



## Clinical trial results:

### A Multicenter, Double-blind, Randomized Study to Assess the Efficacy and Safety of Denosumab Produced by Two Different Processes in Postmenopausal Women With Osteoporosis

#### Summary

EudraCT number	2013-001279-19
Trial protocol	CZ PL DK
Global end of trial date	09 July 2015

#### Results information

Result version number	v1 (current)
This version publication date	15 July 2016
First version publication date	15 July 2016

#### Trial information

##### Trial identification

Sponsor protocol code	20120187
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02157948
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	09 July 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 July 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study are to evaluate

1. whether the efficacy of denosumab (60 mg subcutaneously every 6 months) manufactured by the proposed process referred to as CP4 is not inferior to that of denosumab manufactured by the currently approved commercial process referred to as CP2 based on the change in lumbar spine bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) at 12 months in postmenopausal women with osteoporosis;
2. whether the efficacy of denosumab CP4 (60 mg subcutaneously every 6 months) is equivalent to that of denosumab CP2 based on the change in lumbar spine BMD by DXA at 12 months in postmenopausal women with osteoporosis.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The study protocol and the informed consent form were reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and written approval was received by Amgen before recruitment of subjects and shipment of Amgen investigational product (IP). All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 May 2014
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	Poland: 167
Country: Number of subjects enrolled	Denmark: 142
Country: Number of subjects enrolled	United States: 52
Country: Number of subjects enrolled	Canada: 33
Worldwide total number of subjects	394
EEA total number of subjects	309

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	135
From 65 to 84 years	257
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 21 centers in Poland, Denmark, United States (US), and Canada. The first subject enrolled on 05 May 2014 and the last subject enrolled on 03 July 2014.

### Pre-assignment

Screening details:

Ambulatory postmenopausal women 55 years or older with a BMD value equivalent to a T-score of  $\leq 2.5$  at lumbar spine, total hip, or femoral neck were eligible to enroll.

Five hundred and forty-seven subjects were screened; 394 were enrolled and 153 did not meet eligibility criteria.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Denosumab CP2

Arm description:

Participants received denosumab CP2 60 mg subcutaneously once every 6 months for 1 year.

Arm type	Active comparator
Investigational medicinal product name	Denosumab CP2
Investigational medicinal product code	
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

<b>Arm title</b>	Denosumab CP4
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Arm description:

Participants received denosumab CP4 60 mg subcutaneously once every 6 months for 1 year.

Arm type	Experimental
Investigational medicinal product name	denosumab CP4
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

<b>Number of subjects in period 1</b>	Denosumab CP2	Denosumab CP4
Started	197	197
Received Treatment	196	196
Completed	188	188
Not completed	9	9
Consent withdrawn by subject	4	5
Protocol specified criteria	2	1
Lost to follow-up	3	2
Decision by sponsor	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Denosumab CP2
Reporting group description:	
Participants received denosumab CP2 60 mg subcutaneously once every 6 months for 1 year.	
Reporting group title	Denosumab CP4
Reporting group description:	
Participants received denosumab CP4 60 mg subcutaneously once every 6 months for 1 year.	

Reporting group values	Denosumab CP2	Denosumab CP4	Total
Number of subjects	197	197	394
Age categorical			
Units: Subjects			
< 65 years	65	70	135
≥ 65 years	132	127	259
Age continuous			
Units: years			
arithmetic mean	68	68.3	-
standard deviation	± 6.8	± 7.3	-
Gender categorical			
Units: Subjects			
Female	197	197	394
Male	0	0	0
Race			
Units: Subjects			
White	190	195	385
Asian	4	1	5
Native Hawaiian or Other Pacific Islander	2	1	3
Other	1	0	1
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.			
Units: T-score			
arithmetic mean	-2.75	-2.75	-
standard deviation	± 0.91	± 0.75	-
Serum Type I collagen C-telopeptide (CTX-1)			
Units: ng/mL			
arithmetic mean	0.48	0.501	-
standard deviation	± 0.333	± 0.269	-
Serum Procollagen type 1 N-terminal (P1NP)			
Units: µg/L			
arithmetic mean	62	64.5	-
standard deviation	± 31.7	± 32.8	-



## End points

### End points reporting groups

Reporting group title	Denosumab CP2
Reporting group description:	
Participants received denosumab CP2 60 mg subcutaneously once every 6 months for 1 year.	
Reporting group title	Denosumab CP4
Reporting group description:	
Participants received denosumab CP4 60 mg subcutaneously once every 6 months for 1 year.	

### Primary: Percent Change from Baseline in Lumbar Spine BMD

End point title	Percent Change from Baseline in Lumbar Spine BMD
End point description:	
Lumbar spine bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.	
The primary efficacy analysis subset included all randomized subjects who had a baseline lumbar spine DXA BMD measurement and at least 1 postbaseline lumbar spine DXA BMD measurement. Postbaseline BMD values obtained at the early termination visit were carried forward as the month-12 value.	
End point type	Primary
End point timeframe:	
Baseline and Month 12	

End point values	Denosumab CP2	Denosumab CP4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187 <sup>[1]</sup>	188 <sup>[2]</sup>		
Units: percent change				
arithmetic mean (standard deviation)	5.78 (± 3.44)	5.73 (± 3.08)		

Notes:

[1] - Subjects with a non-missing baseline and at least 1 non-missing postbaseline measurement

[2] - Subjects with a non-missing baseline and at least 1 non-missing postbaseline measurement

### Statistical analyses

Statistical analysis title	Non-inferiority Testing
Statistical analysis description:	
The treatment comparison was analyzed using the analysis of covariance (ANCOVA) model including treatment, baseline BMD value, machine type, and machine type-by-baseline BMD value interaction. The effect of denosumab CP4 on lumbar spine BMD at 12 months relative to the effect of denosumab CP2 was estimated by the least-squares mean of the treatment difference (denosumab CP4 – denosumab CP2) and the corresponding 2-sided 95% confidence interval (CI).	
Comparison groups	Denosumab CP2 v Denosumab CP4



Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
P-value	< 0.001 <sup>[4]</sup>
Method	ANCOVA
Parameter estimate	Difference from CP2
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.57

Notes:

[3] - The lower bound of the 2-sided 95% CI of the between-group difference (denosumab CP4 – denosumab CP2) in percent change from baseline in lumbar spine BMD at 12 months was compared with the non-inferiority margin of -1.44% for assessing non-inferiority.

[4] - One-sided p-value based on the prespecified non-inferiority margin of -1.44% for lumbar spine

<b>Statistical analysis title</b>	Equivalence Testing
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Statistical analysis description:

The treatment comparison was analyzed using the analysis of covariance (ANCOVA) model including treatment, baseline BMD value, machine type, and machine type-by-baseline BMD value interaction. The effect of denosumab CP4 on lumbar spine BMD at 12 months relative to the effect of denosumab CP2 was estimated by the least-squares mean of the treatment difference (denosumab CP4 – denosumab CP2) and the corresponding 2-sided 95% confidence interval (CI).

Comparison groups	Denosumab CP2 v Denosumab CP4
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[5]</sup>
P-value	< 0.001 <sup>[6]</sup>
Method	ANCOVA
Parameter estimate	Difference from CP2
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.57

Notes:

[5] - The lower and upper bounds of the same 2-sided 95% CI of the between-group difference were compared with the equivalence margin of  $\pm 1.44\%$  for assessing equivalence.

[6] - Two-sided p-value based on the prespecified equivalence margin of  $\pm 1.44\%$  for lumbar spine.

## Secondary: Percent Change from Baseline in Serum Type I Collagen C-telopeptide (sCTX)

End point title	Percent Change from Baseline in Serum Type I Collagen C-telopeptide (sCTX)
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End point description:

The bone turnover marker (BTM) efficacy analysis subset includes all randomized subjects who had a baseline measurement and at least one post baseline measurement.

End point type	Secondary
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End point timeframe:

Baseline, month 1, month 6 and month 12

<b>End point values</b>	Denosumab CP2	Denosumab CP4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	197		
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Month 1 (n = 195, 193)	-86.39 (-90.65 to -78.45)	-88.05 (-91.12 to -80.79)		
Month 6 (n = 191, 189)	-76.46 (-85.58 to -60.58)	-79.48 (-87.06 to -66.86)		
Month 12 (n = 187, 188)	-71.34 (-83.33 to -47.13)	-75.44 (-85.88 to -61.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change from Baseline in Serum Procollagen Type 1 N-terminal Propeptide (P1NP)

End point title	Percent Change from Baseline in Serum Procollagen Type 1 N-terminal Propeptide (P1NP)
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End point description:

The bone turnover marker (BTM) efficacy analysis subset includes all randomized subjects who had a baseline measurement and at least one post baseline measurement.

End point type	Secondary
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End point timeframe:

Baseline and month 1, month 6 and month 12

<b>End point values</b>	Denosumab CP2	Denosumab CP4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	197		
Units: percent change				
median (inter-quartile range (Q1-Q3))				
Month 1 (N = 195, 193)	-29.59 (-38.06 to -20.02)	-29.86 (-38.8 to -20.9)		
Month 6 (n = 192, 190)	-76.63 (-82.9 to -66.69)	-77.74 (-85.02 to -70.31)		
Month 12 (n = 186, 188)	-71.44 (-77.64 to -57.35)	-72.08 (-80.24 to -62.4)		

### Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 Months

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	Denosumab CP4
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Reporting group description:

Participants received denosumab CP4 60 mg subcutaneously once every 6 months for 1 year.

Reporting group title	Denosumab CP2
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Reporting group description:

Participants received denosumab CP2 60 mg subcutaneously once every 6 months for 1 year.

Serious adverse events	Denosumab CP4	Denosumab CP2	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 196 (3.06%)	13 / 196 (6.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ovarian tumour			
subjects affected / exposed	1 / 196 (0.51%)	0 / 196 (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 / 196 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 196 (0.00%)	1 / 196 (0.51%)	
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			
Femur fracture			

subjects affected / exposed	0 / 196 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haematoma			
subjects affected / exposed	1 / 196 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			
subjects affected / exposed	1 / 196 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 196 (0.51%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 196 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 196 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 196 (0.00%)	2 / 196 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 196 (0.00%)	2 / 196 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 196 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 196 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 196 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 196 (0.00%)	1 / 196 (0.51%)	
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			
Dyspnoea			
subjects affected / exposed	0 / 196 (0.00%)	1 / 196 (0.51%)	
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	0 / 196 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 196 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 196 (0.51%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Denosumab CP4	Denosumab CP2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 196 (18.37%)	25 / 196 (12.76%)	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 196 (7.65%)	11 / 196 (5.61%)	
occurrences (all)	21	11	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	21 / 196 (10.71%)	15 / 196 (7.65%)	
occurrences (all)	24	16	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2014	<ul style="list-style-type: none"><li>- Reference was removed for the possibility of informed consent for eligible subjects being provided by a legally acceptable representative.</li><li>- The protocol was updated to state that the comparison between denosumab CP2 and CP4, in terms of the change from baseline in lumbar spine BMD, was being performed using noninferiority testing in addition to equivalence testing to conform to guidance received from the US FDA.</li><li>- Minor clarifications were made to the exclusion criteria, and other administrative changes were made where necessary. Typographic and formatting errors were corrected throughout the protocol.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported