current)
This version publication date	29 June 2018
First version publication date	29 June 2018

Trial information

Trial identification

Sponsor protocol code	20101217

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01575873
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	29 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective in the glucocorticoid-continuing (GC-C) subpopulation treated with chronic glucocorticoid therapy (≥ 7.5 mg daily prednisone or its equivalent for ≥ 3 months and planning to continue treatment for a total of at least 6 months) is to demonstrate that treatment with denosumab 60 mg subcutaneously (SC) every 6 months (Q6M) is not inferior to treatment with oral risedronate 5 mg every day (QD) with respect to the percent change from baseline in lumbar spine BMD by dual X-ray absorptiometry (DXA) at 12 months.
The primary objective in the glucocorticoid-initiating (GC-I) subpopulation treated with glucocorticoid therapy (≥ 7.5 mg daily prednisone or its equivalent for < 3 months and planning to continue treatment for a total of at least 6 months) is to demonstrate that treatment with denosumab 60 mg SC Q6M is not inferior to treatment with oral risedronate 5 mg QD with respect to the percent change from baseline in lumbar spine BMD by DXA at 12 months.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The protocol, proposed informed consent form, other written subject information, and any proposed advertising material was submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for written approval.
The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2012
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	Czech Republic: 141
Country: Number of subjects enrolled	Poland: 96
Country: Number of subjects enrolled	Russian Federation: 75
Country: Number of subjects enrolled	Belgium: 59
Country: Number of subjects enrolled	Spain: 42
Country: Number of subjects enrolled	Hungary: 37
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Denmark: 25
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Argentina: 74

Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	United States: 76
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	Korea, Republic of: 33
Worldwide total number of subjects	795
EEA total number of subjects	456

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)	440
From 65 to 84 years	344
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 79 centers in Europe, North America, Latin America, and Korea from 28 March 2012 to 30 June 2015.
Participants who had been taking glucocorticoids for at least 3 months were classed as glucocorticoid continuing; those who were taking glucocorticoids for less than 3 months were classed as glucocorticoid initiating.

Pre-assignment

Screening details:

Eligible patients were randomly assigned in a 1:1 ratio to receive 60 mg denosumab every 6 months or 5 mg oral risedronate daily for 24 months within each subpopulation. Randomization was stratified by sex within each subpopulation.

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	Risedronate: Glucocorticoid-initiating

Arm description:

Participants received 5 mg risedronate orally once a day for 24 months and placebo to densumab by subcutaneous injection on day 1 and at months 6, 12, and 18.

Arm type	Active comparator
Investigational medicinal product name	Placebo for 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 subcutaneous injection once every 6 months

Investigational medicinal product name	Risendronate
Investigational medicinal product code	
Other name	Actonel, Atelvia
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally once a day

Arm title	Denosumab: Glucocorticoid-initiating

Arm description:

Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.

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 once every 6 months	
Investigational medicinal product name	Placebo for risendronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Administered orally once a day	
Arm title	Risedronate: Glucocorticoid-continuing
Arm description:	
Participants received 5 mg risedronate orally once a day for 24 months and placebo to densumab by subcutaneous injection on day 1 and at months 6, 12, and 18.	
Arm type	Active comparator
Investigational medicinal product name	Risendronate
Investigational medicinal product code	
Other name	Actonel, Atelvia
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Administered orally once a day	
Investigational medicinal product name	Placebo for 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 subcutaneous injection once every 6 months	
Arm title	Denosumab: Glucocorticoid-continuing
Arm description:	
Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.	
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 once every 6 months	
Investigational medicinal product name	Placebo for risendronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Administered orally once a day	

Number of subjects in period 1	Risedronate: Glucocorticoid-initiating	Denosumab: Glucocorticoid-initiating	Risedronate: Glucocorticoid-continuing
Started	145	145	252
Received Study Drug	140	142	246
Completed	117	109	178
Not completed	28	36	74
Consent withdrawn by subject	15	20	34
Adverse Event	7	7	9
Administrative decision	1	1	1
Death	3	2	8
Other	-	-	4
Protocol deviation	-	1	-
Lost to follow-up	1	3	13
Requirement for Alternative Therapy	-	-	1
Noncompliance	1	2	4

Number of subjects in period 1	Denosumab: Glucocorticoid-continuing
Started	253
Received Study Drug	251
Completed	186
Not completed	67
Consent withdrawn by subject	34
Adverse Event	12
Administrative decision	-
Death	9
Other	2
Protocol deviation	1
Lost to follow-up	5
Requirement for Alternative Therapy	1
Noncompliance	3

Baseline characteristics

Reporting groups	
Reporting group title	Risedronate: Glucocorticoid-initiating
Reporting group description:	
Participants received 5 mg risedronate orally once a day for 24 months and placebo to densumab by subcutaneous injection on day 1 and at months 6, 12, and 18.	
Reporting group title	Denosumab: Glucocorticoid-initiating
Reporting group description:	
Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.	
Reporting group title	Risedronate: Glucocorticoid-continuing
Reporting group description:	
Participants received 5 mg risedronate orally once a day for 24 months and placebo to densumab by subcutaneous injection on day 1 and at months 6, 12, and 18.	
Reporting group title	Denosumab: Glucocorticoid-continuing
Reporting group description:	
Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.	

Reporting group values	Risedronate: Glucocorticoid-initiating	Denosumab: Glucocorticoid-initiating	Risedronate: Glucocorticoid-continuing
Number of subjects	145	145	252
Age Categorical Units: Subjects			
< 50 years	5	2	26
50 - 64 years	75	55	130
65 - 74 years	38	50	62
≥ 75 years	27	38	34
Age Continuous Units: years			
arithmetic mean	64.4	67.5	61.3
standard deviation	± 10.0	± 10.1	± 11.1
Gender Categorical Units: Subjects			
Female	93	93	185
Male	52	52	67
Race Units: Subjects			
White	123	122	223
Other	11	12	11
Asian	9	9	12
Black or African American	2	2	4
American Indian or Alaska Native	0	0	1
Multiple	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	18	20	54
Not Hispanic or Latino	127	125	198
Menopausal Status			

Units: Subjects			
Premenopause	7	10	25
Postmenopause	83	82	157
Unknown	3	1	3
NA - Male	52	52	67
Lumbar Spine Bone Mineral Density (BMD) T-score			
The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old. Normal is a T-score of −1.0 or higher; Osteopenia is defined as between −1.0 and −2.5; Osteoporosis is defined as −2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman. Data are reported for participants with observed values (143, 144, 252, and 249 subjects in each reporting group respectively).			
Units: T-score			
arithmetic mean	-1.06	-0.92	-1.96
standard deviation	± 1.57	± 1.86	± 1.38
Total Hip BMD T-score			
The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old. Normal is a T-score of −1.0 or higher; Osteopenia is defined as between −1.0 and −2.5; Osteoporosis is defined as −2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman. Data are reported for participants with observed values (142, 142, 250, and 249 subjects in each reporting group respectively).			
Units: T-score			
arithmetic mean	-0.98	-1.14	-1.56
standard deviation	± 1.07	± 1.00	± 0.96

Reporting group values	Denosumab: Glucocorticoid-continuing	Total	
Number of subjects	253	795	
Age Categorical Units: Subjects			
< 50 years	33	66	
50 - 64 years	114	374	
65 - 74 years	73	223	
≥ 75 years	33	132	
Age Continuous Units: years			
arithmetic mean	61.5		
standard deviation	± 11.6	-	
Gender Categorical Units: Subjects			
Female	185	556	
Male	68	239	
Race Units: Subjects			
White	230	698	
Other	13	47	
Asian	6	36	
Black or African American	4	12	
American Indian or Alaska Native	0	1	
Multiple	0	1	
Ethnicity Units: Subjects			

Hispanic or Latino	43	135	
Not Hispanic or Latino	210	660	
Menopausal Status Units: Subjects			
Premenopause	24	66	
Postmenopause	159	481	
Unknown	2	9	
NA - Male	68	239	
Lumbar Spine Bone Mineral Density (BMD) T-score			
The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old. Normal is a T-score of −1.0 or higher; Osteopenia is defined as between −1.0 and −2.5; Osteoporosis is defined as −2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman. Data are reported for participants with observed values (143, 144, 252, and 249 subjects in each reporting group respectively).			
Units: T-score			
arithmetic mean	-1.92		
standard deviation	± 1.38	-	
Total Hip BMD T-score			
The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old. Normal is a T-score of −1.0 or higher; Osteopenia is defined as between −1.0 and −2.5; Osteoporosis is defined as −2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman. Data are reported for participants with observed values (142, 142, 250, and 249 subjects in each reporting group respectively).			
Units: T-score			
arithmetic mean	-1.66		
standard deviation	± 0.96	-	

End points

End points reporting groups

Reporting group title	Risedronate: Glucocorticoid-initiating
Reporting group description:	
Participants received 5 mg risedronate orally once a day for 24 months and placebo to densumab by subcutaneous injection on day 1 and at months 6, 12, and 18.	
Reporting group title	Denosumab: Glucocorticoid-initiating
Reporting group description:	
Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.	
Reporting group title	Risedronate: Glucocorticoid-continuing
Reporting group description:	
Participants received 5 mg risedronate orally once a day for 24 months and placebo to densumab by subcutaneous injection on day 1 and at months 6, 12, and 18.	
Reporting group title	Denosumab: Glucocorticoid-continuing
Reporting group description:	
Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.	

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 at the lumbar spine was measured by dual-energy x-ray absorptiometry (DXA).	
End point type	Primary
End point timeframe:	
Baseline and month 12	

End point values	Risedronate: Glucocorticoid-initiating	Denosumab: Glucocorticoid-initiating	Risedronate: Glucocorticoid-continuing	Denosumab: Glucocorticoid-continuing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126[1]	119[2]	211[3]	209[4]
Units: percent change				
least squares mean (confidence interval 95%)	0.8 (0.2 to 1.5)	3.8 (3.1 to 4.5)	2.3 (1.7 to 2.9)	4.4 (3.8 to 5.0)

Notes:

[1] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[2] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[3] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[4] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

Statistical analyses

Statistical analysis title	GC-I Subpopulation Non-inferiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently in the glucocorticoid-

continuing and glucocorticoid-initiating subpopulations. A fixed-sequence testing procedure was used to control the experiment-wise type 1 error rate at a two-sided 5% significance level within each subpopulation.
The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for treatment, baseline BMD, sex, machine type, and baseline BMD-by-machine type interaction.

Comparison groups	Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.001 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	3.9

Notes:

[5] - Non-inferiority was shown if the lower bound of the two-sided 95% CI for the difference between the least-squares means (denosumab minus risedronate) was higher than the prespecified non-inferiority margin of −1.1 percentage points for the glucocorticoid-initiating subpopulation.
[6] - One-sided p-value based on the prespecified noninferiority margin for lumbar spine of -1.1%.

Statistical analysis title	GC-C Subpopulation Non-inferiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.
The glucocorticoid-continuing subpopulation was analyzed using an ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use (< 12 months vs ≥ 12 months).

Comparison groups	Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	< 0.001 [8]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	3

Notes:

[7] - Non-inferiority was shown if the lower bound of the two-sided 95% CI for the difference between the least-squares means (denosumab minus risedronate) was higher than the prespecified non-inferiority margin of −0.7 percentage points for the glucocorticoid-continuing subpopulation.
[8] - One-sided p-value based on the prespecified noninferiority margins for lumbar spine of -0.7%.

Secondary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 (Superiority Analysis)

End point title	Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 (Superiority Analysis)

End point description:

Bone mineral density at the lumbar spine was measured by dual-energy x-ray absorptiometry (DXA).

End point type	Secondary

End point timeframe:

Baseline and month 12

End point values	Risedronate: Glucocorticoid-initiating	Denosumab: Glucocorticoid-initiating	Risedronate: Glucocorticoid-continuing	Denosumab: Glucocorticoid-continuing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126[9]	119[10]	211[11]	209[12]
Units: percent change				
least squares mean (confidence interval 95%)	0.8 (0.2 to 1.5)	3.8 (3.1 to 4.5)	2.3 (1.7 to 2.9)	4.4 (3.8 to 5.0)

Notes:

[9] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[10] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[11] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

[12] - Randomized participants with a baseline and month 12 measurement for the lumbar spine BMD.

Statistical analyses

Statistical analysis title	GC-I Subpopulation Superiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.
The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. LS Mean difference was calculated as Denosumab - Risedronate.

Comparison groups	Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	3.9

Notes:

[13] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

Statistical analysis title	GC-C Subpopulation Superiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level. The glucocorticoid-continuing subpopulation was analyzed using an

ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use. LS Mean difference = Denosumab - Risedronate.

Comparison groups	Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [14]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	3

Notes:

[14] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

Secondary: Percent Change From Baseline in Total Hip Bone Mineral Density at Month 12

End point title	Percent Change From Baseline in Total Hip Bone Mineral Density at Month 12

End point description:

Bone mineral density at the total hip was measured by dual-energy x-ray absorptiometry (DXA).

End point type	Secondary

End point timeframe:

Baseline and month 12

End point values	Risedronate: Glucocorticoid-initiating	Denosumab: Glucocorticoid-initiating	Risedronate: Glucocorticoid-continuing	Denosumab: Glucocorticoid-continuing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	128[15]	119[16]	215[17]	217[18]
Units: percent change				
least squares mean (confidence interval 95%)	0.2 (-0.2 to 0.7)	1.7 (1.2 to 2.2)	0.6 (0.2 to 1.0)	2.1 (1.7 to 2.5)

Notes:

[15] - Randomized participants with a baseline and month 12 measurement for the total hip BMD.

[16] - Randomized participants with a baseline and month 12 measurement for the total hip BMD.

[17] - Randomized participants with a baseline and month 12 measurement for the total hip BMD.

[18] - Randomized participants with a baseline and month 12 measurement for the total hip BMD.

Statistical analyses

Statistical analysis title	GC-I Subpopulation Superiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.
The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for

treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. LS mean difference = Denosumab - Risedronate.

Comparison groups	Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [19]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.1

Notes:

[19] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

Statistical analysis title	GC-C Subpopulation Superiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level. The glucocorticoid-continuing subpopulation was analyzed using an ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use. LS Mean difference = Denosumab - Risedronate.

Comparison groups	Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [20]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.1

Notes:

[20] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

Secondary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 24

End point title	Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 24

End point description:

Bone mineral density at the lumbar spine was measured by dual-energy x-ray absorptiometry (DXA).

End point type	Secondary

End point timeframe:

Baseline and month 24

End point values	Risedronate: Glucocorticoid-initiating	Denosumab: Glucocorticoid-initiating	Risedronate: Glucocorticoid-continuing	Denosumab: Glucocorticoid-continuing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	113[21]	107[22]	174[23]	183[24]
Units: percent change				
least squares mean (confidence interval 95%)	1.7 (0.8 to 2.7)	6.2 (5.3 to 7.2)	3.2 (2.3 to 4.1)	6.4 (5.5 to 7.2)

Notes:

[21] - Randomized participants with a baseline and month 24 measurement for the lumbar spine BMD.

[22] - Randomized participants with a baseline and month 24 measurement for the lumbar spine BMD.

[23] - Randomized participants with a baseline and month 24 measurement for the lumbar spine BMD.

[24] - Randomized participants with a baseline and month 24 measurement for the lumbar spine BMD.

Statistical analyses

Statistical analysis title	GC-I Subpopulation Superiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.
The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. LS mean difference = Denosumab - Risedronate.

Comparison groups	Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [25]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	5.8

Notes:

[25] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

Statistical analysis title	GC-C Subpopulation Superiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level. The glucocorticoid-continuing subpopulation was analyzed using an ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use. LS Mean difference = Denosumab - Risedronate.

Comparison groups	Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [26]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	4.3

Notes:

[26] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

Secondary: Percent Change From Baseline in Total Hip Bone Mineral Density at Month 24

End point title	Percent Change From Baseline in Total Hip Bone Mineral Density at Month 24

End point description:

Bone mineral density at the total hip was measured by dual-energy x-ray absorptiometry (DXA).

End point type	Secondary

End point timeframe:

Baseline and month 24

End point values	Risedronate: Glucocorticoid-initiating	Denosumab: Glucocorticoid-initiating	Risedronate: Glucocorticoid-continuing	Denosumab: Glucocorticoid-continuing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	111[27]	104[28]	176[29]	181[30]
Units: percent change				
least squares mean (confidence interval 95%)	-0.0 (-0.6 to 0.6)	3.1 (2.4 to 3.7)	0.5 (-0.1 to 1.0)	2.9 (2.4 to 3.5)

Notes:

[27] - Randomized participants with a baseline and month 24 measurement for the total hip BMD.

[28] - Randomized participants with a baseline and month 24 measurement for the total hip BMD.

[29] - Randomized participants with a baseline and month 24 measurement for the total hip BMD.

[30] - Randomized participants with a baseline and month 24 measurement for the total hip BMD.

Statistical analyses

Statistical analysis title	CG-I Subpopulation Superiority Analsyis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level.
The glucocorticoid-initiating subpopulation was analyzed using an ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. LS mean difference = Denosumab - Risedronate.

Comparison groups	Risedronate: Glucocorticoid-initiating v Denosumab: Glucocorticoid-initiating

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [31]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	3.9

Notes:

[31] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

Statistical analysis title	GC-C Subpopulation Superiority Analysis

Statistical analysis description:

Analyses of the primary and secondary endpoints were performed independently within each subpopulation using a fixed-sequence testing procedure to control the experiment-wise type 1 error rate at a two-sided 5% significance level. The glucocorticoid-continuing subpopulation was analyzed using an ANCOVA model adjusted for treatment, baseline BMD, sex, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use. LS Mean difference = Denosumab - Risedronate.

Comparison groups	Risedronate: Glucocorticoid-continuing v Denosumab: Glucocorticoid-continuing
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [32]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	3.2

Notes:

[32] - 2-sided p-value corresponding to the 2-sided 95% confidence interval

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 Months

Adverse event reporting additional description:

One participant was randomized to risedronate but received denosumab in error; this participant was included in the denosumab group for safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Denosumab

Reporting group description:

Participants received 60 mg denosumab by subcutaneous injection on day 1 and at months 6, 12, and 18. Participants also received placebo to risedronate orally once a day for 24 months.

Reporting group title	Risedronate

Reporting group description:

Participants received 5 mg risedronate orally once a day for 24 months and placebo to densumab by subcutaneous injection on day 1 and at months 6, 12, and 18.

Serious adverse events	Denosumab	Risedronate	
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 394 (23.35%)	98 / 385 (25.45%)	
number of deaths (all causes)	13	9	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer metastatic			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillary leak syndrome			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal arteritis			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	2 / 394 (0.51%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colectomy			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileostomy			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	1 / 394 (0.25%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm surgery			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenectomy			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sigmoidectomy			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal decompression			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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			
Asthenia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Eosinophilic granulomatosis with polyangiitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
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			
Cervix haematoma uterine			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystocele			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Alveolitis allergic			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 394 (0.25%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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	0 / 394 (0.00%)	5 / 385 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary fibrosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Behaviour disorder due to a general medical condition			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood creatinine increased			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
White blood cell count increased			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
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			
Acetabulum fracture			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	3 / 394 (0.76%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fibula fracture			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			

subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital megaureter			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve sclerosis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic valve stenosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardiac failure			
subjects affected / exposed	3 / 394 (0.76%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 394 (0.51%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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			
Ataxia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 394 (0.76%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			

subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	2 / 394 (0.51%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 394 (0.76%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 394 (0.25%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 394 (0.25%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 394 (0.25%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
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	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestinal ulcer			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar hernia			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dyskinesia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (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			

Dermatomyositis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus generalised			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (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	2 / 394 (0.51%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus nephritis			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 394 (0.25%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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			
Ankylosing spondylitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 394 (0.25%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposed bone in jaw			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed connective tissue disease			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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 / 394 (0.51%)	5 / 385 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 394 (0.25%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	2 / 394 (0.51%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	2 / 394 (0.51%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sjogren's syndrome			

subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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			
Abdominal abscess			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (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	2 / 394 (0.51%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 394 (0.51%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic fever			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node tuberculosis			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 394 (1.78%)	8 / 385 (2.08%)	
occurrences causally related to treatment / all	0 / 8	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 394 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Serratia infection			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 394 (0.25%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection bacterial			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (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			
Dehydration			
subjects affected / exposed	2 / 394 (0.51%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 394 (0.25%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketosis			

subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis calcarea			
subjects affected / exposed	0 / 394 (0.00%)	1 / 385 (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: 5 %

Non-serious adverse events	Denosumab	Risedronate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 394 (19.54%)	76 / 385 (19.74%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 394 (5.33%)	15 / 385 (3.90%)	
occurrences (all)	23	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 394 (5.84%)	33 / 385 (8.57%)	
occurrences (all)	26	44	
Back pain			
subjects affected / exposed	24 / 394 (6.09%)	21 / 385 (5.45%)	
occurrences (all)	24	22	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	20 / 394 (5.08%)	19 / 385 (4.94%)	
occurrences (all)	21	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2011	• Exploratory objectives clarified: HR-pQCT data to be collected in a subset of subjects only, and PK/BTM samples are only to be collected in subjects participating in the PK/BTM substudy • Added statement that subjects in the transiliac bone biopsy substudy are to receive tetracycline or tetracycline derivative prior to the bone biopsy procedure
15 February 2012	• Entry criteria clarified: - Subjects less than 50 years old and without an osteoporotic fracture will not be eligible to enroll. - Subjects initiating biologics within 4 weeks prior to screening will not be eligible to enroll; however, administration of biologic medications will not be proscribed during the study - Subjects with a history of infection immediately prior to screening will not be eligible to enroll.
29 June 2012	• Entry criteria clarified: - GC-C subjects ≥ 50 years of are required to have a BMD value equivalent to a T-score ≤ -2.0 at the lumbar spine, total hip, or femoral neck; or a BMD value equivalent to a T-score ≤ -1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture. - Subjects administering > 1 biologic agent for the treatment of underlying inflammatory disease to be excluded - Subjects with a history of Addison's disease to be excluded - Clarified the existing exclusion criterion of recent tooth extraction or dental surgery • Secondary objectives were separated with respect to lumbar spine and total hip. • Information on choice of noninferiority margins was updated. • Clarified that safety analyses would be done in the combined subpopulations • Added information regarding a DRT • Added criteria for permanent withholding of denosumab and risedronate due to serious infection • Added urine dipstick pregnancy tests at day 10 and months 6, 12, and 18, and clarified that any female subject who becomes pregnant should permanently discontinue investigational product
22 February 2013	• Incorporated updated procedures of reporting adverse events and serious adverse events to IRB/IECs and regulatory authorities • Replaced the DRT with a DMC for ongoing monitoring of study data • Clarified that the noninferiority comparison will only be performed for the primary efficacy endpoint within each subpopulation
30 June 2016	• Bone biopsy assessment added at 24 months for the bone biopsy substudy to bring the number of evaluable specimens closer to the protocol-indicated number (due to difficulties in recruitment to the substudy and some collected specimens being unevaluable) • Noted that analysis of HR-pQCT data will be performed at the end of the study (month 24) • Updated safety language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported