



USA-162-82041

## An Overview of **Prolia® (denosumab)**

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## Disclosure

This program for Prolia® (denosumab) is promotional, presented on Amgen's behalf, and has been reviewed consistent with Amgen's internal review policies.

Prolia®(denosumab)  
helps you treat  
patients  
**at high  
risk for  
fracture  
with 5  
indications**

1

Treatment of **postmenopausal women with osteoporosis at high risk for fracture**, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy

In postmenopausal women with osteoporosis, Prolia® reduces the incidence of vertebral, nonvertebral, and hip fractures

2

Treatment to **increase bone mass in men with osteoporosis at high risk for fracture**, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy

3

Treatment to **increase bone mass in men at high risk for fracture receiving androgen-deprivation therapy for nonmetastatic prostate cancer**

In these patients, Prolia® also reduced the incidence of vertebral fractures

4

Treatment to **increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer**

5

Treatment of **glucocorticoid-induced osteoporosis in men and women at high risk of fracture** who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

# **Prolia® (denosumab) contraindications**

## **Hypocalcemia**

Prolia® is contraindicated in patients with hypocalcemia

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®

## **Pregnancy**

Prolia® may cause fetal harm when administered to a pregnant woman

In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®

## **Hypersensitivity**

Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product

Reactions have included anaphylaxis, facial swelling, and urticaria

# Discussion topics

1

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Postmenopausal  
osteoporosis and  
fracture risk

2

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Prolia® (denosumab)  
indications and mechanism  
of action (MOA)

3

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Clinical studies in  
postmenopausal  
osteoporosis

4

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Important Safety  
Information

5

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Dosing and  
administration

## Modules

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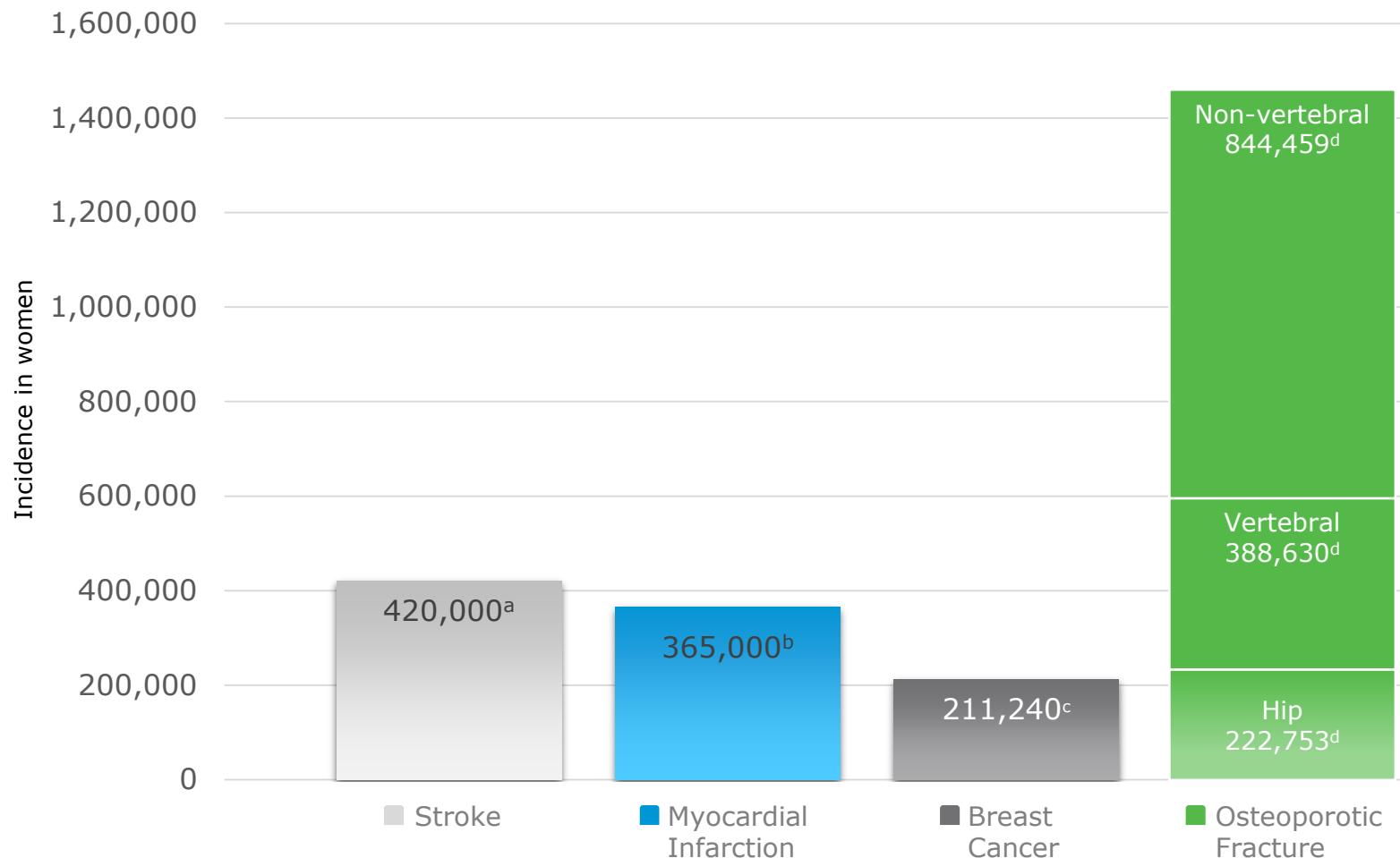
- Mechanism of disease
- Additional clinical studies

# **Postmenopausal osteoporosis and fracture risk**

# Osteoporotic fracture in postmenopausal women is a significant public health issue<sup>1</sup>

Incidence rates are not meant to imply relative importance of various diseases shown

## Estimated yearly incidence <sup>2-4</sup>



<sup>a</sup>2005 estimate of new and recurrent cases, all ages; <sup>b</sup>2005 estimate of new and recurrent cases, ages  $\geq$  35 years; <sup>c</sup>2005 estimate, all ages <sup>d</sup>2005 estimate, age  $\geq$  50 years.

1. US Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General. 2004;
2. Burge R, et al. *J Bone Miner Res*. 2007; 22:465-475; 3. Rosamond W, et al. *Circulation*. 2008; 117:e25-e146;
4. American Cancer Society. Cancer Facts & Figures 2005. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2005/cancer-facts-and-figures-2005.pdf>. 2005.



**Age: 67**

**BMD T-scores: Spine –3.0; Hip –2.2**

## Recognize the critical need to reduce fracture risk for women with postmenopausal osteoporosis

**1 in 2**

1 in 2 US women  
over the age of 50  
will have a fracture  
related to  
osteoporosis in her  
remaining lifetime<sup>1</sup>

**↑ 85%**

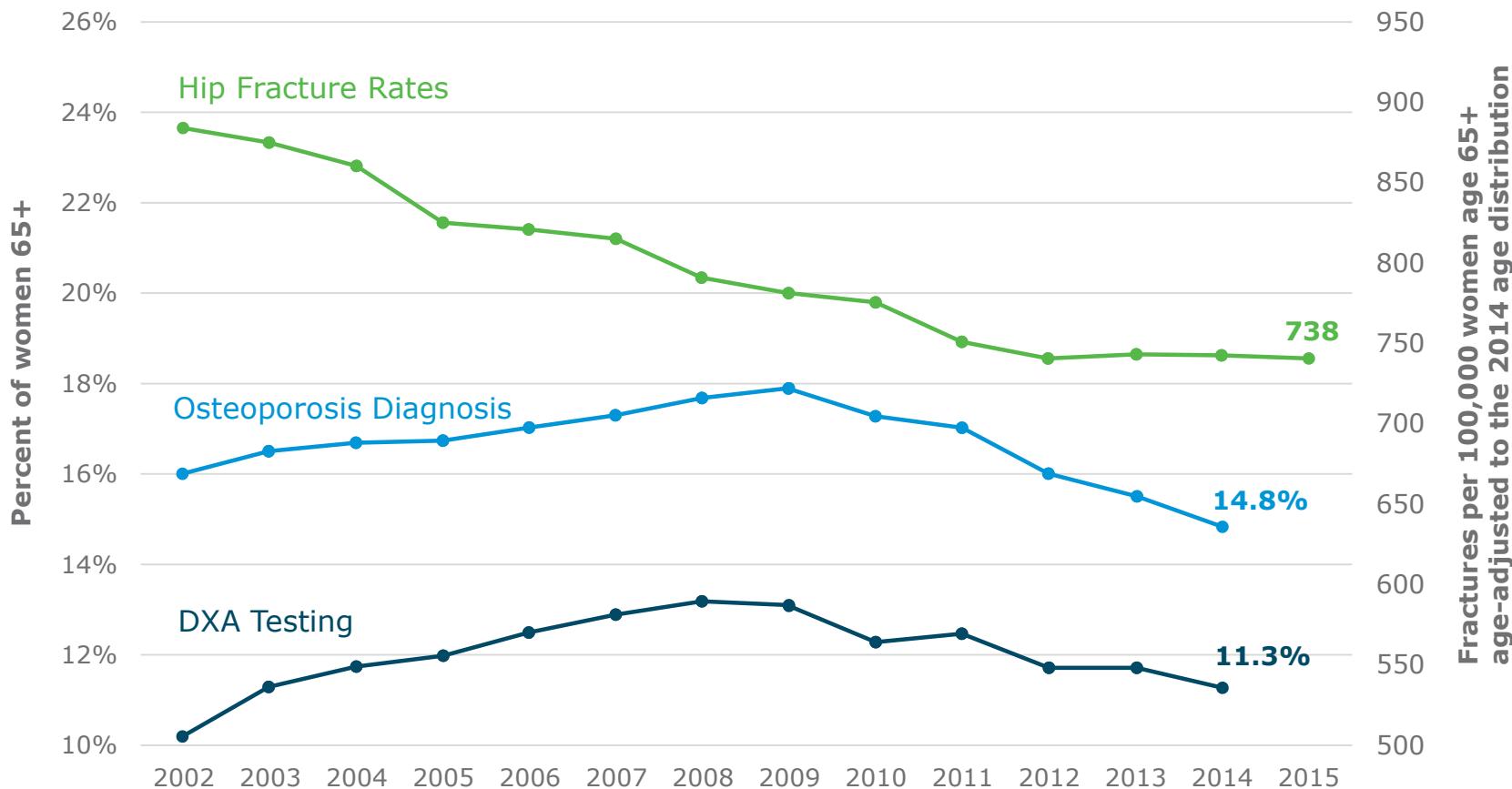
Globally, a prior  
fracture in women is  
associated with an  
85% increased risk of  
subsequent fracture<sup>2,\*</sup>

\*Risk ratio associated with a history of prior fracture in women without adjustment for BMD.

1. US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General*. 2004; 2. Kanis JA, et al. Bone. 2004;35:375-382.

# Reduction in hip fracture rate plateaued while osteoporosis testing and diagnosis declined

US hip fracture trends<sup>1,\*</sup>



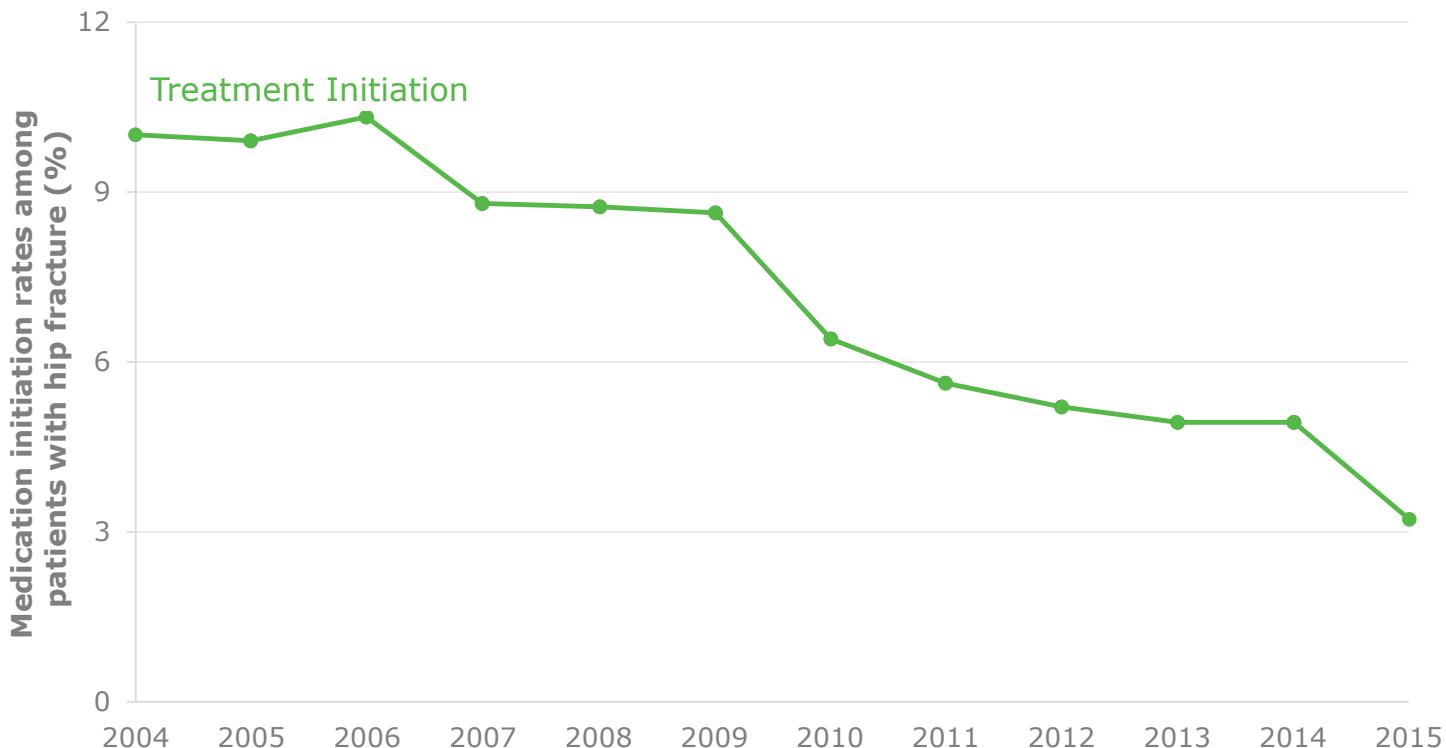
\*Age-adjusted incidence of hip fractures in US female Medicare recipients aged 65 and older from 2001-2015

1. Adapted from Lewiecki EM, et al. *Osteoporos Int.* 2018;29(3):717-722.

# Post-hip fracture treatment rates

have been on a steady decline since 2009

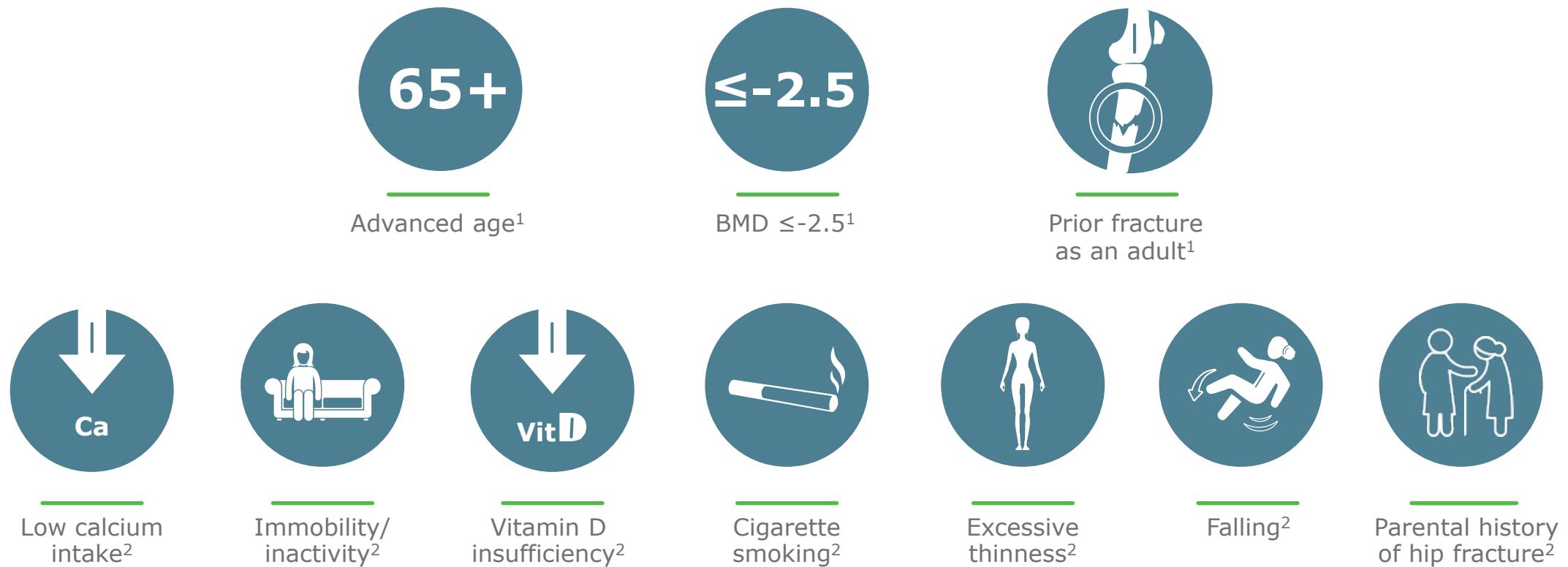
Osteoporosis treatment initiation  
in patients following hip fracture<sup>1,\*</sup>



\*Data in this figure are from a total of 97,169 patients 50 years and older with hip fracture who were not taking any osteoporosis treatment prior to the hip fracture, of whom 6,743 (6.9%) initiated treatment. Confidence intervals = 95%.

1. Desai RJ, et al. JAMA Network Open. 2018;1(3):e180826.

# Common risk factors for identifying postmenopausal women at high risk for fracture



BMD = bone mineral density.

1. Kanis JR, et al *Osteoporos Int*. 2002;13:527-536; 2. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC; 2013.

# Which of these women **are at high risk for fracture?**



**AGE 65**

## BMD T-SCORES

-3.2 (lumbar spine) /  
-2.3 (total hip)

## HISTORY

Anorexia;  
Low calcium and  
vitamin D

**AGE 75**

-2.5 (lumbar spine)  
-2.7 (total hip)

Mother fractured hip  
at age 77

**AGE 68**

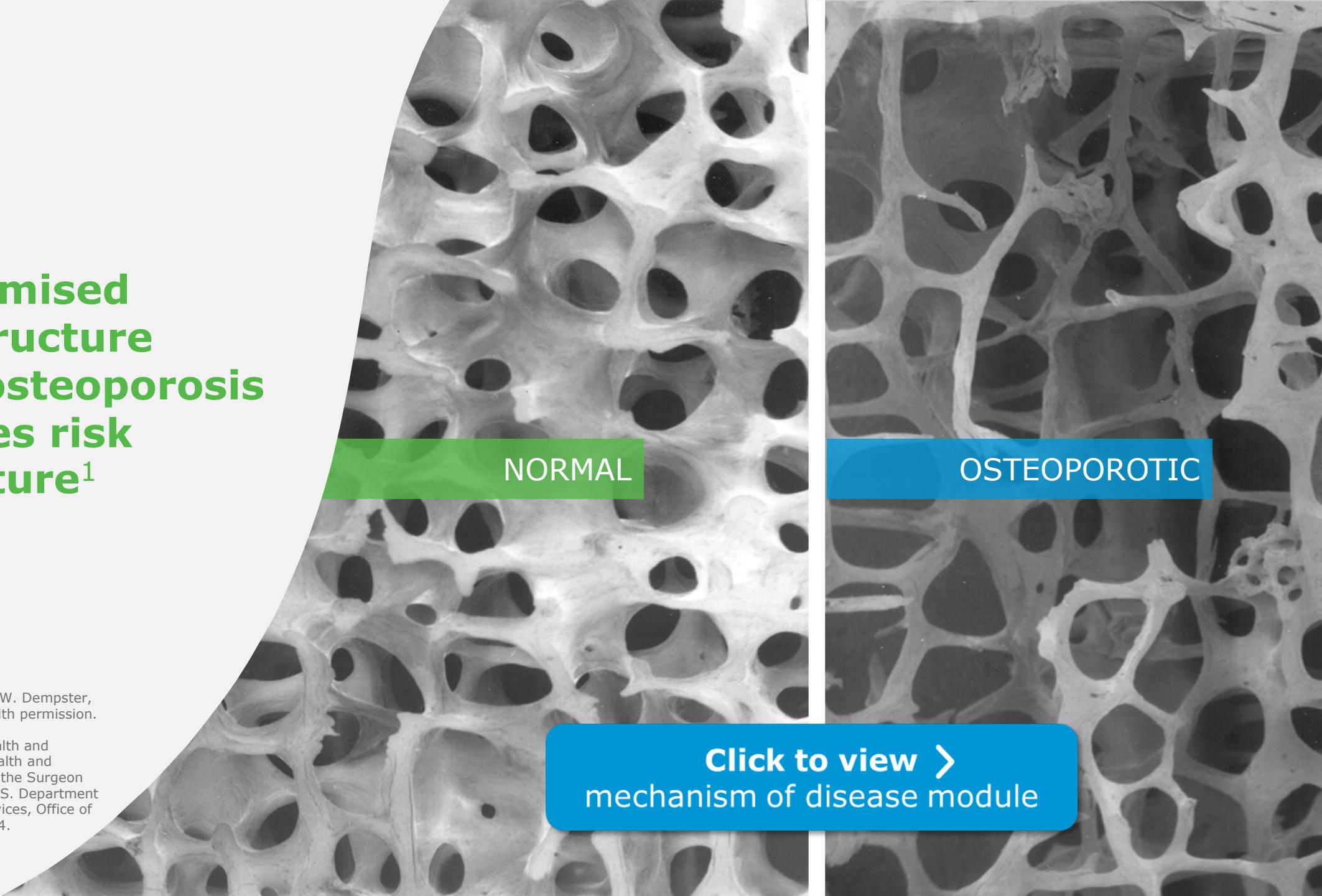
-1.9 (lumbar spine) /  
-2.7 (hip)

Wrist fracture  
at age 65

# Compromised bone structure due to osteoporosis increases risk for fracture<sup>1</sup>

Images courtesy of David W. Dempster,  
PhD. 2000. Reproduced with permission.

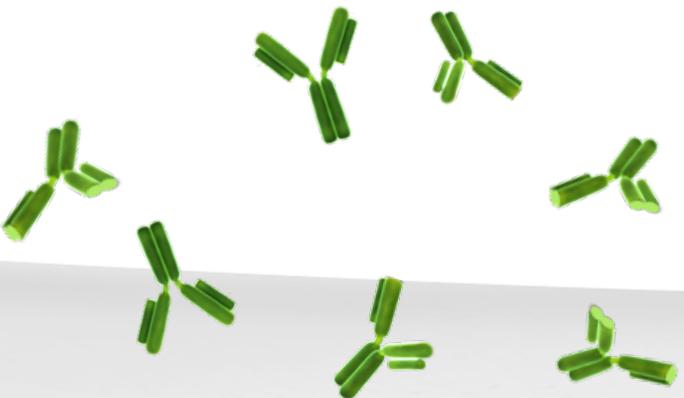
1. U.S. Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General, 2004.



**Click to view >**  
mechanism of disease module

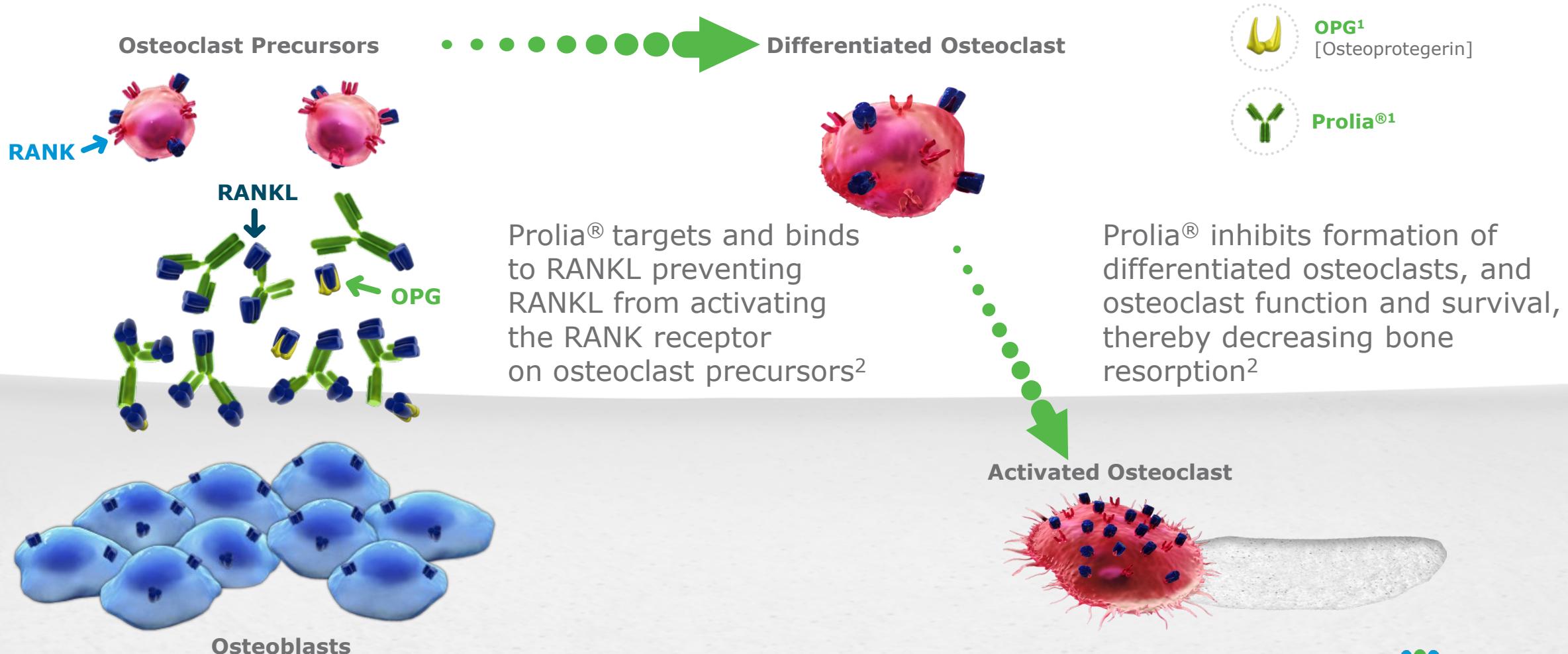
# Prolia® (denosumab) helps you treat patients at high risk\* for fracture

It's the first FDA-approved RANK ligand inhibitor for postmenopausal patients with osteoporosis at high risk for fracture



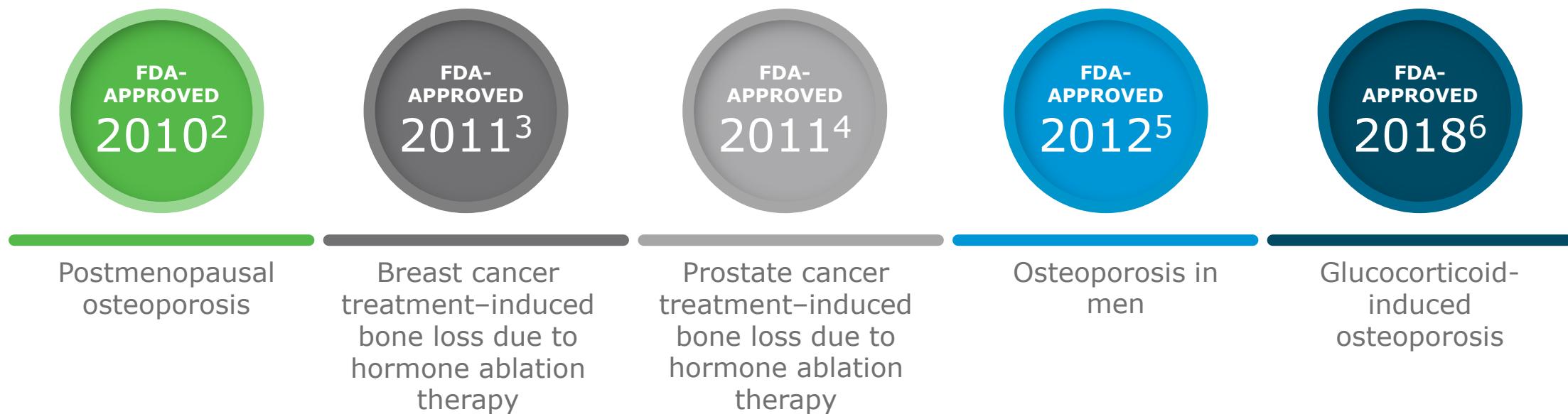
\*High risk for fracture is defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. Prolia® (denosumab) prescribing information, Amgen.

# Prolia® (denosumab) mechanism of action<sup>1,2</sup>



1. Adapted from Boyle WJ, et al. *Nature*. 2003;423:337-342; 2. Prolia® (denosumab) prescribing information, Amgen.

# Prolia® (denosumab) helps you treat patients **at high risk for fracture with 5 indications<sup>1</sup>**



1. Prolia® (denosumab) prescribing information, Amgen; 2. Prolia® (denosumab) FDA approval letter. June 1, 2010; 3. Prolia® (denosumab) FDA approval letter. September 16, 2011; 4. Prolia® (denosumab) FDA approval letter. September 16, 2011; 5. Prolia® (denosumab) FDA approval letter. September 20, 2012; 6. Prolia® (denosumab) FDA approval letter. May 18, 2018.

Prolia® (denosumab)  
**pivotal phase 3 trial**

# Prolia® (denosumab) is approved for **treatment of postmenopausal women with osteoporosis at high risk for fracture**

**INDICATION:** Prolia® is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, **OR** multiple risk factors for fracture; **OR** patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia® reduces the incidence of vertebral, nonvertebral, and hip fractures.

## CONTRAINDICATIONS

**Prolia® is contraindicated in patients with hypocalcemia**

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®

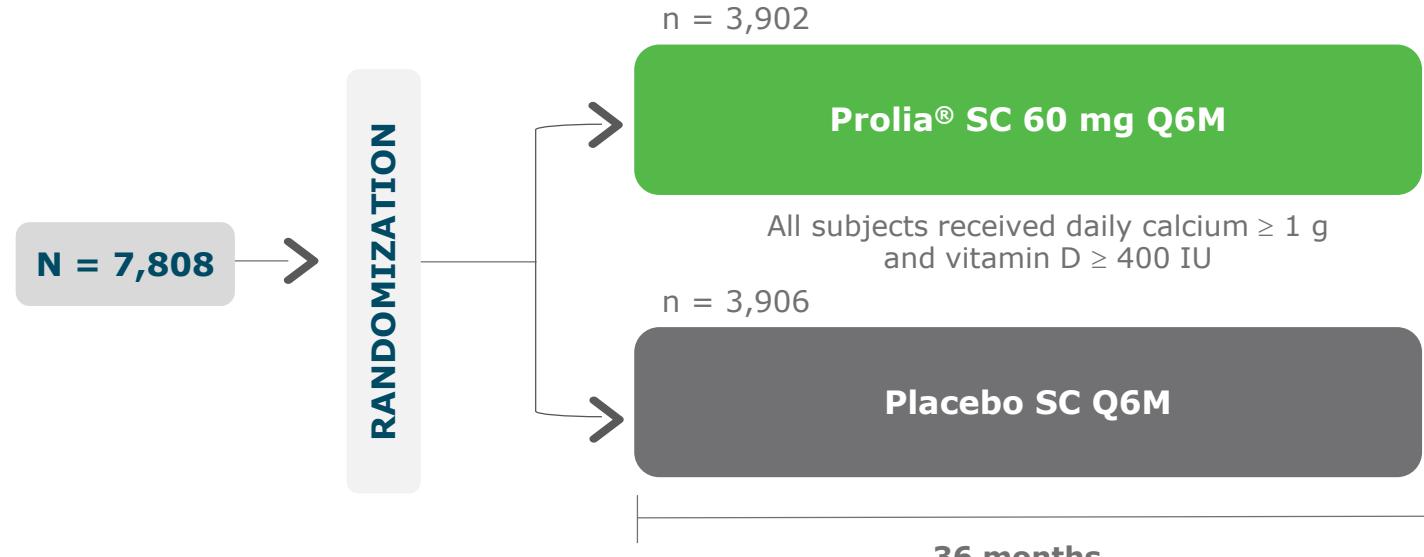
**Prolia® may cause fetal harm when administered to a pregnant woman**

In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®

**Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product**

Reactions have included anaphylaxis, facial swelling, and urticaria

Study design  
**Prolia®  
 (denosumab)  
 efficacy  
 and safety**  
 were studied in  
 a 3-year, pivotal  
 phase 3 fracture  
 trial<sup>1</sup>

**Key Inclusion Criteria**

- Women aged 60 to 91 years
- T-score from < -2.5 to -4.0 at lumbar spine or total hip

**Key Exclusion Criteria**

- Any severe or > 2 moderate vertebral fractures

**Primary Endpoint**

- Incidence of new vertebral fractures at month 36

**Secondary Endpoints**

- Time to first nonvertebral and hip fractures

SC = subcutaneous; Q6M = every 6 months.

1. Cummings SR, et al. *N Engl J Med.* 2009;361:756-765.

## Select baseline patient characteristics<sup>1,2</sup>

Similar baseline characteristics of the patients in both treatment groups

Wide age range: **60 to 91** | Mean age: **72**

Mean T-score BMD between **< -1.89 to -2.84** at lumbar spine, total hip, and femoral neck

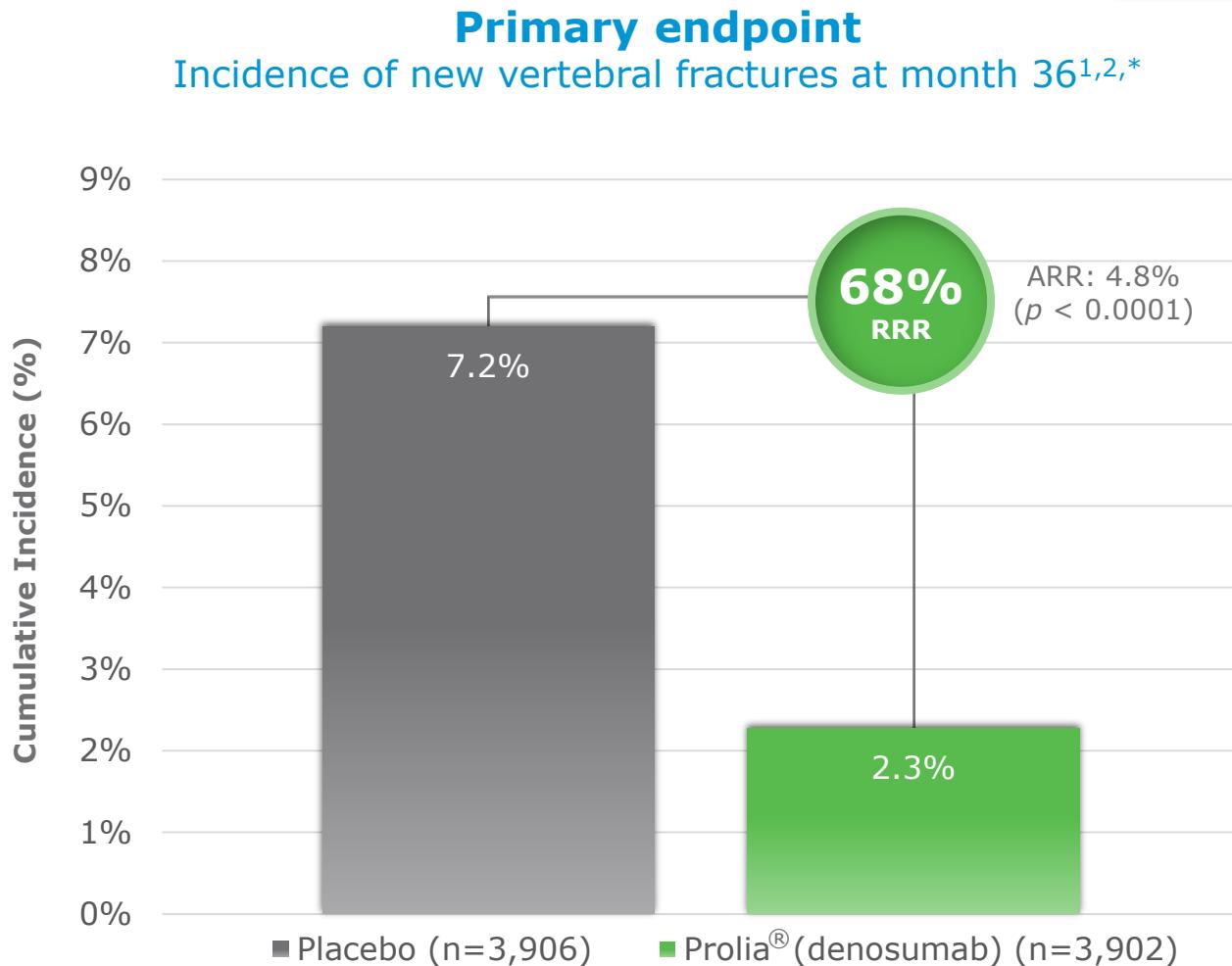
**~3/4 patients** had no prior history of vertebral fractures

**~70% of patients** had no prior use of osteoporosis medications

Full baseline characteristics >

1. Cummings SR, et al. *N Engl J Med.* 2009;361:756-765; 2. Data on file, Amgen; 2008.

**Prolia® (denosumab)  
significantly  
reduced  
vertebral  
fracture risk  
at 3 years<sup>1,2</sup>**



- **Year 1 (0 to 12 months): 61% RRR**  
(ARR 1.4%,  $p < 0.0001$ )
- **Year 2 (0 to 24 months): 71% RRR**  
(ARR 3.5%,  $p < 0.0001$ )

RRR = relative risk reduction; ARR = absolute risk reduction.

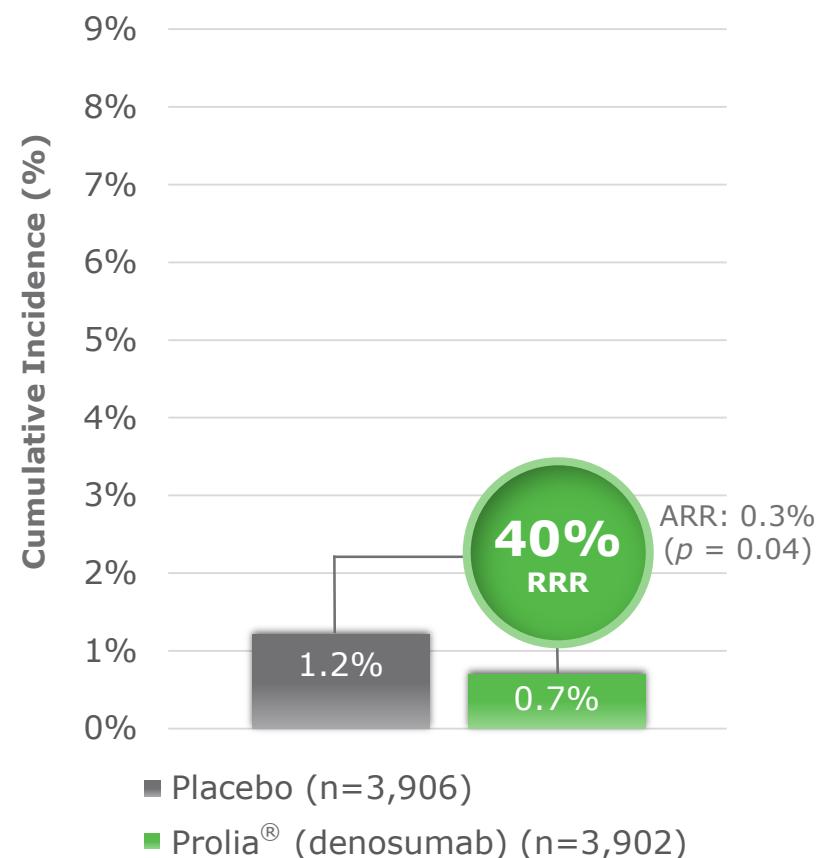
\*Includes 7,395 patients with a baseline and at least 1 postbaseline radiograph.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Adapted from Cummings SR, et al. *N Engl J Med.* 2009;361:756-765.

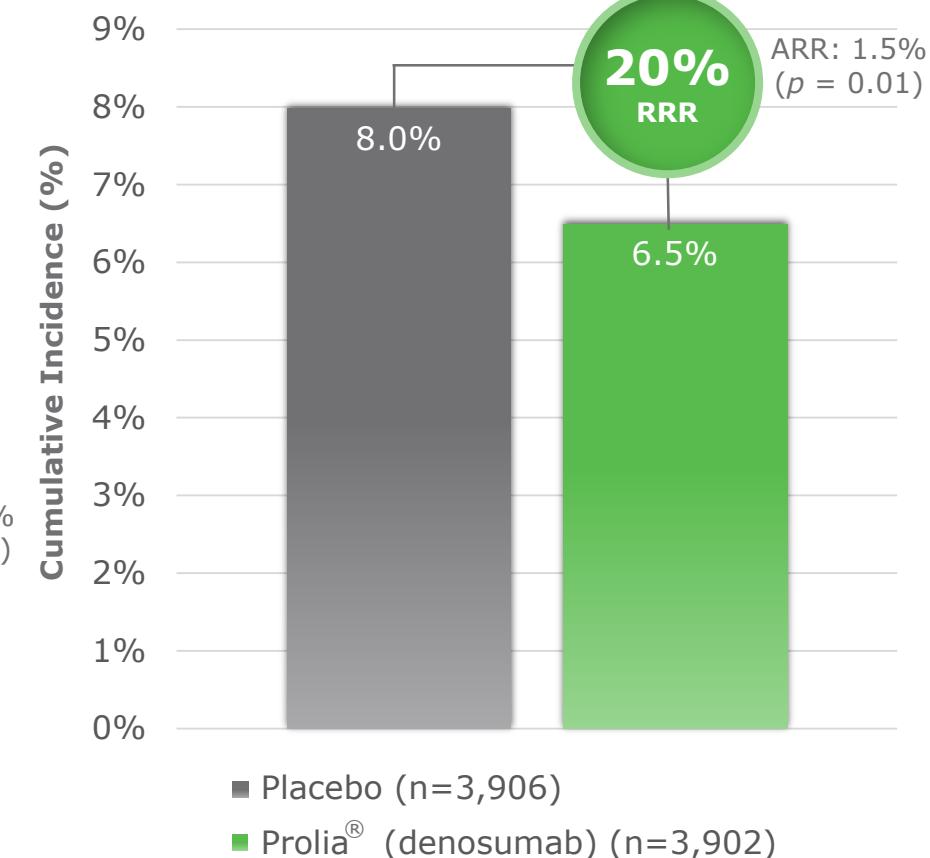
# Prolia® (denosumab) significantly reduced hip and nonvertebral fracture risk at 3 years<sup>1,2</sup>

## Fracture risk reduction of Prolia® vs placebo<sup>1,2</sup>

### Hip fracture



### Nonvertebral fracture\*



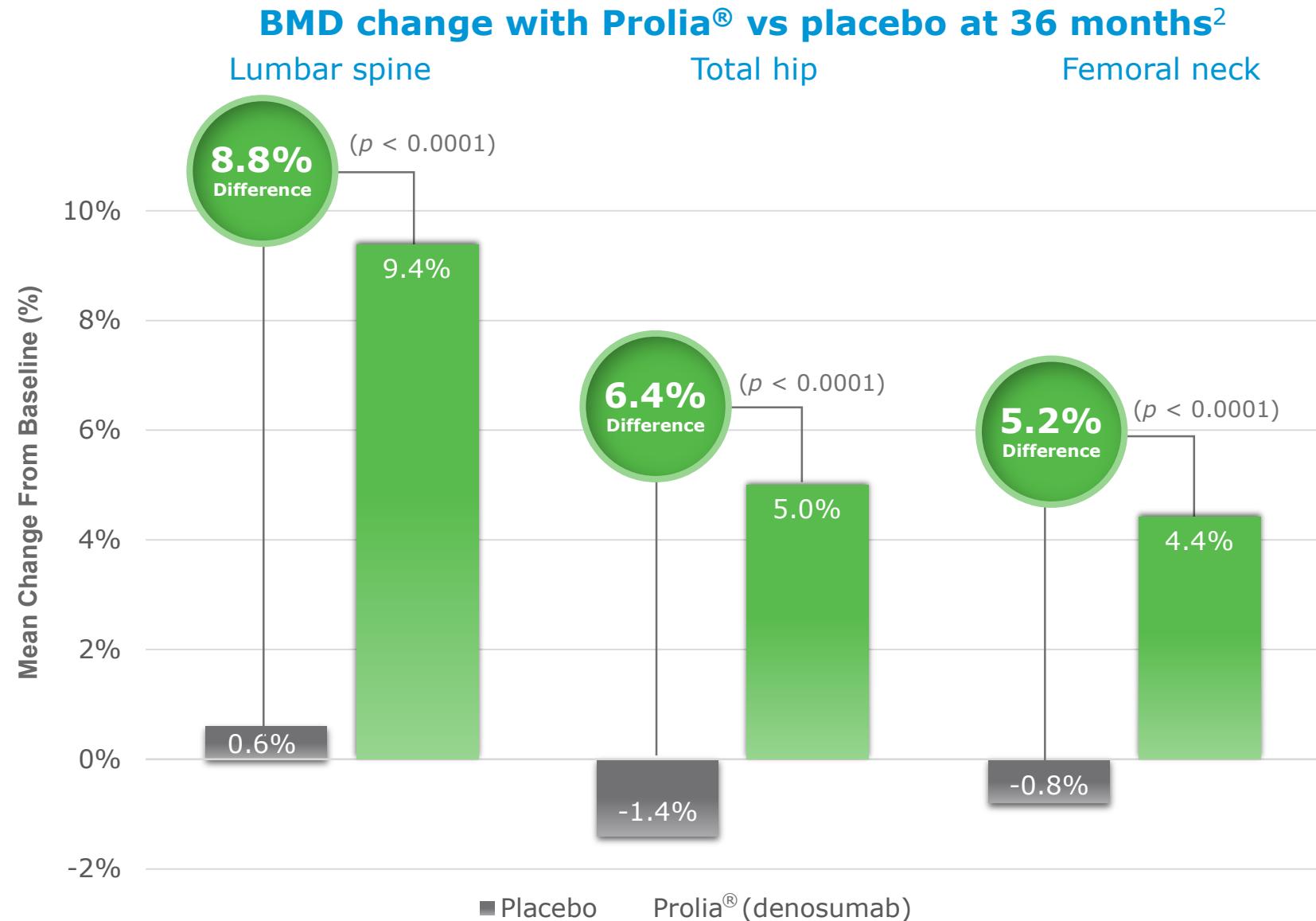
RRR = relative risk reduction; ARR = absolute risk reduction.

\*Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Adapted from Cummings SR, et al. *N Engl J Med.* 2009;361:756-765.

# Prolia® (denosumab) significantly increased BMD at key sites at 3 years<sup>1,2</sup>

- Prolia® increased bone mass and strength in both cortical and trabecular bone<sup>3</sup>
- Prolia® patient bone biopsies showed normal bone architecture and quality<sup>1</sup>
  - 53 bone biopsy specimens taken from transiliac crest<sup>1</sup>



BMD = bone mineral density.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Data on file, Amgen; 2008; 3. Keaveny TM, et al. *J Bone Miner Res*. 2014;29:158-165.

# Adverse reactions from the Prolia® (denosumab) Prescribing Information

Adverse reactions occurring in ≥ 2% of postmenopausal women with osteoporosis and more frequently in Prolia®-treated patients than in placebo-treated patients

Event	Prolia® (n = 3,886) n (%)	Placebo (n = 3,876) n (%)	Event	Prolia® (n = 3,886) n (%)	Placebo (n = 3,876) n (%)
Back pain	1,347 (34.7)	1,340 (34.6)	Insomnia	126 (3.2)	122 (3.1)
Pain in extremity	453 (11.7)	430 (11.1)	Myalgia	114 (2.9)	94 (2.4)
Musculoskeletal pain	297 (7.6)	291 (7.5)	Angina pectoris	101 (2.6)	87 (2.2)
Hypercholesterolemia	280 (7.2)	236 (6.1)	Rash	96 (2.5)	79 (2.0)
Cystitis	228 (5.9)	225 (5.8)	Pharyngitis	91 (2.3)	78 (2.0)
Vertigo	195 (5.0)	187 (4.8)	Asthenia	90 (2.3)	73 (1.9)
Upper respiratory tract infection	190 (4.9)	167 (4.3)	Pruritus	87 (2.2)	82 (2.1)
Edema peripheral	189 (4.9)	155 (4.0)	Flatulence	84 (2.2)	53 (1.4)
Sciatica	178 (4.6)	149 (3.8)	Spinal osteoarthritis	82 (2.1)	64 (1.7)
Pneumonia	152 (3.9)	150 (3.9)	Gastroesophageal reflux disease	80 (2.1)	66 (1.7)
Bone pain	142 (3.7)	117 (3.0)	Atrial fibrillation	79 (2.0)	77 (2.0)
Abdominal pain upper	129 (3.3)	111 (2.9)	Herpes zoster	79 (2.0)	72 (1.9)
Anemia	129 (3.3)	107 (2.8)			

**The most common adverse reactions (> 5% and more common than those seen with placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis**

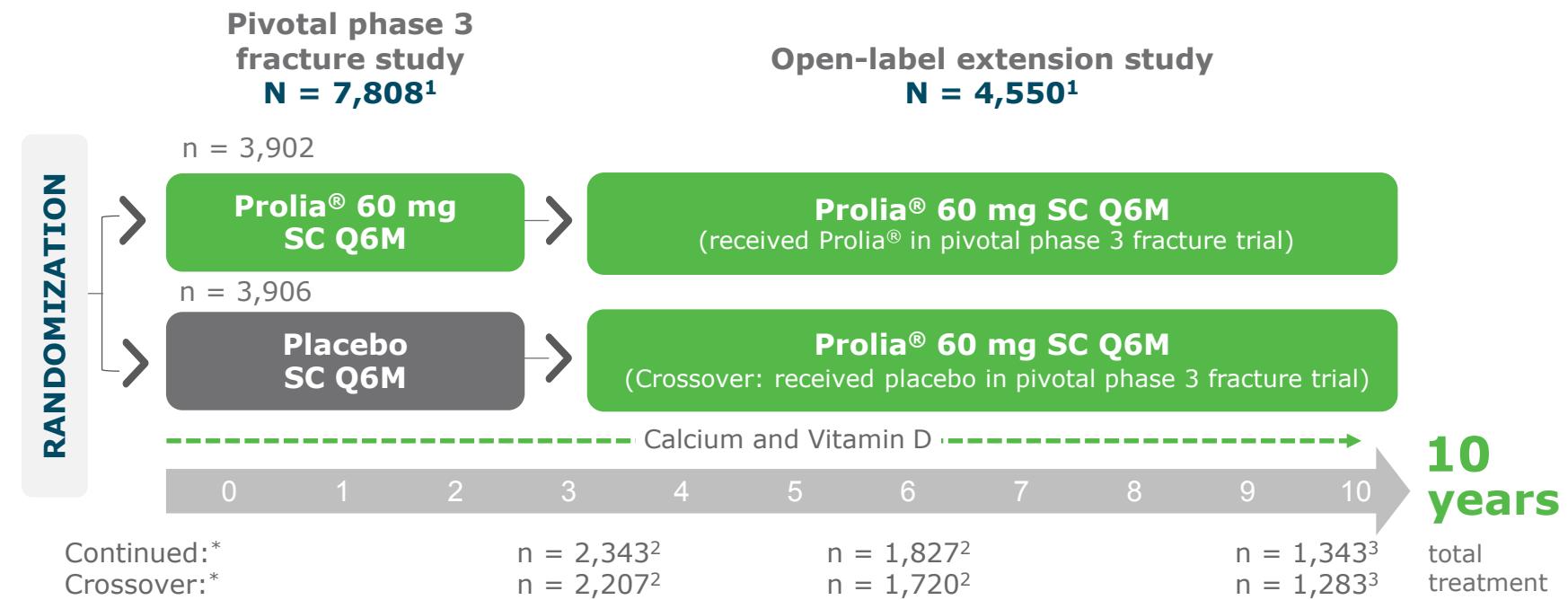
# **Open-label extension study**

of the Prolia® (denosumab) pivotal phase 3 fracture trial

## Study design

# Prolia® (denosumab) pivotal, phase 3, open-label extension<sup>1-4</sup>

Consider open-label extension study limitations when interpreting results. The open-label extension study was not blinded, not controlled, and includes inherent self-selection bias. A total of 351 patients (7.7%) had adverse events (AEs) that led to discontinuation of Prolia®, and 277 patients (6.1%) had AEs that led to discontinuation from the study<sup>4</sup>.



SC = subcutaneous; Q6M = every 6 months.

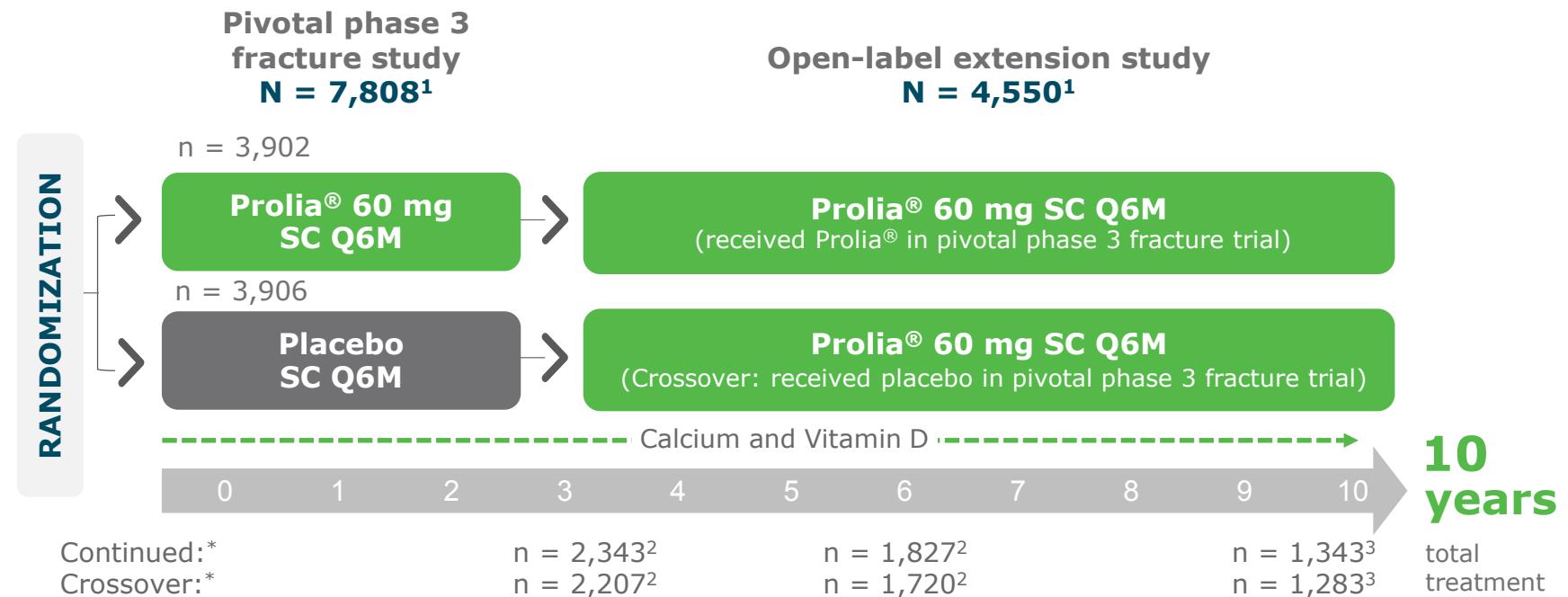
\*At year 3, n-values represent patients who began the open-label extension study. At years 6 and 10, n-values represent patients who completed those respective years of the open-label extension study.<sup>2,3</sup>

1. Bone HG, et al. Presented at: American Society for Bone and Mineral Research; October 9-12, 2015; Seattle, WA; 2. Bone HG, et al. *J Clin Endocrinol Metab.* 2013;98:4483-4492; 3. Bone HG, et al. *Lancet Diabetes Endocrinol.* 2017;5(7):513-523; 4. Data on file, Amgen; 2015.

## Study design

# Prolia® (denosumab) pivotal, phase 3, open-label extension<sup>1-4</sup>

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### Study Design

- 7-year, international, multicenter, open-label, single-arm extension study
- All patients receive Prolia® 60 mg SC QSM, daily calcium, and vitamin D

### Primary Endpoint

- Safety and tolerability of up to 10 years of Prolia® administration

### Secondary Endpoints

- Percent change from baseline in BMD during 10 years of Prolia® administration
- Incidence of vertebral and nonvertebral fractures during 10 years of Prolia® administration

BMD = bone mineral density; SC = subcutaneous; Q6M = every 6 months.

\*At year 3, n-values represent patients who began the open-label extension study. At years 6 and 10, n-values represent patients who completed those respective years of the open-label extension study.<sup>2,3</sup>

1. Bone HG, et al. Presented at: American Society for Bone and Mineral Research; October 9-12, 2015; Seattle, WA; 2. Bone HG, et al. *J Clin Endocrinol Metab.* 2013;98:4483-4492; 3. Bone HG, et al. *Lancet Diabetes Endocrinol.* 2017;5(7):513-523; 4. Data on file, Amgen; 2015

# Prolia® (denosumab) adverse event (AE) profile

exposure-adjusted  
subject incidence of  
AEs (rates per 100  
subject-years)<sup>1,2</sup>

EVENT	PIVOTAL PHASE 3 FRACTURE TRIAL <sup>1</sup> Years 1-3 (Rates per 100 Subject-years)		OPEN-LABEL EXTENSION STUDY <sup>2</sup> Years 4-10 (Rates per 100 Subject-years)	
	Prolia® (n = 3,879)	Placebo (n = 3,883)	Continued Prolia® (n = 2,343)	Crossover Prolia® (n = 2,206)
All AEs	154.3	156.1	97.0	96.8
Infections	29.3	30.7	19.9	20.7
Malignancies	1.8	1.6	2.0	2.0
Eczema	1.1	0.6	0.9	0.9
Hypocalcemia	0.0	< 0.1	< 0.1	< 0.1
Serious AEs	10.6	10.4	10.3	10.1
Infections	1.5	1.3	1.5	1.4
- Cellulitis or erysipelas	0.1	< 0.1	< 0.1	< 0.1

**Osteonecrosis of the jaw from extension study<sup>3</sup>**  
5.2 per 10,000 subject-years\*

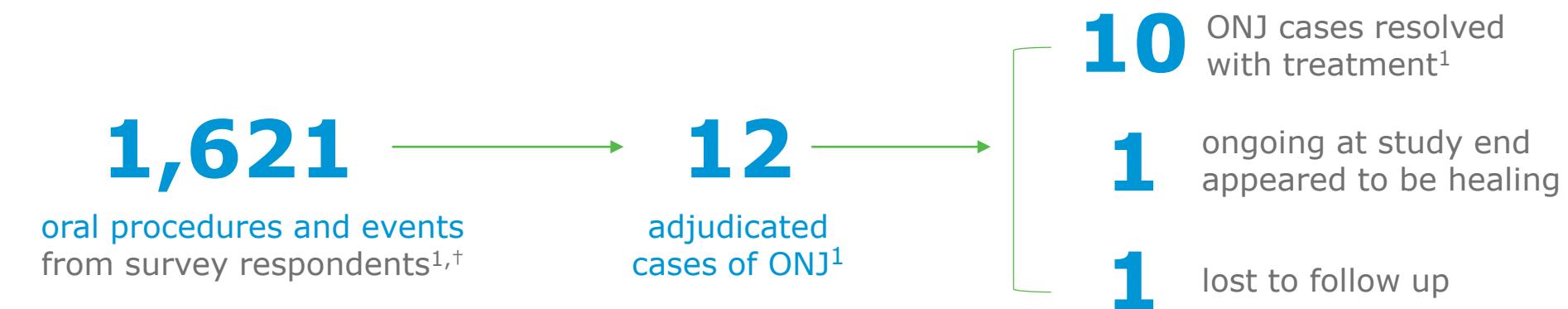
**Atypical femoral fracture from extension study<sup>3</sup>**  
0.8 per 10,000 subject-years\*

\*Exposure-adjusted subject incidence during the open-label extension study (years 4-10); rates include both the continued and crossover groups.

1. Bone HG, et al. *J Clin Endocrinol Metab*. 2013;98:4483-4492; 2. Bone HG, et al. Presented at: American Society for Bone and Mineral Research; October 9-12, 2015; Seattle, WA; 3. Bone HG, et al. *Lancet Diabetes Endocrinol*. 2017;5(7):513-523.

# Osteonecrosis of the jaw (ONJ) from open-label extension study

There were 13 adjudicated cases of ONJ from the OLE study: 12 among women who participated in an oral procedure and event (OPE) survey; 1 additional case in a woman who did not complete the survey\*



\* ONJ was resolved in the woman who did not complete the survey

<sup>†</sup> Of the 4,550 patients enrolled in 7-yr extension study; 3,591 subjects participated in self-reporting invasive OPEs through an oral event questionnaire administered every 6 months beginning in year 3 of OLE through the end of the study. OPEs included dental implants, tooth extraction, natural tooth loss, scaling or root planing and jaw surgery.<sup>1</sup> OPEs may be underestimated due to limited capture of events in medical charts and possible recall bias in patients with the events that occurred in the first 2.5 years of the extension study.<sup>1</sup>

Amgen continues to monitor ONJ through post-marketing pharmacovigilance activities.

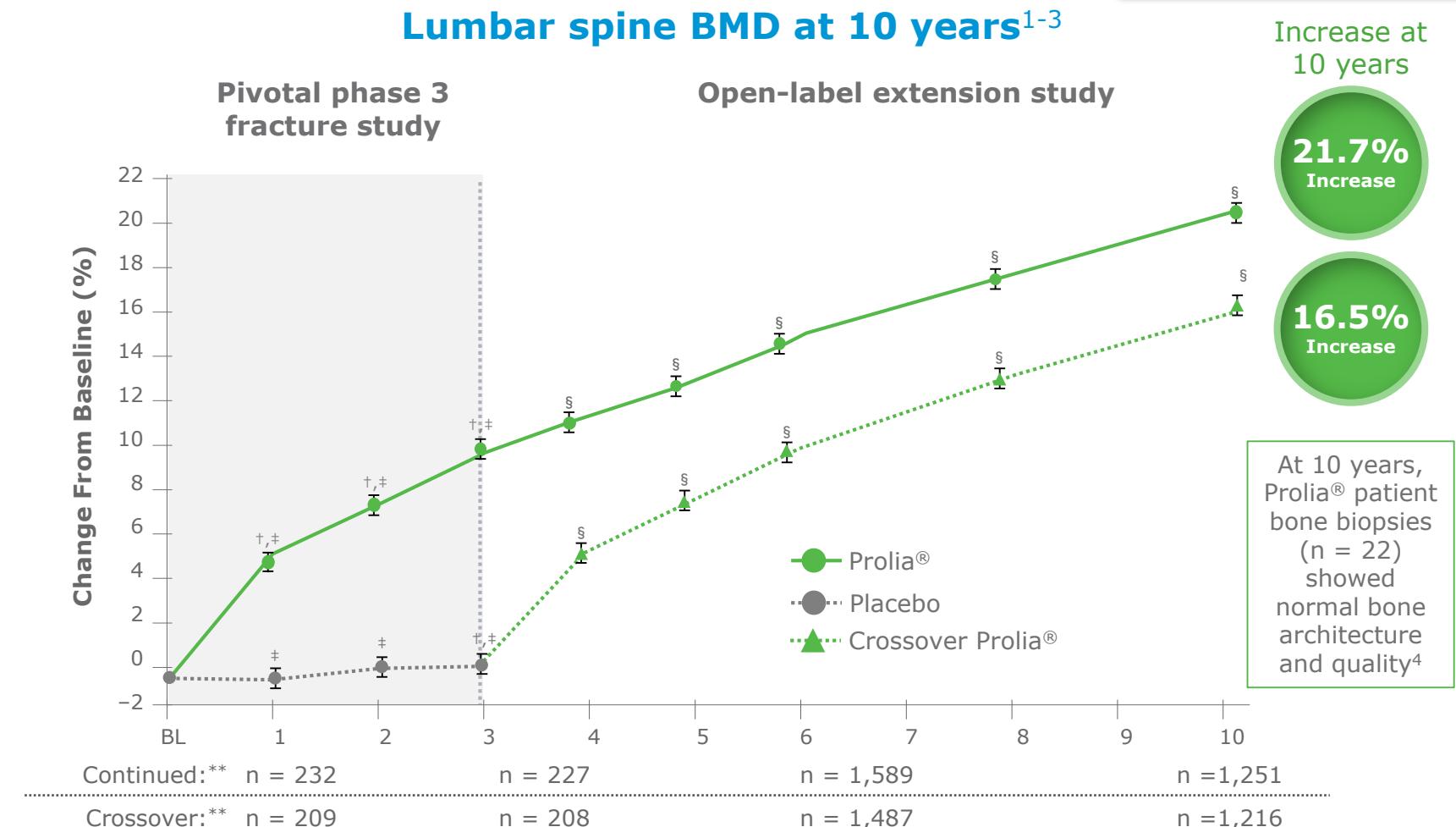
**Advise patients to maintain good oral hygiene during treatment with Prolia® and to inform their dentist prior to dental procedures that they are receiving Prolia®. Patients should inform their physician or dentist if they experience persistent pain and/or slow healing of the mouth or jaw after dental surgery.<sup>2</sup>**

OLE = Open Label Extension

1. Watts NB, et al. Presented at: World Congress on Osteoporosis (WCO), April 19-22, 2018, Krakow, Poland; 2. Prolia® (denosumab) prescribing information, Amgen.

# Prolia® (denosumab) continued to increase lumbar spine BMD at 10 years\*

BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy



Lumbar spine mean (95% CI).

\*BMD measured as a secondary endpoint; †p<0.05 compared with pivotal phase 3 fracture trial baseline; ‡Represents the subjects from BMD substudy of pivotal phase 3 fracture trial; §p < 0.05 compared with both pivotal phase 3 fracture trial and extension study baselines; \*\*The n values represent number of subjects with observed BMD data during the pivotal phase 3 trial. In the open-label extension study, subjects were required to have 1 BMD measurement at baseline and at least 1 BMD measurement post-baseline to be included in the analysis. As such, the number of subjects measured in the open-label extension is greater than the number of subjects measured in the first 3 years.

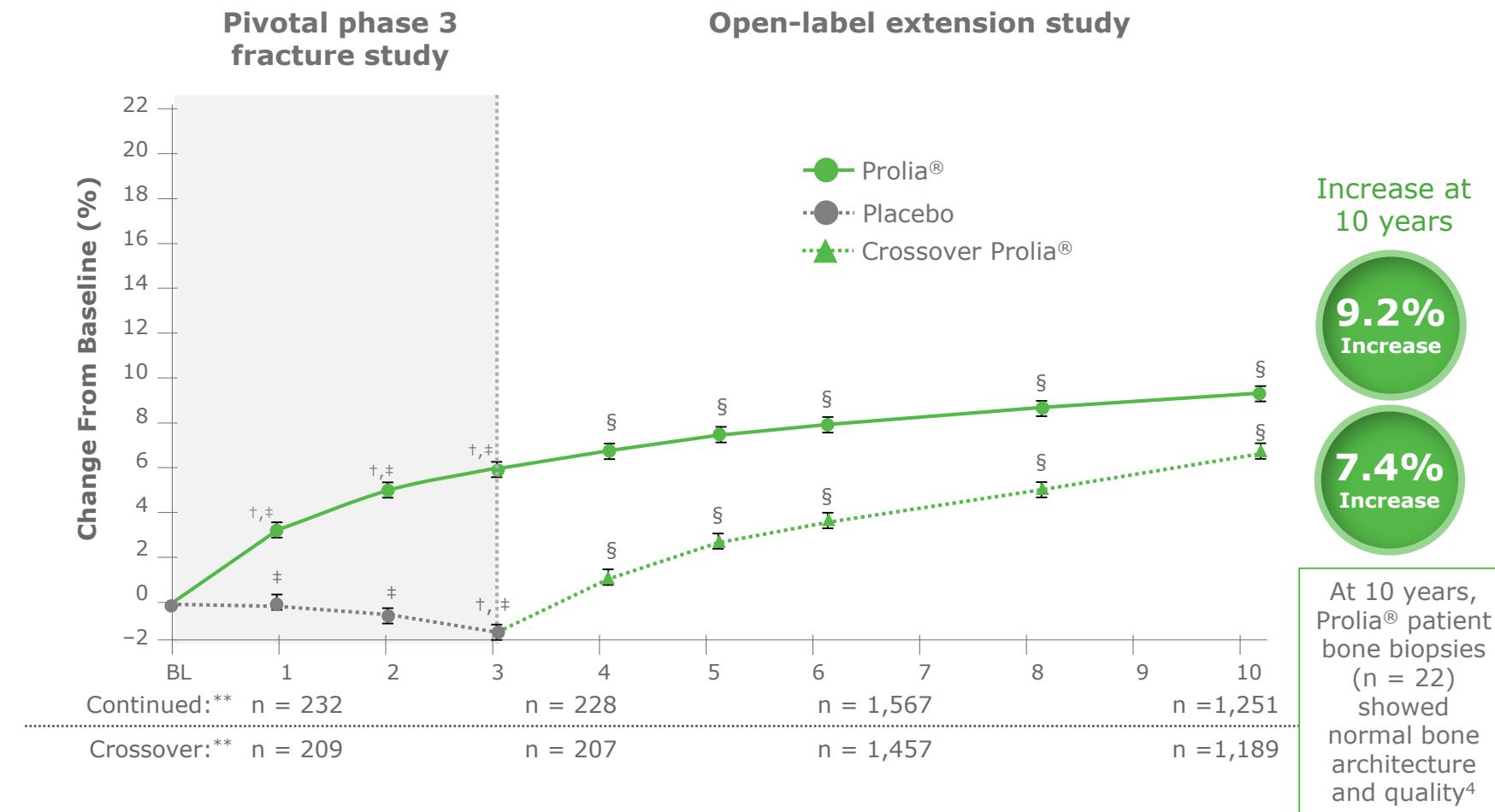
1. Bone HG, et al. Lancet Diabetes Endocrinol. 2017;5(7):513-523; 2. Data on file, Amgen; 2008; 3. Data on file, Amgen; 2015; 4. Dempster DW, et al. Presented at: Annual Meeting of the American Society for Bone and Mineral Research. September 16-19, 2016; Atlanta, GA. Abstract 1005.

# Prolia® (denosumab) continued to increase total hip BMD at 10 years\*

BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy

## Total hip BMD at 10 years<sup>1-3</sup>

open-label extension study

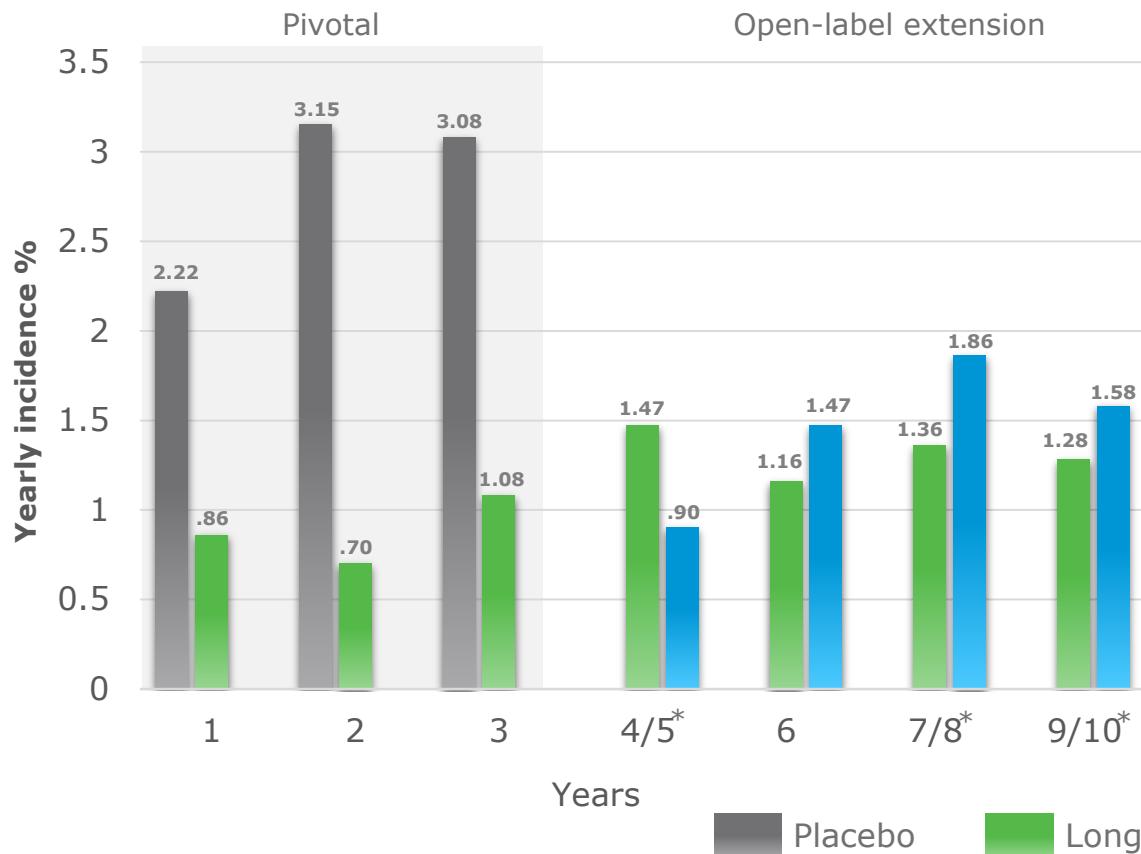


\*BMD measured as a secondary endpoint; †p<0.05 compared with pivotal phase 3 fracture trial baseline; ‡Represents the subjects from BMD substudy of pivotal phase 3 fracture trial; §p< 0.05 compared with both pivotal phase 3 fracture trial and extension study baselines; \*\*The n values represent number of subjects with observed BMD data. For baseline and year 3, these values represent observed BMD data during the pivotal phase 3 trial. In the open-label extension study, subjects were required to have 1 BMD measurement at baseline and at least 1 BMD measurement post-baseline to be included in the analysis. As such, the number of subjects measured in the open-label extension is greater than the number of subjects measured in the first 3 years.

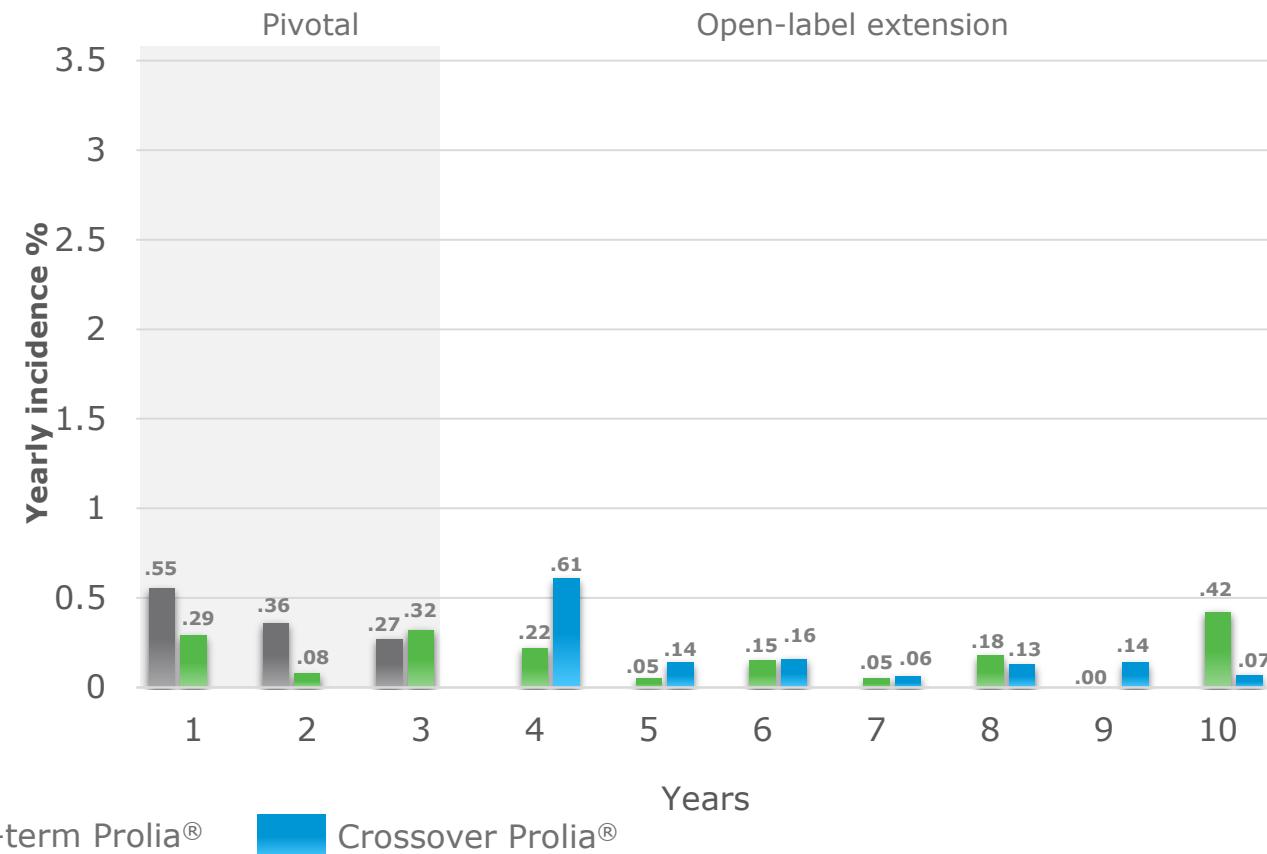
1. Bone HG, et al. *Lancet Diabetes Endocrinol.* 2017;5(7):513-523; 2. Data on file, Amgen; 2008; 3. Data on file, Amgen; 2015; 4. Dempster DW, et al. Presented at: Annual Meeting of the American Society for Bone and Mineral Research. September 16-19, 2016; Atlanta, GA. Abstract 1005.

# Incidence of fractures with Prolia® (denosumab) through 10 years in the pivotal and open-label extension study<sup>1,2,\*,+†</sup>

Yearly incidence of new vertebral fractures



Yearly incidence of hip fractures



Consider open-label study limitations when considering results

\*Annualized incidence (2-year incidence/2).

†For new vertebral fractures, percentages are crude incidence (95% CI); lateral radiographs (lumbar and thoracic) were not obtained at extension years 1, 4, and 6 (long-term denosumab treatment years 4, 7, and 9). Percentages for hip fractures are Kaplan-Meier estimates (95% CI).

1. Bone HG, et al. *Lancet Diabetes Endocrinol.* 2017;5(7):513-523; 2. Data on file, Amgen; 2015.

# Important Safety Information

## **CONTRAINDICATIONS:**

Prolia® is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia®. Prolia® is contraindicated in women who are pregnant and may cause fetal harm. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®. Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling, and urticaria.

## **SAME ACTIVE INGREDIENT:**

Prolia® contains the same active ingredient (denosumab) found in XGEVA®. Patients receiving Prolia® should not receive XGEVA®.

## **HYPERSENSITIVITY:**

Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia®. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of Prolia®.

## **HYPOCALCEMIA:**

Hypocalcemia may worsen with the use of Prolia®, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, including treatment with other calcium-lowering drugs, clinical monitoring of calcium and mineral levels is highly recommended within 14 days of Prolia® injection. Concomitant use of calcimimetic drugs may worsen hypocalcemia risk and serum calcium should be closely monitored. Adequately supplement all patients with calcium and vitamin D.



# Important Safety Information

## **OSTEONECROSIS OF THE JAW:**

ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia®. An oral exam should be performed by the prescriber prior to initiation of Prolia®. A dental examination with appropriate preventive dentistry is recommended prior to treatment in patients with risk factors for ONJ such as invasive dental procedures, diagnosis of cancer, concomitant therapies (eg, chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders. Good oral hygiene practices should be maintained during treatment with Prolia®. The risk of ONJ may increase with duration of exposure to Prolia®.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia® should be considered based on individual benefit-risk assessment.

# Important Safety Information

## **ATYPICAL FEMORAL FRACTURES:**

Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving Prolia®. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-resorptive agents.

During Prolia® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be evaluated to rule out an incomplete femur fracture. Interruption of Prolia® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

## **MULTIPLE VERTEBRAL FRACTURES (MVF) FOLLOWING DISCONTINUATION OF PROLIA® TREATMENT:**

Following discontinuation of Prolia® treatment, fracture risk increases, including the risk of multiple vertebral fractures. New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of Prolia®. Prior vertebral fracture was a predictor of multiple vertebral fractures after Prolia® discontinuation. Evaluate an individual's benefit/risk before initiating treatment with Prolia®. If Prolia® treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy.

# Important Safety Information

## SERIOUS INFECTIONS:

In a clinical trial (N = 7,808) in women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia® group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear were more frequent in patients treated with Prolia®.

Endocarditis was also reported more frequently in Prolia®-treated patients. The incidence of opportunistic infections and the overall incidence of infections were similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia®, prescribers should assess the need for continued Prolia® therapy.

## DERMATOLOGIC ADVERSE REACTIONS:

In the same clinical trial in women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate with Prolia® compared to placebo. Most of these events were not specific to the injection site. Consider discontinuing Prolia® if severe symptoms develop.

## MUSCULOSKELETAL PAIN:

Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking Prolia®. Consider discontinuing use if severe symptoms develop.

# Important Safety Information

## SUPPRESSION OF BONE TURNOVER:

In clinical trials in women with postmenopausal osteoporosis, Prolia® resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for these consequences, including ONJ, atypical fractures, and delayed fracture healing.

## ADVERSE REACTIONS:

The most common adverse reactions (> 5% and more common than placebo) in women with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions (> 5% and more common than placebo) in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. Pancreatitis has been reported with Prolia®.

In women with postmenopausal osteoporosis, the overall incidence of new malignancies was 4.3% in the placebo group and 4.8% in the Prolia® group. In men with osteoporosis, new malignancies were reported in no patients in the placebo group and 4 (3.3%) patients in the Prolia® group. A causal relationship to drug exposure has not been established.

The most common adverse reactions (> 3% and more common than active-control group) in patients with glucocorticoid-induced osteoporosis are back pain, hypertension, bronchitis, and headache.

The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia® in patients with bone loss receiving ADT for prostate cancer or adjuvant AI therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. Additionally, in Prolia®-treated men with prostate cancer receiving ADT, a greater incidence of cataracts was observed.

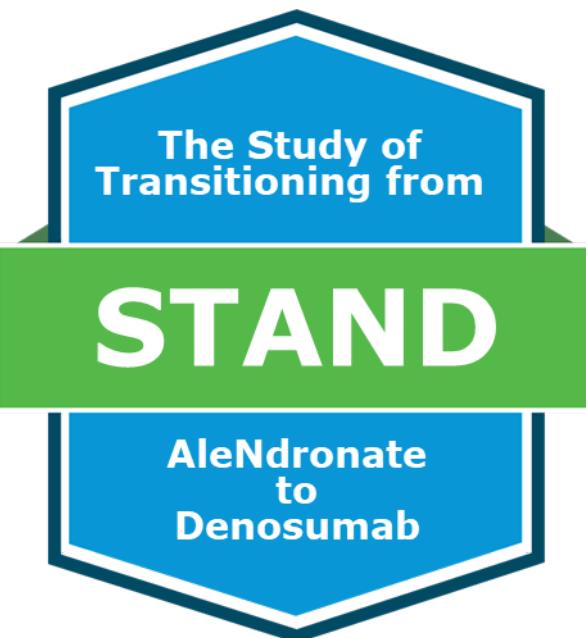
Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

**Please see accompanying Prolia® full Prescribing Information, including Medication Guide.**

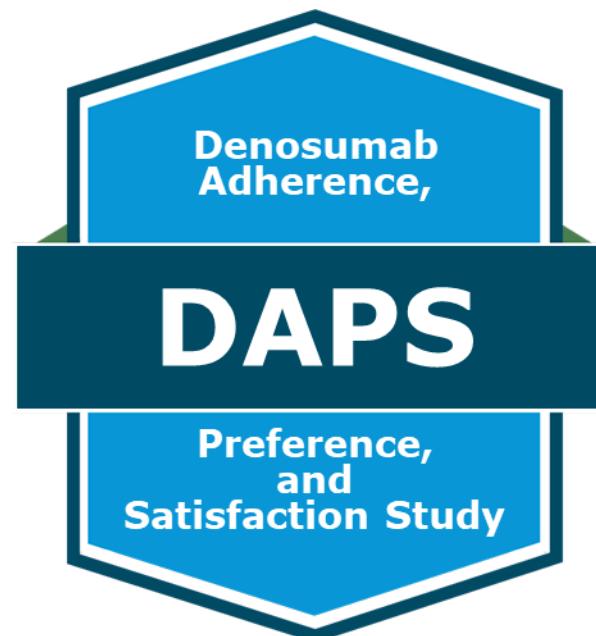
Prolia® (denosumab) prescribing information, Amgen.

## **Additional studies**

Postmenopausal osteoporosis



[view study >](#)



[view study >](#)

# Dosing and administration

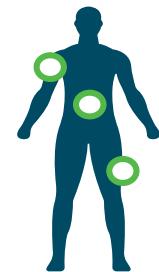
Be confident that your Prolia® (denosumab)  
**patients are receiving 6 months  
of therapy with each injection**



**60 MG  
SC injection**



**Administered as  
1 shot Q6M  
by a healthcare  
professional**



**In the upper arm,  
upper thigh,  
or abdomen**

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®

- Adequately supplement all patients with calcium and vitamin D

Pregnancy must be ruled out prior to administration of Prolia®

Multiple vertebral fractures have been reported following Prolia® discontinuation

Prolia® can be considered in patients with renal impairment with no dose adjustment necessary

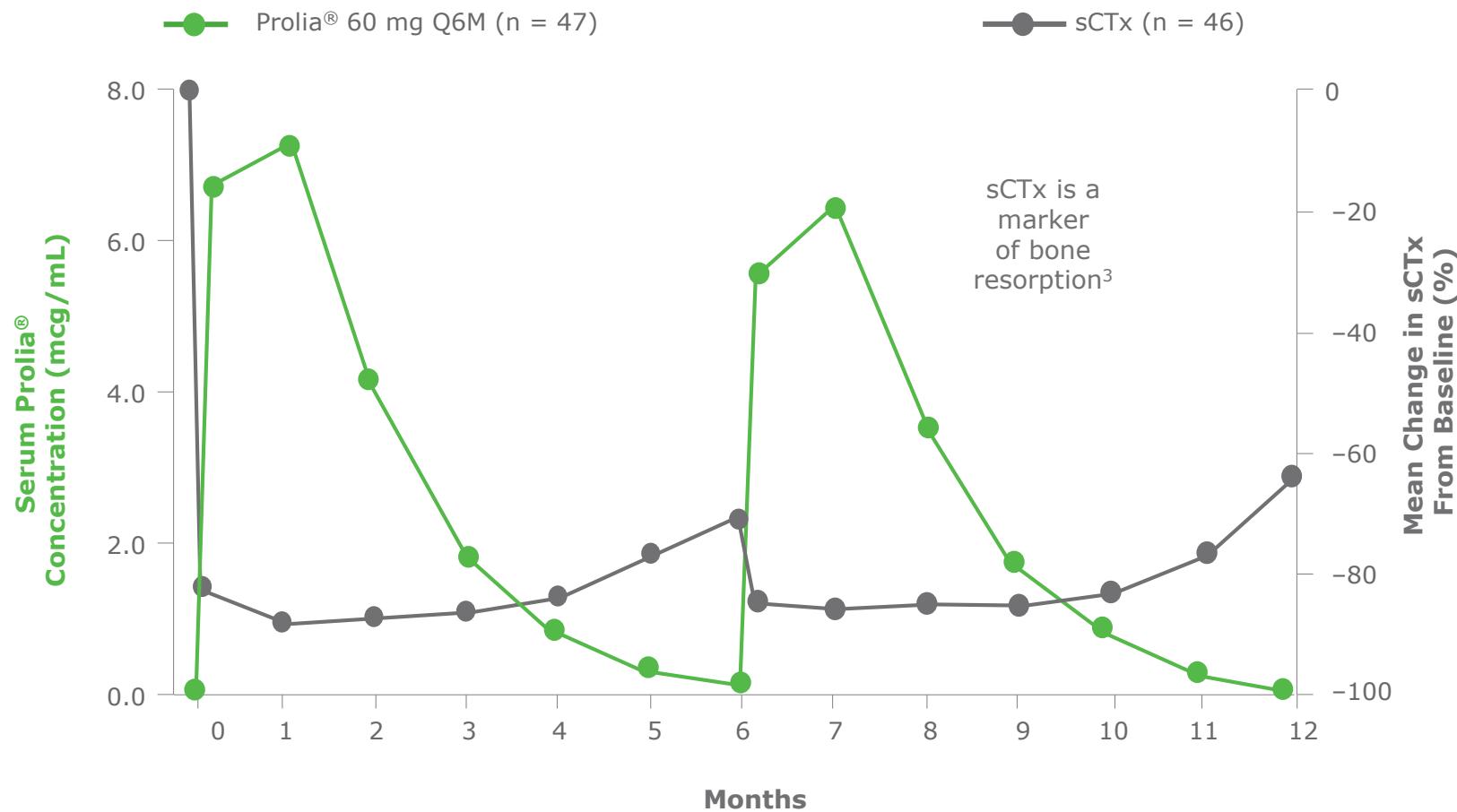
- Patients with severe renal impairment ( $\text{CrCl} < 30 \text{ mL/min}$ ) are at increased risk for hypocalcemia
- Clinical monitoring of calcium, phosphorus, and magnesium is highly recommended in patients with severe renal impairment

CrCl = creatinine clearance; Q6M = every 6 months; SC = subcutaneous.  
Prolia® (denosumab) prescribing information, Amgen.

# Prolia® (denosumab) should be administered Q6M due to its pharmacokinetics & pharmacodynamics (PK/PD) profile

Following discontinuation of Prolia® treatment, fracture risk increases, including the risk of multiple vertebral fractures. Evaluate an individual's benefit/risk before initiating treatment with Prolia®. If Prolia® treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy<sup>4</sup>

## Prolia® effects on sCTx levels over the 6-month dosing interval<sup>1,2,\*</sup>

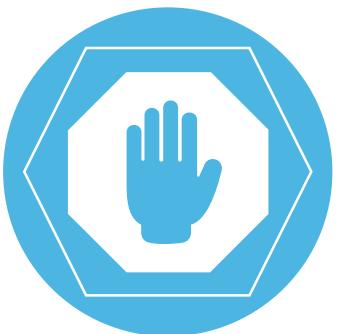


sCTx = serum C-telopeptide cross-link of type 1 collagen.

\*Results from a randomized, placebo-controlled, phase 2 dose-ranging study evaluating the PK and PD properties of denosumab in postmenopausal women (N = 412). Data shown are from patients assigned to the denosumab 60 mg Q6M arm.  
1. Adapted from: McClung MR, et al. *N Engl J Med.* 2006;354:821-831; 2. Peterson MC, et al. Presented at: ASBMR; September 23-27, 2005; Nashville, TN. Abstract SU446 and poster; 3. Vasikaran SD. *Crit Rev Clin Lab Sci.* 2008;45:221-258;  
4. Prolia® (denosumab) prescribing information, Amgen.

# A drug holiday from Prolia® (denosumab) is not recommended

per 2016 AACE/ACE guidelines<sup>1</sup>



Do not skip or delay Prolia® injections. If Prolia® treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy<sup>2</sup>

- **If treatment is stopped**, bone mineral density returns to pretreatment values within 18 months, and fracture risk increases, including the risk of multiple vertebral fracture<sup>2</sup>
- **Patients only experience the benefits of Prolia® while on treatment**

## Important Safety Information

Following discontinuation of Prolia® treatment, fracture risk increases, including the risk of multiple vertebral fractures. Evaluate an individual's benefit/risk before initiating treatment with Prolia®. If Prolia® treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy.<sup>2</sup>

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology.

1. Camacho PM, et al. *Endocr Pract.* 2016;22:1111-1118; 2. Prolia® (denosumab) prescribing information, Amgen

Whether switching to Prolia® (denosumab) or starting Prolia® as initial therapy,  
**97% of insured patients have access\* to Prolia®<sup>1</sup>**

## Buy and Bill

81% of Medicare Part B patients pay \$50 or less out of pocket every 6 months<sup>2,†,‡</sup>

- Nearly 77% of Medicare Part B patients have supplemental insurance, meaning they will pay \$0 per syringe of Prolia®<sup>2,†,‡</sup>



## AMGEN ASSIST®

Choose the Amgen Assist® service that's right for you—insurance verification, financial support options, and more



## Pharmacy

80% of Medicare D patients with access to Prolia® have first-line access with no step edit<sup>1,†</sup>



## Prolia® Field Reimbursement Specialist

When you need someone who can help you with questions about local coverage and how to manage the insurance claims process, connect with a Prolia® Field Reimbursement Specialist

\*Access is defined as the ability for a patient to obtain Prolia®, although patient OOP cost and insurance requirements may vary.

<sup>†</sup>Data from 10/2007-6/2018;

<sup>‡</sup>Data do not include medical benefit out-of-pocket (OOP) costs related to office visits or administration of Prolia®. This sample includes Medicare patients with supplemental coverage (e.g., Medigap) that may require additional monthly premiums. Individual OOP costs will vary.

1. Data on file, Amgen. 2016; 2. Data on file, Amgen. 2015.

# For your postmenopausal patients with osteoporosis at high risk for fracture – consider Prolia® (denosumab)

Identify patients with risk factors for osteoporotic fracture and consider treatment

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Prolia® is proven to significantly increase BMD and reduce fracture risk at key sites of the body at 3 years<sup>1-3</sup>

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Long-term use of Prolia® has been studied for up to 10 years in the pivotal phase 3 fracture trial and open-label extension<sup>4</sup>

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Prolia® is administered by a healthcare professional as 1 shot SC every 6 months<sup>1</sup>  
A drug holiday is not recommended with Prolia® per the 2016 AACE/ACE guidelines<sup>5</sup>

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- Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®. Adequately supplement all patients with calcium and vitamin D.
- Multiple vertebral fractures have been reported following Prolia® discontinuation.

Please see accompanying Prolia® full Prescribing Information, including Medication Guide.

SC = subcutaneous.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Data on file, Amgen; 2008; 3. Cummings SR, et al. *N Engl J Med.* 2009;361:756-765; 4. Bone HG, et al. Presented at: American Society for Bone and Mineral Research (ASBMR); October 9-12, 2015; Seattle, WA; 5. Camacho PM, et al. *Endocr Pract.* 2016;22:1111-1118.

# Prolia® (denosumab) helps you treat patients at high risk for fracture with 5 indications<sup>1</sup>



Postmenopausal  
osteoporosis

**Studying the effect  
of transitioning to  
Denosumab or  
Zoledronic Acid on  
BMD**

**Click to view >**



Breast cancer  
treatment-induced  
bone loss due to hormone  
ablation therapy

**Hormone Ablation Therapy  
(HALT) Pivotal Trials**

**Click to view >**



Prostate cancer  
treatment-induced  
bone loss due to  
hormone ablation therapy



Osteoporosis in  
men

**Prolia® for treatment  
of osteoporosis  
in men**

**Click to view >**



Glucocorticoid-  
induced  
osteoporosis

**Head-to-Head Study  
of Patients with  
Glucocorticoid-  
Induced Osteoporosis**

**Click to view >**

BMD = bone mineral density.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Prolia® (denosumab) FDA approval letter. June 1, 2010; 3. Prolia® (denosumab) FDA approval letter. September 16, 2011; 4. Prolia® (denosumab) FDA approval letter. September 16, 2011; 5. Prolia® (denosumab) FDA approval letter. September 20, 2012; 6. Prolia® (denosumab) FDA approval letter. May 18, 2018.

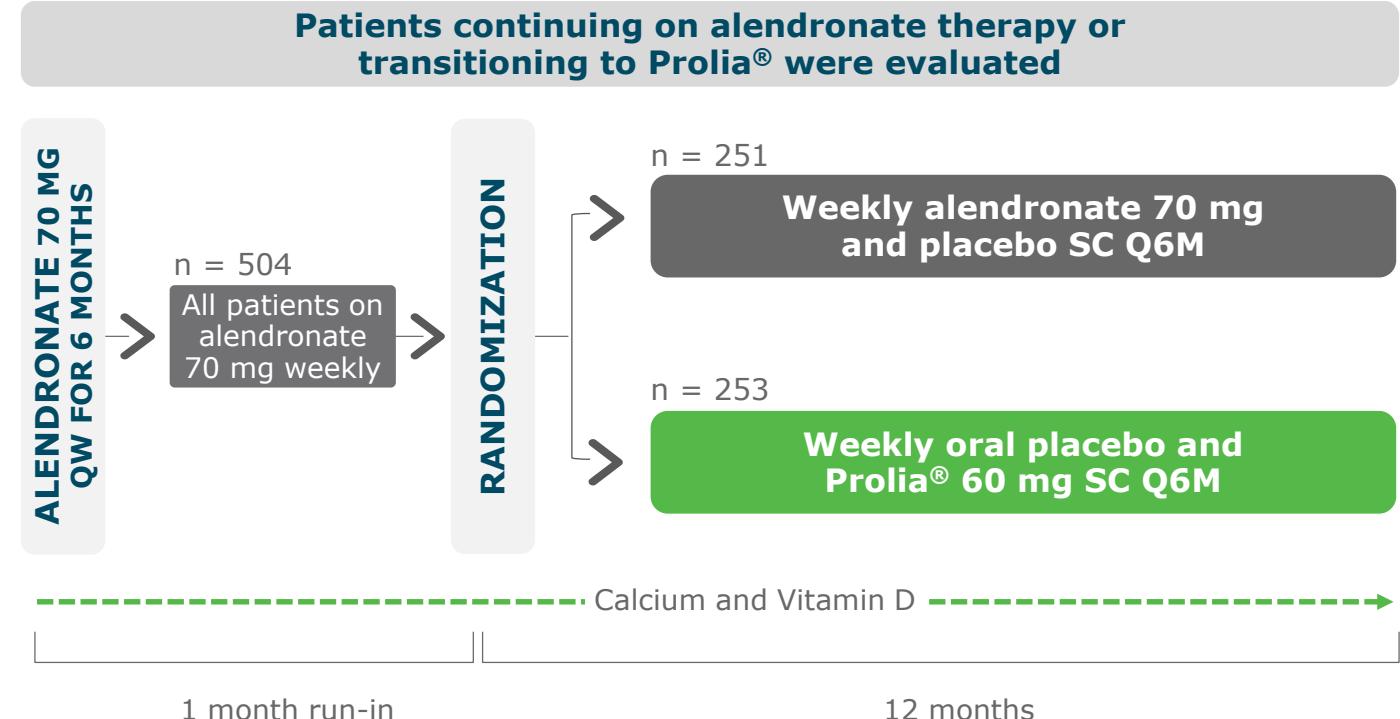


This concludes our presentation  
**THANK YOU**

# The Study of Transitioning from AleNdronate to Denosumab (**STAND**)

## Study design

# A study evaluating patients continuing on alendronate or transitioning to Prolia® (denosumab)



### Primary Endpoint

- Percent change in total hip BMD from baseline to month 12

### Select Secondary Endpoints

- Percent change in BMD at lumbar spine at 12 months
- Safety endpoints included AEs, changes in safety laboratory analytes, serum calcium levels, and vital signs

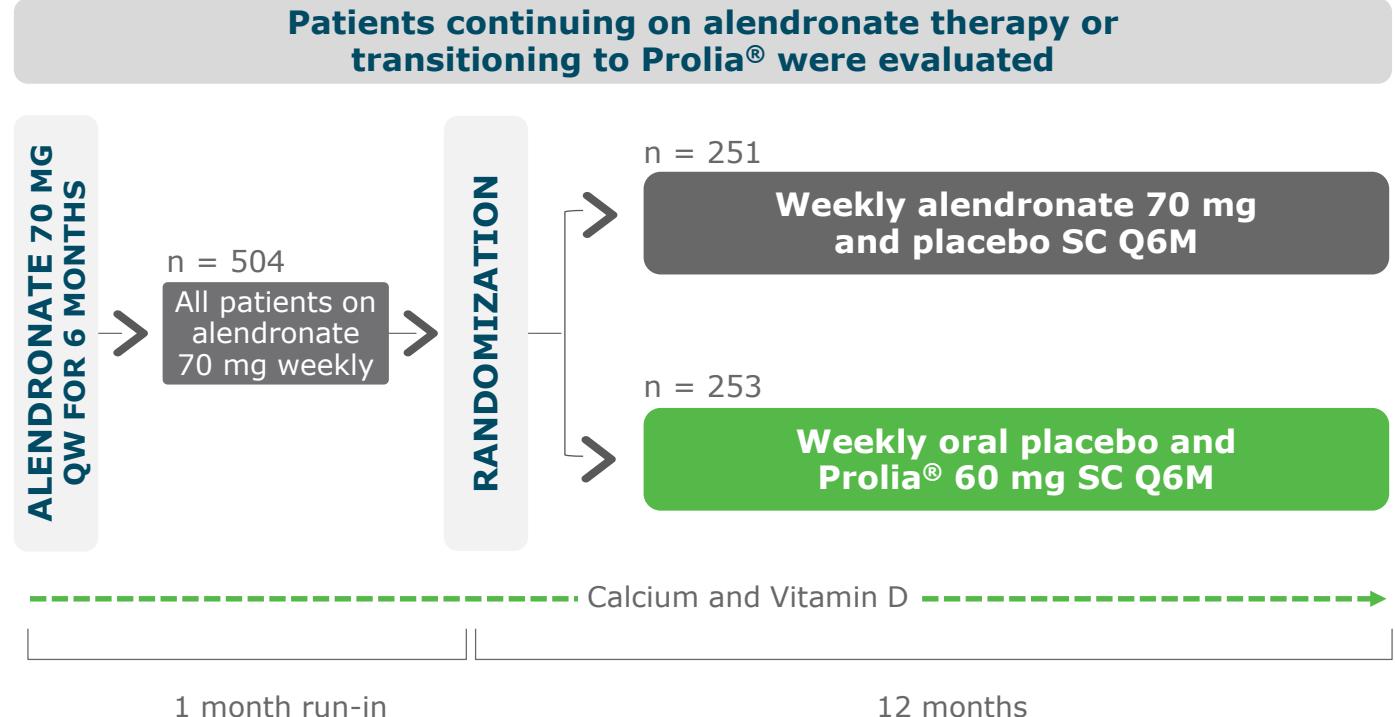
### Key Inclusion Criteria

- Postmenopausal women with a BMD T-score of  $\leq -2.0$  and  $\geq -4.0$  at the lumbar spine or total hip
- Patients must have been receiving alendronate 70 mg/week for  $\geq 6$  months prior to screening

QW = once a week; SC = subcutaneous; Q6M = every 6 months; BMD= bone mineral density; AEs: adverse events.  
Kendler DL et al. *J Bone Miner Res.* 2010;25:72-78.

## Study design

# A study evaluating patients continuing on alendronate or transitioning to Prolia® (denosumab)



A step-down multiple testing procedure was used

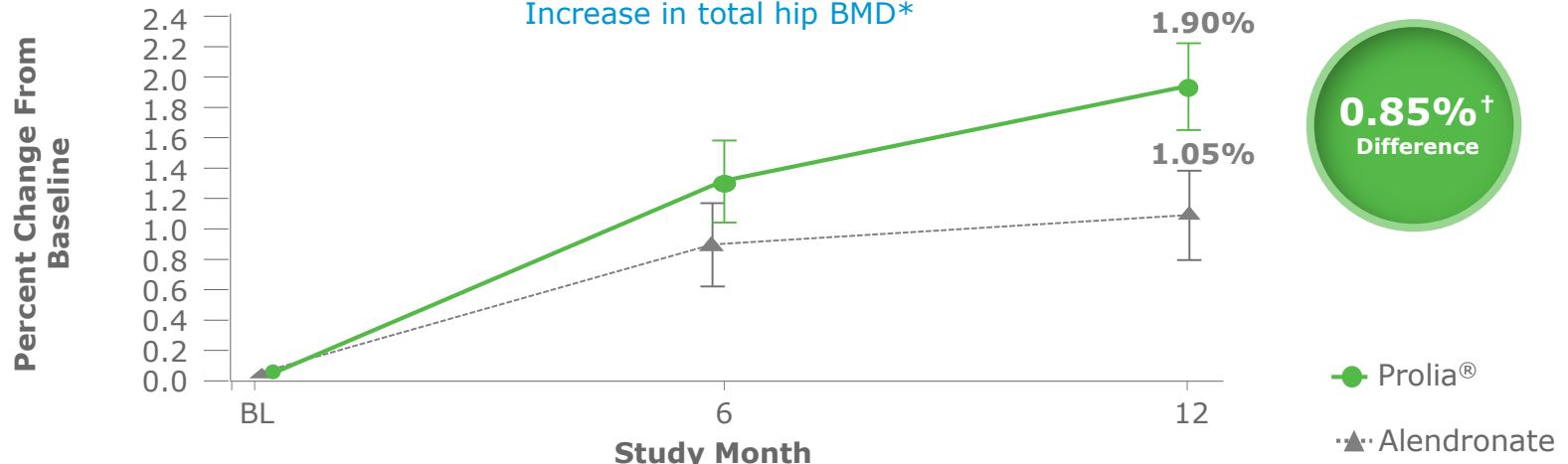
1. If noninferiority of denosumab for total hip BMD at month 12 was demonstrated by a lower bound of the 95% CI to be greater than -0.35%, then;
2. Superiority for the percent reduction in CTX-1 at month 3 would be tested, and if the p value was < 0.05, superiority would be stated, and;
3. Superiority of total hip BMD at month 12 would be tested; if the p value was < 0.05, then superiority would be demonstrated, and;
4. Noninferiority at the lumbar spine would be tested and demonstrated if the lower bound of the 95% CI was greater than -0.22%

QW = once a week; SC = subcutaneous; Q6M = every 6 months; BMD = bone mineral density; CTX-1 = type 1 C-telopeptide.  
Kendler DL et al. J Bone Miner Res. 2010;25:72-78.

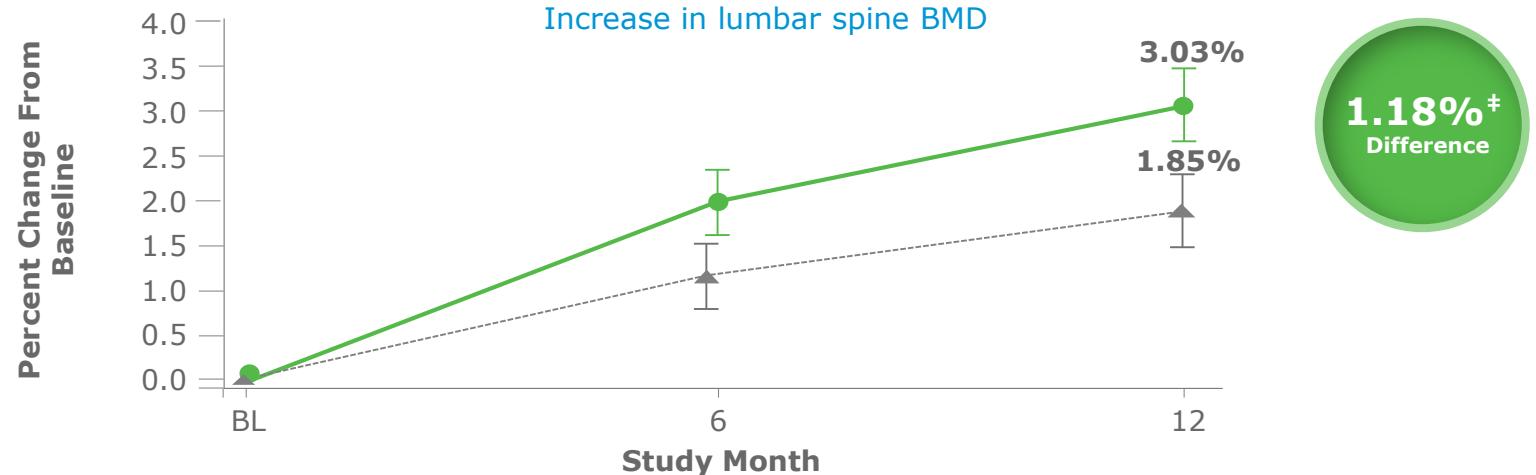
**Prolia®  
(denosumab)  
showed  
statistically  
significant  
changes in total  
hip and lumbar  
spine BMD  
at 12 months with  
patients who  
transitioned from  
alendronate**

BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy. Head-to-head fracture studies have not been conducted.

## Prolia® demonstrated noninferiority and superiority (vs alendronate) in total hip BMD



## Prolia® demonstrated noninferiority and showed statistically significant changes in lumbar spine BMD



\*Primary efficacy endpoint; †95% CI, 0.44%–1.25%,  $p < 0.01$ ; ‡95% CI, 0.63–1.73,  $p < 0.01$ . The lower limit of the CI excluded the prespecified noninferiority margin (−0.35% for total hip), thus showing the noninferiority of Prolia® compared with alendronate. The lower limit of the CI excluded the prespecified noninferiority margin (−0.22% for lumbar spine), thus showing the noninferiority of Prolia® compared with alendronate.  
Kandler DL, et al. *J Bone Miner Res*. 2010;25:72–81.

**Overall, a similar number of participants in each treatment group reported adverse events (AEs) during the study (78% Prolia®, 79% alendronate)**

Event	Prolia® (N = 253) n (%)	Alendronate (N = 249) n (%)
<b>Any AE</b>	197 (77.9)	196 (78.7)
<b>Leading to study discontinuation</b>	3 (1.2)	2 (0.8)
<b>Death</b>	1 (0.4)	0 (0.0)
<b>Selected AEs</b>		
Clinical fractures*	8 (3.2)	4 (1.6)
Gastrointestinal-related disorders	58 (22.9)	60 (24.1)
Infections	111 (43.9)	93 (37.3)
Neoplasms (benign or malignant)	9 (3.6)	9 (3.6)
<b>Serious AEs</b>	15 (5.9)	16 (6.4)
<b>Selected serious AEs</b>		
Infections	1 (0.4)	3 (1.2)
Neoplasms (benign or malignant)	3 (1.2)	3 (1.2)

**The most frequent AEs in the Prolia® and alendronate groups, respectively, were nasopharyngitis (13.4% and 10.8%), back pain (10.7% and 11.6%), bronchitis (6.3% and 5.6%), arthralgia (5.9% and 10.4%), constipation (5.1% and 4.8%), and pain in an extremity (4.7% and 8.4%)**

\*On-study clinical fractures were as follows: Prolia®: 2 foot, 2 wrist, 1 radius, 1 fibula, 1 humerus, 1 pelvis, 1 rib, 1 tibia; alendronate: 1 foot, 1 wrist, 1 radius, 1 sacrum.  
Kendler DL, et al. *J Bone Miner Res.* 2010;25:72-81.

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## **Denosumab Adherence Preference Satisfaction (DAPS) study**

Consider the results of a randomized, open-label study of Prolia® vs alendronate<sup>1</sup>

1. Freemantle N, et al. *Osteoporos Int.* 2012;23:317-326.

# Comparing Prolia® (denosumab) vs alendronate in a randomized, open-label crossover study<sup>1</sup>

Subjects were postmenopausal women age 55 or older, with no prior bisphosphonate or denosumab treatment, and BMD between -2.0 and -4.0 at the lumbar spine, total hip, or femoral neck.

ALN = alendronate

DMAB = denosumab

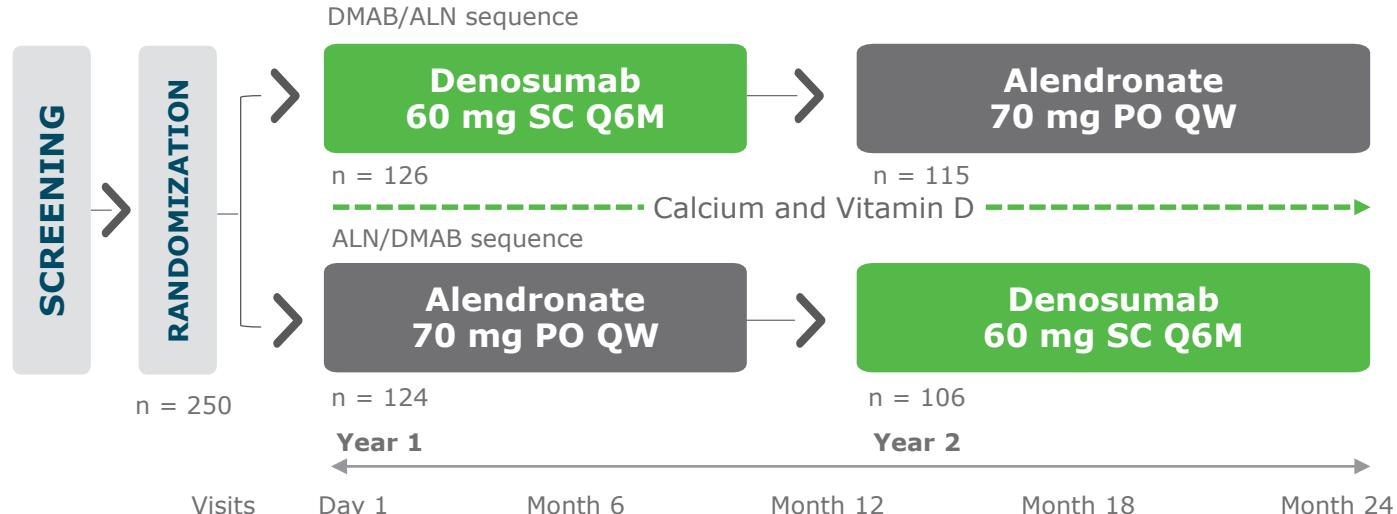
PO = by mouth

Q6M = once every 6 months

QW = once a week

SC = subcutaneous

**Patients were evaluated in treatment crossover sequences over 2 years<sup>1,\*</sup>**



## Primary Endpoint<sup>1</sup>

- Adherence during the first year (end of treatment period 1)

## Select Secondary Endpoints<sup>1,2</sup>

- Adherence to treatment at the end of treatment period 2
- Subject preference at the end of year 2, as assessed in a validated Preference and Satisfaction Questionnaire (PSQ)
- Proportion of subjects satisfied with treatment at the end of each treatment period, as assessed in the PSQ

## Study Design Limitations

- **Consider open-label study limitations when interpreting results. This open-label study was not blinded and not controlled**
- Patients knew their adherences and BMD were being monitored, which may have influenced treatment adherence
- Use of 1-year treatment periods limits conclusions that can be made about long-term compliance
- Provision of medication in this study removed any influence of treatment cost on adherence
- Adherence results measures in clinical studies are higher than in clinical practice

\*For subjects who wished to withdraw from treatment in treatment period 1 prior to the month 12 visit but still remain in the study, the treatment crossover could occur any time prior to the month 12 visit.

1. Freemantle N, Satram-Hoang S, Tang ET, et al. *Osteoporos Int.* 2012;23:317-326; 2. Data on file, Amgen; 2011.

**At both 12  
and 24  
months,  
a greater percentage  
of patients were  
adherent on Prolia®  
(denosumab)  
vs alendronate<sup>1</sup>**

**Prolia® compliance:**

Received 2 Prolia® injections 6 months apart ( $\pm$  4 weeks)

**Prolia® persistence:**

Received both injections and completed treatment within the allotted time

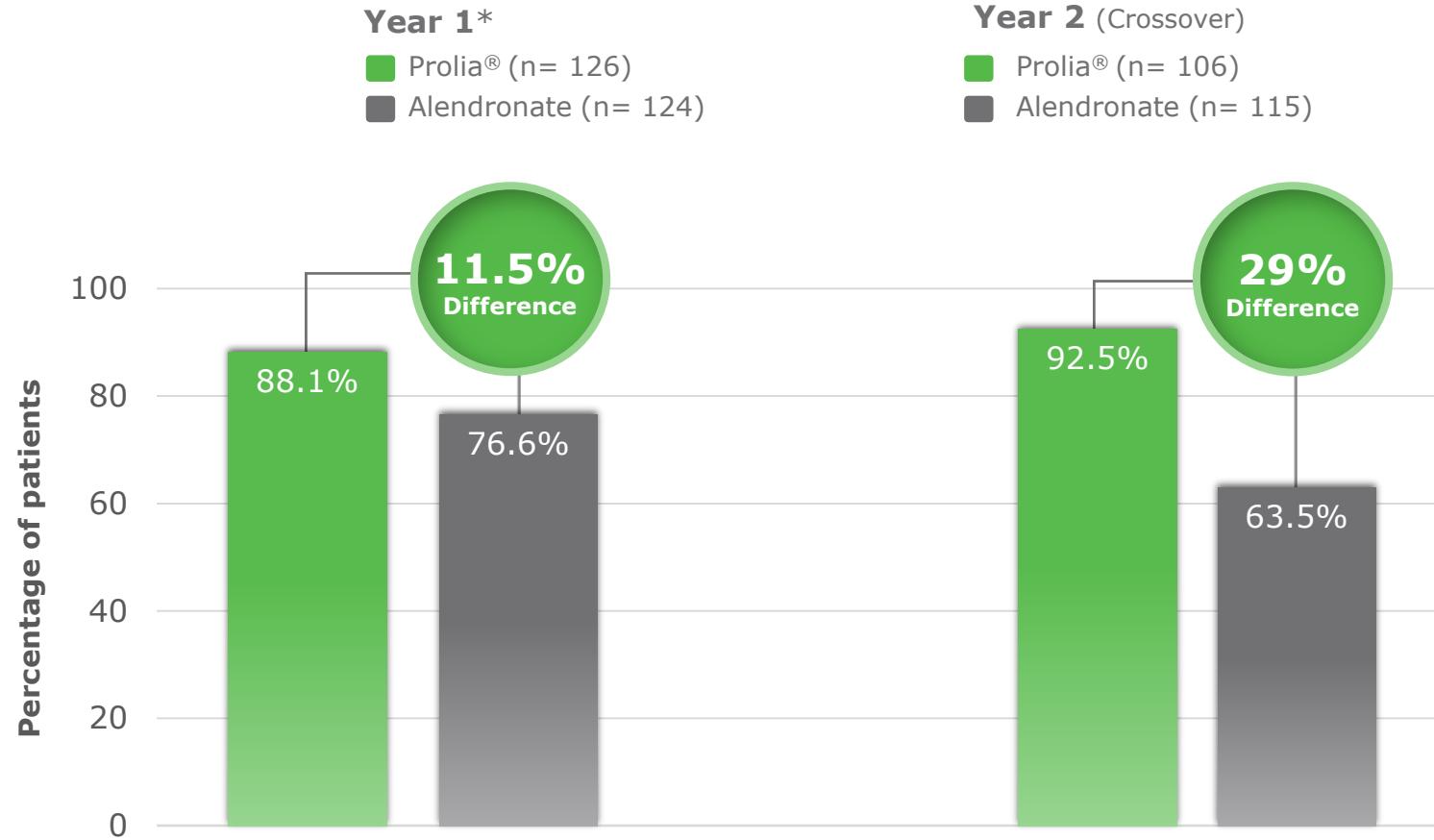
**Alendronate compliance:**

Took  $\geq$  80% of once-weekly tablets

**Alendronate persistence:**

Took  $\geq$  2 tablets in the last month and completed treatment within the allotted time

## Treatment adherence<sup>1</sup>



**Results suggest a treatment sequence effect (treatment-by-period interaction):** Adherence rates in the alendronate group were lower after crossover from Prolia®, and rates were higher in the Prolia® group after crossover from alendronate. Transitioning from biannual to weekly administration may have been more difficult than the converse<sup>1</sup>

Adherence was defined as a composite of being both compliant and persistent with therapy.<sup>1</sup>

\*Primary endpoint

1. Freemantle N, Satram-Hoang S, Tang ET, et al. *Osteoporos Int.* 2012;23:317-326.

# The Preference and Satisfaction Questionnaire (PSQ) is a validated instrument

## Preference<sup>1</sup>

Patients' preference for Prolia® (denosumab) was not affected by treatment sequence (before or after alendronate)

## Satisfaction<sup>1,\*</sup>

Through a PSQ, patients reported their level of satisfaction with either Prolia® (6-month injection) or alendronate (weekly pill) on a 5-point scale (not at all, a little, moderately, quite, or very satisfied)

More patients reported that they were "quite" or "very" satisfied with Prolia® than alendronate (at 12 and 24 months, combined) in terms of:

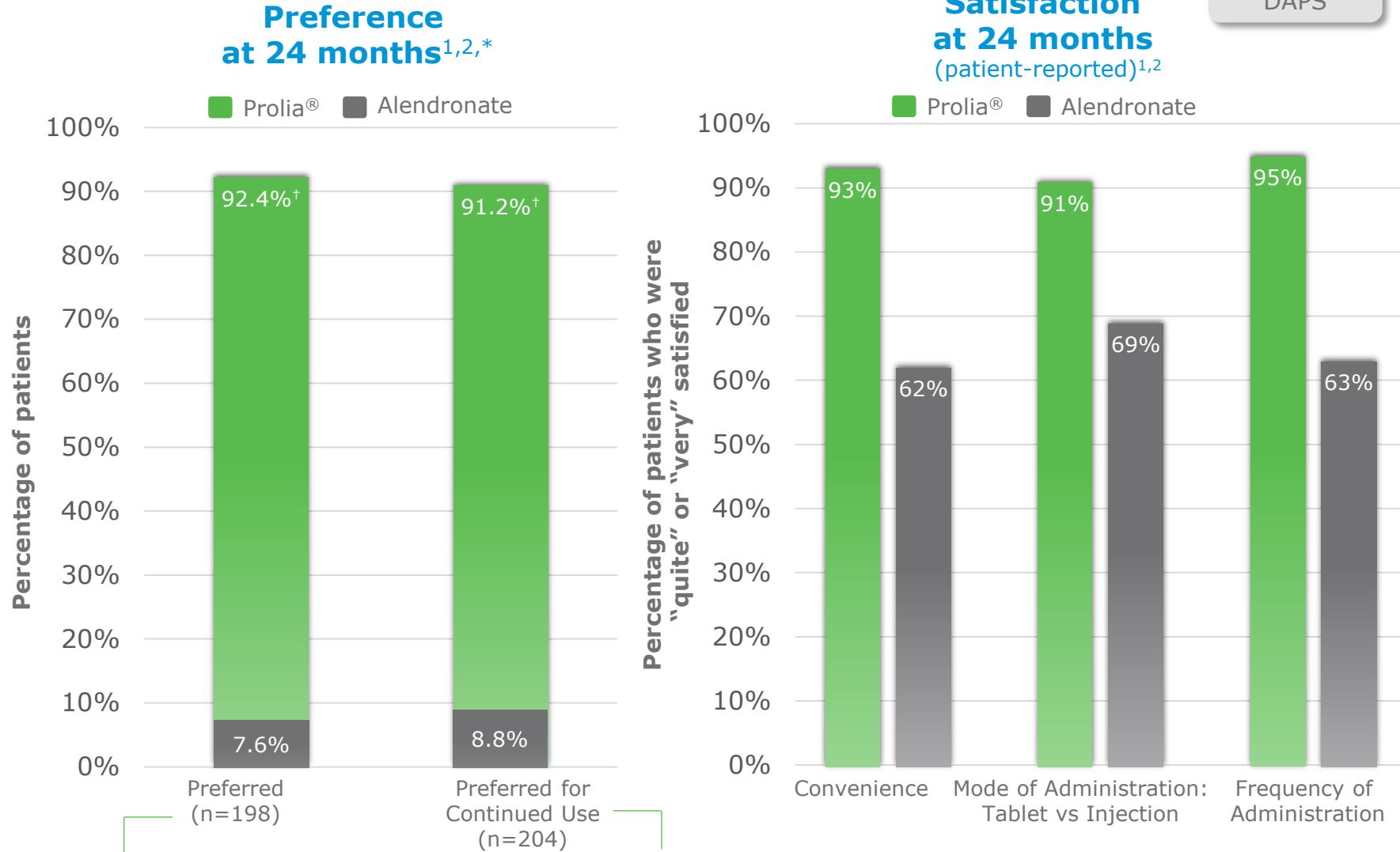
- Convenience (93% with Prolia®; 62% with alendronate)
- Mode of administration: tablet or injection (91% with Prolia®; 69% with alendronate)
- Frequency of administration (95% with Prolia®; 63% with alendronate)

Patients' satisfaction for Prolia® was not affected by treatment sequence.

\*Satisfaction includes combined data from both groups in both periods.

1. Freemantle N, Satram-Hoang S, Tang ET, et al. *Osteoporos Int.* 2012;23:317-326.

# More patients expressed overall preference and greater satisfaction with Prolia® (denosumab) (vs alendronate)<sup>1,2</sup>



*Assessed via PSQ by asking:*  
"Which do you prefer: the weekly pill, the 6-month injection, or no preference?"

\*Graph reflects the more than 93% of respondents who expressed a preference for one treatment over the other.  
<sup>†</sup>p < 0.0001.

1. Freemantle N, Satram-Hoang S, Tang ET, et al. *Osteoporos Int.* 2012;23:317-326; 2. Data on file, Amgen; 2011.

**Overall, a similar number of participants in each treatment group reported adverse events (AEs) (65.7% on Prolia®, 63.2% on alendronate)<sup>1,2</sup>**

<b>Event</b>	<b>Overall Study</b>	
	<b>Prolia® (N = 230) n (%)</b>	<b>Alendronate (N= 228) n (%)</b>
<b>Any AE</b>	151 (65.7)	144 (63.2)
<b>Serious AEs</b>	8 (3.5)	9 (3.9)
<b>AEs of fracture*</b>	4 (1.7)	2 (0.9)
AEs of osteoporotic fracture <sup>†</sup>	3 (1.3)	1 (0.4)
<b>AEs ≥ 5% frequency in either treatment group</b>		
Arthralgia	14 (6.1)	15 (6.6)
Pain in extremity	14 (6.1)	9 (3.9)
Back pain	9 (3.9)	13 (5.7)
Osteoarthritis	8 (3.5)	8 (3.5)
Headache	7 (3.0)	10 (4.4)
Cough	6 (2.6)	11 (4.8)

#### **Serious Adverse Events<sup>1,2</sup>**

- The only serious adverse event in more than 1 subject was osteoarthritis, which was reported for three (1.3%) subjects during Prolia® treatment
- No deaths, osteonecrosis of the jaw, or atypical femoral fractures were reported

Includes only treatment-emergent adverse events occurring on or before the end of the specific treatment period.

N= number of patients reporting at least 1 dose of study drug during the specific treatment period

n= number of patients at least one adverse event during the specific treatment period.

\*On-study fractures were as follows: Prolia®- 2 foot, 1 pubis, 1 ulna; alendronate - 1 fibula, 1 humerus.

<sup>†</sup>On -study osteoporotic fractures were as follows: Prolia®- 2 foot, 1 ulna; alendronate - 1 humerus.

1. Freemantle N, Satram-Hoang S, Tang ET, et al. *Osteoporos Int.* 2012;23:317-326.; 2. Data on file, Amgen; 2011.

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The effects of  
**transitioning to Prolia® (denosumab)  
or zoledronic acid (ZOL)**  
on bone mineral density in postmenopausal osteoporosis

Miller PD, et al. *J Clin Endocrinol Metab.* 2016;101:3163-3170.

# Evaluating the effect of **Prolia®** **(denosumab)** **or zoledronic acid** after transitioning from an oral bisphosphonate<sup>1</sup>

## **OBJECTIVE:**<sup>1</sup>

The objective of the study was to compare the effect of transitioning from oral bisphosphonates to Prolia® or zoledronic acid (ZOL) on bone mineral density (BMD) and bone turnover

## **BACKGROUND:**<sup>1</sup>

Osteoporosis is a chronic, progressive condition that generally requires long-term management

## **METHODS:**<sup>1</sup>

- 1-year, multicenter, international, randomized, double-blind, double-dummy, active-controlled, parallel-group trial
- Subjects were randomized 1:1 to one of two treatment arms
- Participants were required to take 1,000 mg or greater elemental calcium and 800 IU or greater vitamin D daily
- DXA scans were performed in duplicate at baseline and month 12 or early termination visit for the lumbar spine and left proximal femur (for total hip and femoral neck), unless the left was unsuitable for analysis, in which case the right was used; and nondominant forearm (1/3 radius).

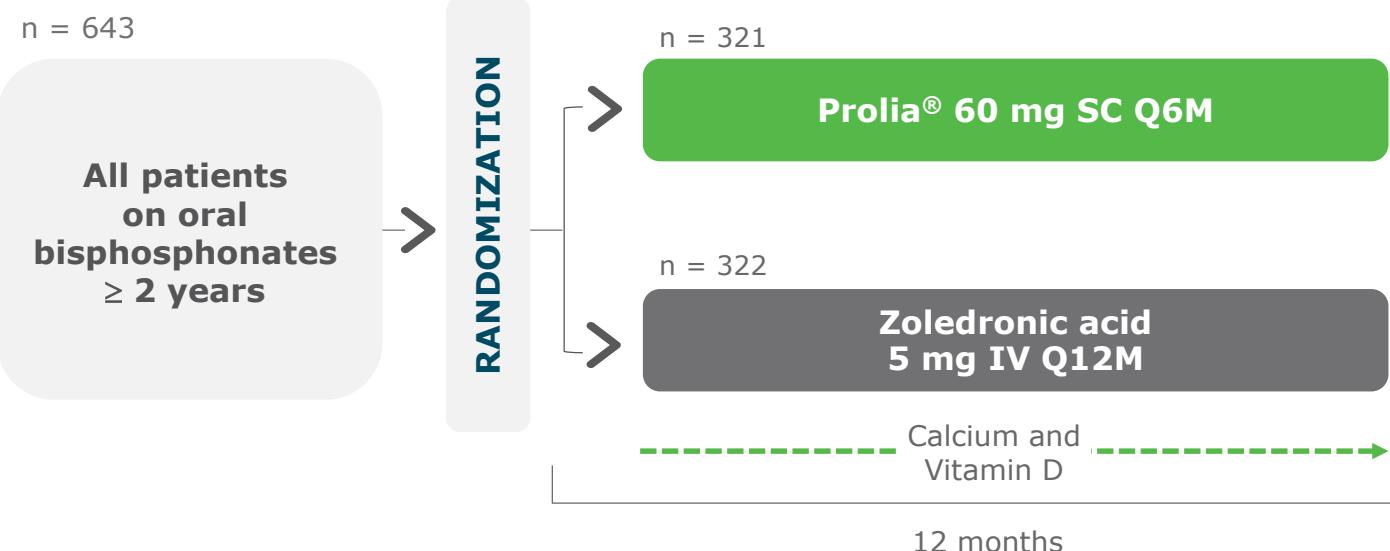
IU = international unit.

1. Miller PD, et al. *J Clin Endocrinol Metab.* 2016;101:3163-3170.

## Study design

# Evaluating the effect of Prolia® (denosumab) or zoledronic acid after transitioning from an oral bisphosphonate<sup>1</sup>

## Patients transitioning to Prolia® or zoledronic acid were evaluated<sup>1</sup>



### Primary Endpoint<sup>1</sup>

- Mean percent change from baseline in lumbar spine BMD at month 12

### Select Additional Endpoints<sup>1</sup>

- Mean percent change from baseline in total hip BMD at month 12
- Safety endpoints for all subjects who received 1 or more doses of study drug
- Postmenopausal women aged 55 or older who received oral bisphosphonate therapy for ≥ 2 years or longer immediately before screening

### Key Inclusion Criteria<sup>1</sup>

- T-score of -2.5 or less at the lumbar spine, total hip, or femoral neck, two or more lumbar vertebrae, and one hip and baseline serum CTX-1 of ≤500 pg/mL

BMD = bone mineral density; Q6M = once every 6 months; Q12M = once every 12 months; SC = subcutaneous;  
CTX-1 = C-telopeptide of type 1 collagen.

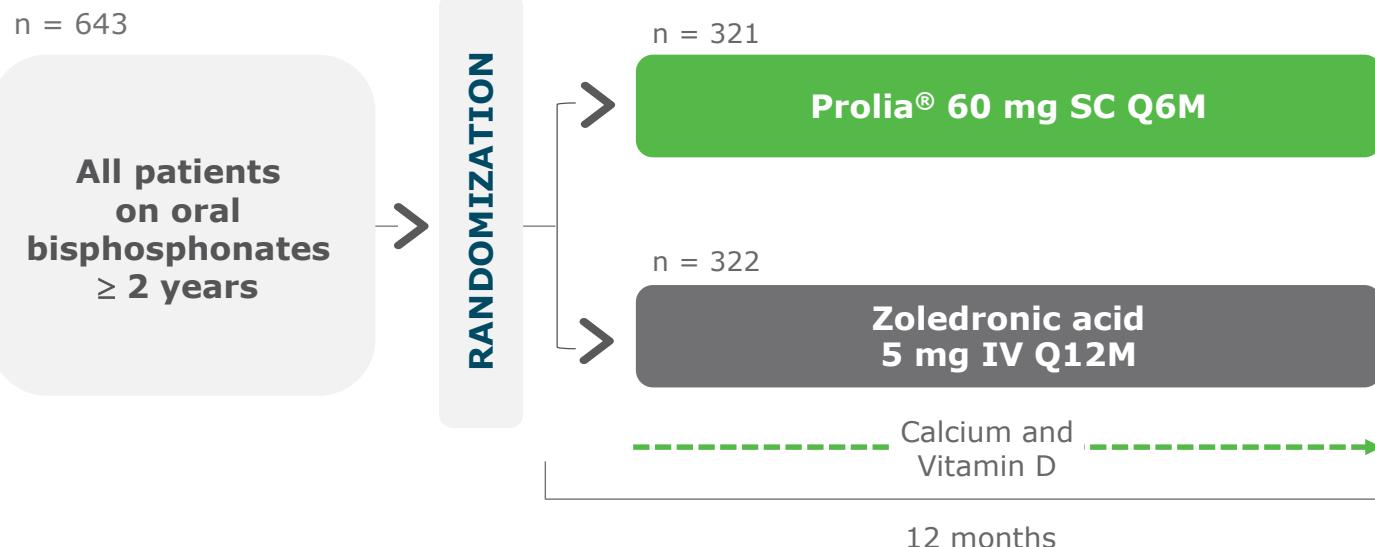
1. Miller PD, et al. *J Clin Endocrinol Metab.* 2016;101:3163-3170

## Study design

# Evaluating the effect of Prolia® (denosumab) or zoledronic acid after transitioning from an oral bisphosphonate<sup>1</sup>

## Statistical Analysis<sup>1</sup>

- The primary hypothesis\* was that treatment with denosumab was not inferior to ZOL for the mean percentage change from baseline in lumbar spine BMD at month 12 based on a margin of -0.46%<sup>1</sup>
- Secondary hypotheses included:<sup>1</sup>
  - Noninferiority in total hip BMD with Prolia® vs ZOL based on a margin of -0.51%
  - Superiority of denosumab for the mean percentage change from baseline in lumbar spine BMD at month 12
  - Superiority of denosumab for the mean percentage change from baseline in total hip BMD at month 12
- Only if the primary noninferiority hypothesis was demonstrated was the individual secondary hypothesis tested in the prespecified sequence



BMD = bone mineral density; Q6M = once every 6 months; Q12M = once every 12 months; SC = subcutaneous.

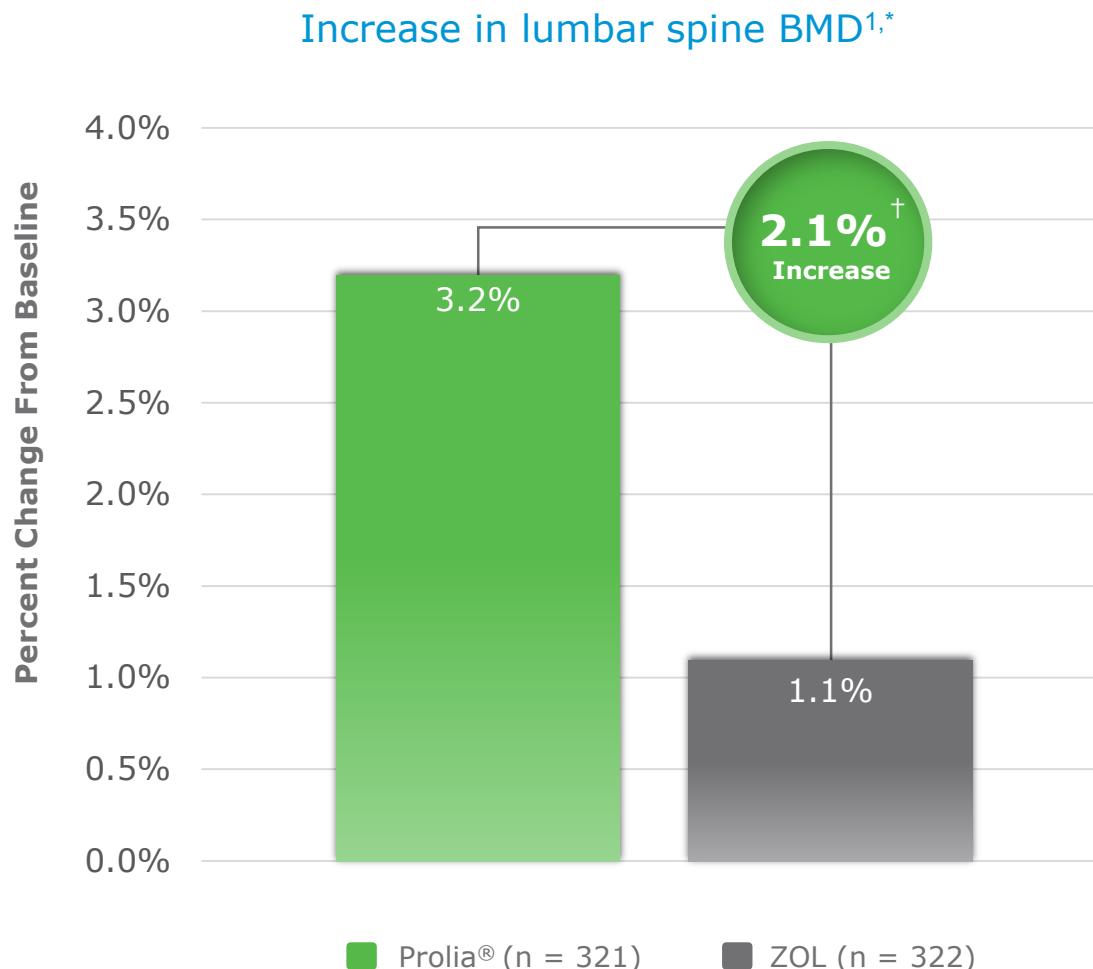
\* A stepdown sequential testing procedure was used to maintain the overall type I error rate at 5% among BMD endpoints.

1. Miller PD, et al. *J Clin Endocrinol Metab*. 2016;101:3163-3170

# Prolia® (denosumab) demonstrated noninferiority and superiority (vs zoledronic acid) in lumbar spine BMD at 12 months

BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy. Head-to-head fracture studies have not been conducted

## Lumbar spine BMD were evaluated in patients transitioning to Prolia® or zoledronic acid (ZOL)<sup>1</sup>



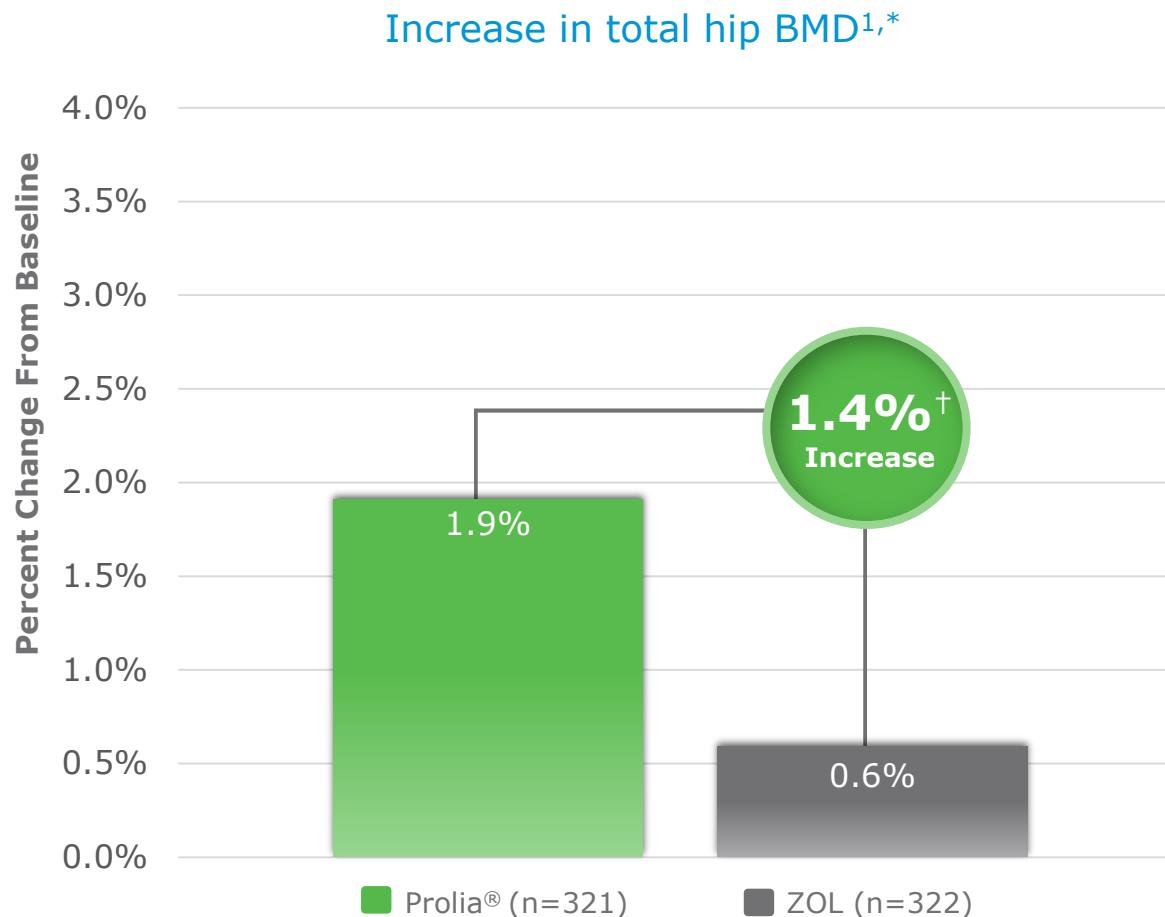
\*Primary efficacy endpoint.

<sup>†</sup>(95% CI 1.6% - 2.6%),  $p < 0.0001$  for noninferiority and superiority.  
1. Miller PD, et al. *J Clin Endocrinol Metab*. 2016;101:3163-3170.

**Total hip BMD were evaluated in patients transitioning to Prolia® or zoledronic acid (ZOL)<sup>1</sup>**

**Prolia®  
(denosumab)  
demonstrated  
noninferiority  
and superiority  
(vs zoledronic acid)  
in total hip BMD  
at 12 months**

BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy. Head-to-head fracture studies have not been conducted



\*Primary efficacy endpoint.

†(95% CI 1.0% – 1.7%),  $p < 0.0001$  for noninferiority and superiority.

1. Miller PD, et al. *J Clin Endocrinol Metab*. 2016;101:3163-3170.

**Overall, a similar number of participants in each treatment group** reported adverse events (AEs) during the study (62.2% in each treatment group)<sup>1</sup>

Event	Prolia® (denosumab) (N = 320) n (%)	zoledronic acid (N = 320) n (%)
<b>All AEs</b>	199 (62.2)	199 (62.2)
<b>Serious AEs</b>	25 (7.8)	29 (9.1)
<b>AEs leading to discontinuation of study drug</b>	4 (1.3)	9 (2.8)
<b>Fatal AEs</b>	0 (0.0)	1 (0.3)
<b>Selected AEs of interest</b>		
Atypical femoral fracture	2 (0.6)	1 (0.3)
AEs potentially related to hypersensitivity	12 (3.8)	6 (1.9)
Serious infection	5 (1.6)	6 (1.9)
Malignancy	5 (1.6)	8 (2.5)
Cardiac disorders	11 (3.4)	4 (1.3)
Vascular disorders	13 (4.1)	16 (5.0)
Eczema*	5 (1.6)	1 (0.3)
Musculoskeletal pain	43 (13.4)	63 (19.7)

N = number of subjects who received 1 or more doses of study drug; n = number of subjects reporting 1 or more events.

\*Events included eczema, dermatitis, and allergic dermatitis.

1. Miller PD, et al. *J Clin Endocrinol Metab*. 2016;101:3163-3170.

# Prolia® (denosumab) helps you treat patients at high risk for fracture with 5 indications<sup>1</sup>



Postmenopausal  
osteoporosis

**Studying the effect  
of transitioning to  
Denosumab or  
Zoledronic Acid on  
BMD**

**Click to view >**



Breast cancer  
treatment-induced  
bone loss due to hormone  
ablation therapy

**Hormone Ablation Therapy  
(HALT) Pivotal Trials**

**Click to view >**



Prostate cancer  
treatment-induced  
bone loss due to  
hormone ablation therapy

**FDA-  
APPROVED  
2012<sup>5</sup>**

Osteoporosis in  
men

**Prolia® for treatment  
of osteoporosis  
in men**

**Click to view >**



Glucocorticoid-  
induced  
osteoporosis

**Head-to-Head Study  
of Patients with  
Glucocorticoid-  
Induced Osteoporosis**

**Click to view >**

BMD = bone mineral density.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Prolia® (denosumab) FDA approval letter. June 1, 2010; 3. Prolia® (denosumab) FDA approval letter. September 16, 2011; 4. Prolia® (denosumab) FDA approval letter. September 16, 2011; 5. Prolia® (denosumab) FDA approval letter. September 20, 2012; 6. Prolia® (denosumab) FDA approval letter. May 18, 2018.



This concludes our presentation  
**THANK YOU**

## **Hormone AbLation Therapy (HALT)-induced bone loss**

Prolia® (denosumab) is the only FDA-approved therapy for cancer treatment-induced bone loss due to hormone ablation therapy

# Rapid bone loss is a complication of Hormone Ablation Therapy (HALT) used for treatment of prostate and breast cancer

## Androgen-deprivation therapy (ADT)

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- ADT suppresses androgen levels and androgen-receptor-mediated effects at the tissue level
- About 50% of men with prostate cancer will use ADT at some point during their disease<sup>1</sup>

## Aromatase inhibitor (AI) therapy

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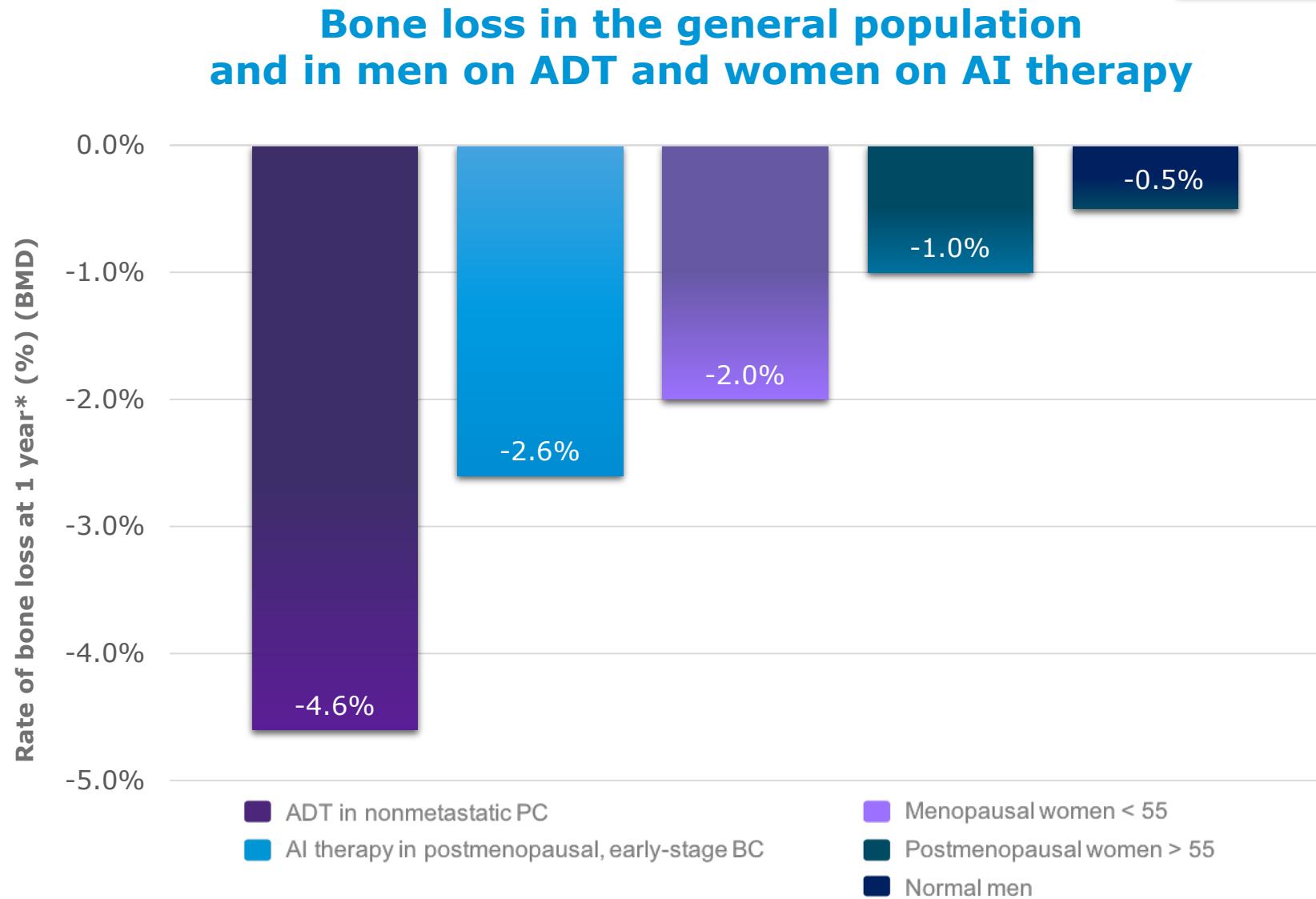
- In postmenopausal women, a small amount of estrogen is produced in fat tissue by the enzyme aromatase
- AIs block aromatase from making estrogen
- Clinical guidelines recommend treatment with AIs for ER+ breast cancer for up to 10 years<sup>2</sup>

ER+ = estrogen receptor positive

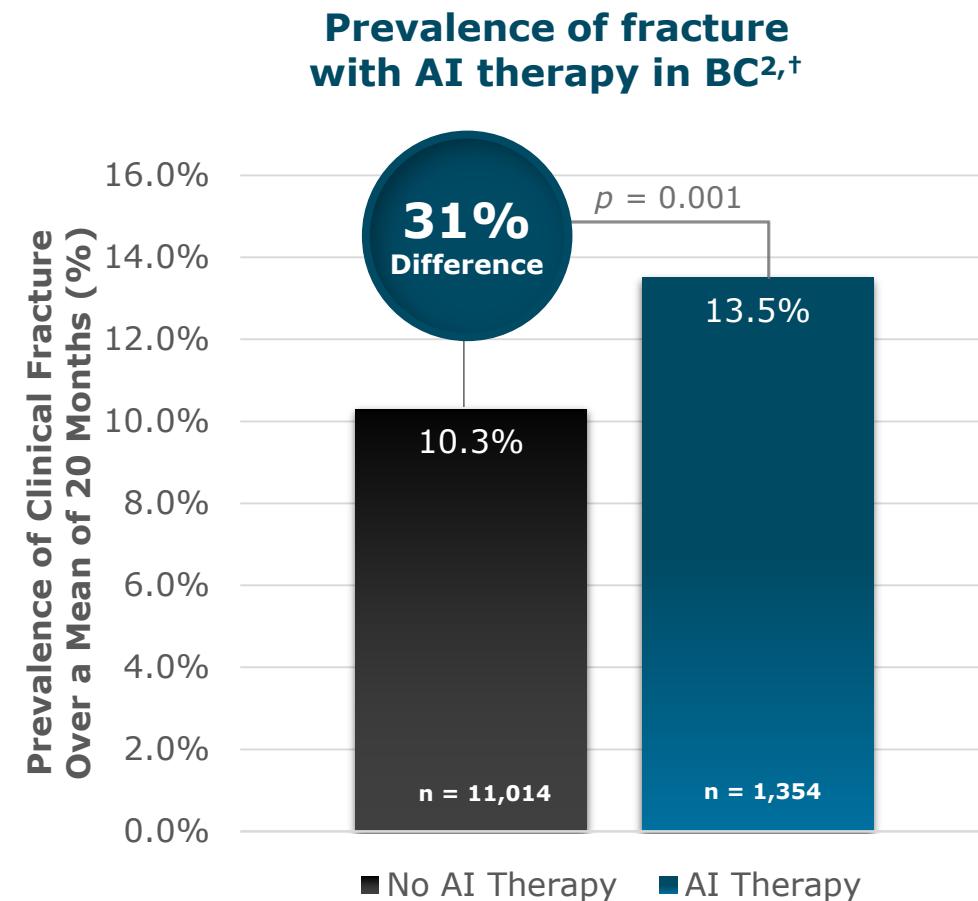
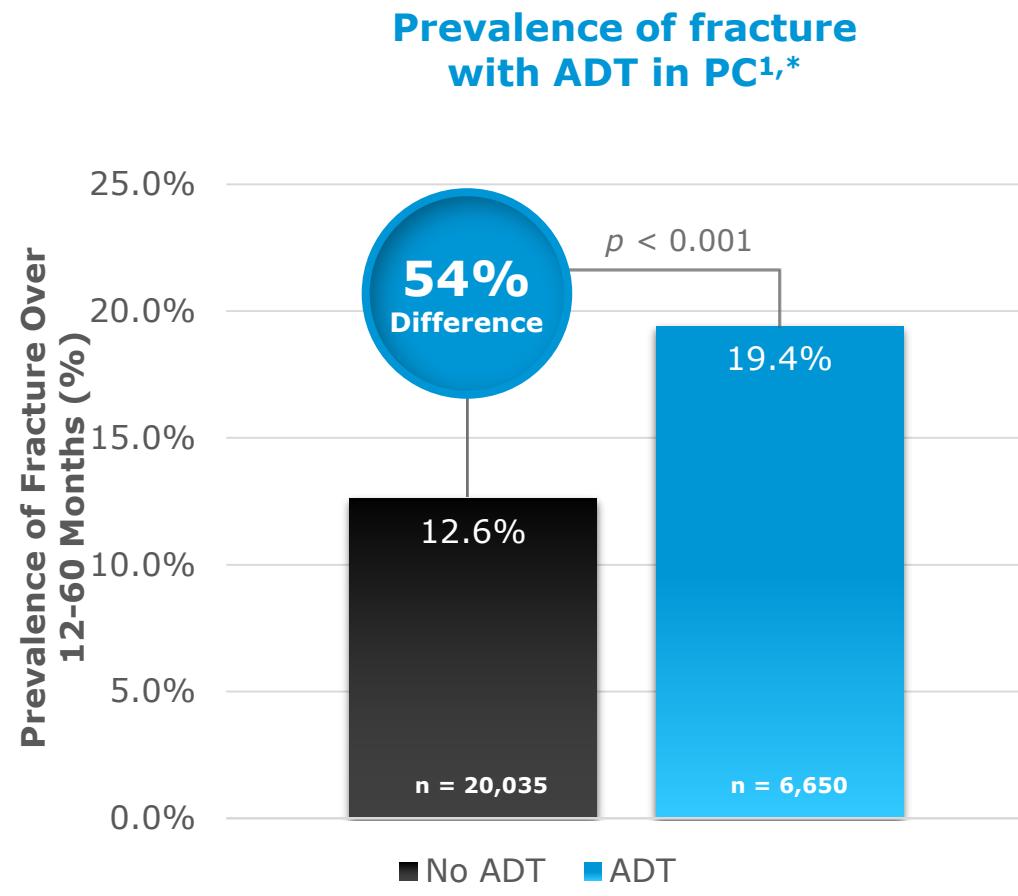
1. Meng MV, et al. *Urology*. 2002;60(3 suppl 1):7-11; 2. Burstein HJ. *J Clin Oncol*. 2018 Nov 19;JCO1801160. doi: 10.1200/JCO.18.01160.

# Androgen-Deprivation Therapy (ADT) and Aromatase Inhibitor (AI) Therapy induces bone loss

Reference data were obtained from prospective studies that measured bone loss at different sites (e.g., lumbar spine or total hip)



# ADT and AI are associated with increased fracture risk



\*Data from a toxic effect subanalysis of a study of men in the linked database of the National Cancer Institute's SEER program and Medicare with PC diagnosis in 1992–1997; †Data from a claims-based retrospective cohort study covering the years 1998–2005 involving patients with and without bone metastases. ADT was gonadotropin-releasing hormone, agonist therapy, or orchectomy.

SEER = Surveillance, Epidemiology, and End Results.

1. Shahinian VB, et al. *N Engl J Med*. 2005;352:154-164; 2. Mincey BA, et al. *Clin Breast Cancer*. 2006;7:127-132.

# Prolia® (denosumab) is approved for men receiving androgen-deprivation therapy (ADT) for prostate cancer

**INDICATION:** Prolia® is indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.

In these patients Prolia® also reduced the incidence of vertebral fractures.

## CONTRAINDICATIONS

---

**Prolia® is contraindicated in patients with hypocalcemia**

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®

---

**Prolia® may cause fetal harm when administered to a pregnant woman**

In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®

---

**Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product**

Reactions have included anaphylaxis, facial swelling, and urticaria

# Prolia® (denosumab) is approved for **women receiving adjuvant aromatase inhibitor (AI) therapy for breast cancer**

**INDICATION:** Prolia® is indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

## CONTRAINDICATIONS

---

**Prolia® is  
contraindicated in  
patients with  
hypocalcemia**

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®

---

**Prolia® may cause  
fetal harm when  
administered to a  
pregnant woman**

In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®

---

**Prolia® is contraindicated in  
patients with a history of  
systemic hypersensitivity  
to any component of the product**

Reactions have included anaphylaxis, facial swelling, and urticaria

Prolia®  
(denosumab)  
in prostate and  
breast cancer  
on HALT:

## Primary and select secondary endpoints

MEN with  
nonmetastatic  
prostate cancer  
receiving ADT

WOMEN with  
nonmetastatic  
breast cancer  
receiving AI  
therapy

### Primary Endpoint<sup>1,2</sup>

- Percentage change from baseline at month 24 in lumbar spine BMD

### Select Secondary Endpoints<sup>1,2</sup>

- Percentage change from baseline at month 36 in lumbar spine, total hip, and femoral neck BMD
- Incidence of newly diagnosed vertebral fracture over 36 months

### Primary Endpoint<sup>2,3</sup>

- Percentage change in lumbar spine BMD from baseline to 12 months

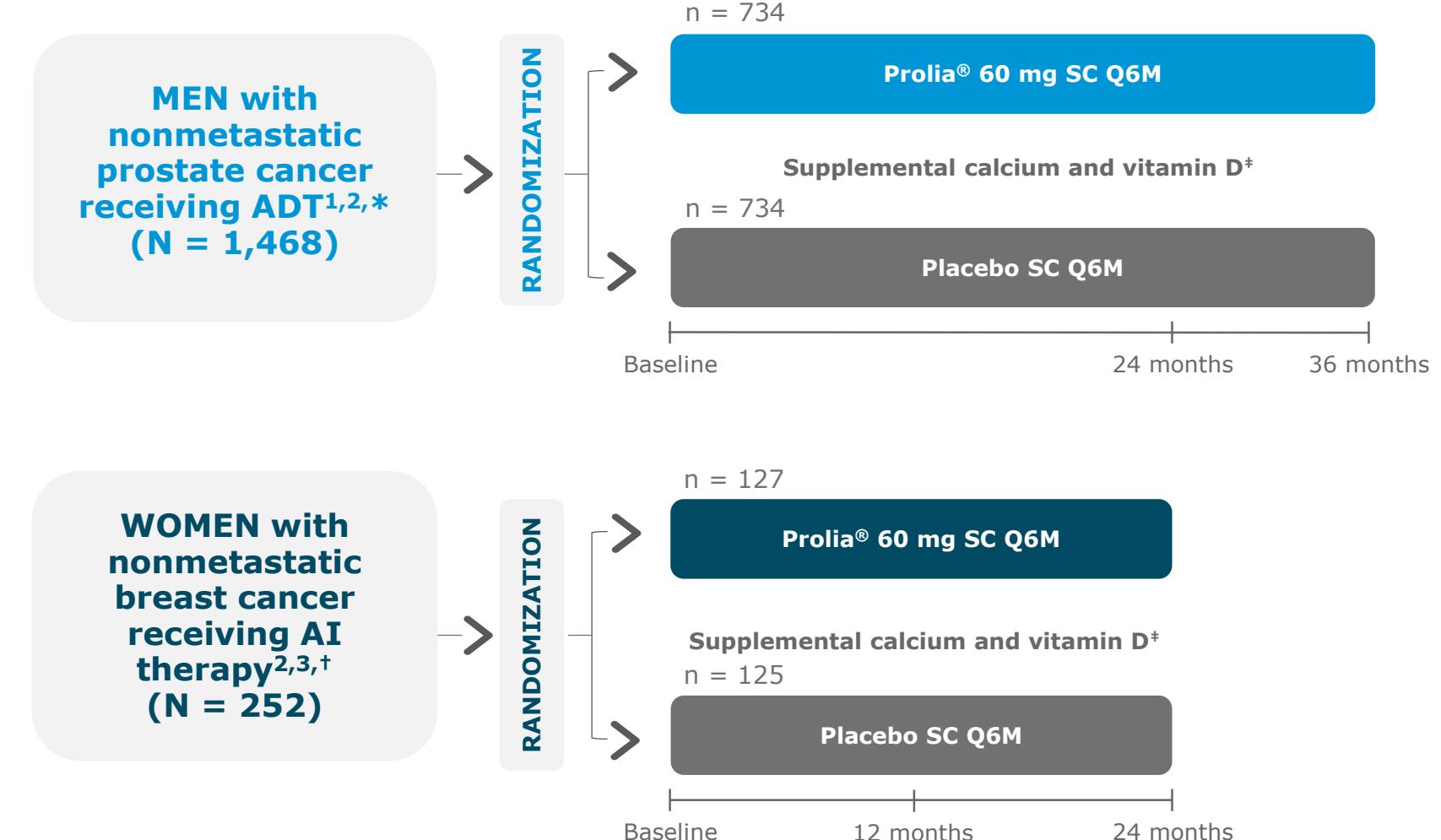
Percentage change in:

- Lumbar spine BMD from baseline to 24 months
- Total hip BMD from baseline to 24 months
- Femoral neck BMD from baseline to 24 months

1. Smith MR, et al. *N Engl J Med.* 2009;361:745-755; 2. Prolia® (denosumab) prescribing information, Amgen; 3. Ellis GK, et al. *J Clin Oncol.* 2008;26:4875-4882.

## Study design

**Prolia®  
(denosumab)  
in prostate  
and breast  
cancer  
patients on  
HALT:  
2 randomized,  
multinational,  
double-blind phase 3  
studies**



Q6M = once every 6 months; SC = subcutaneous.

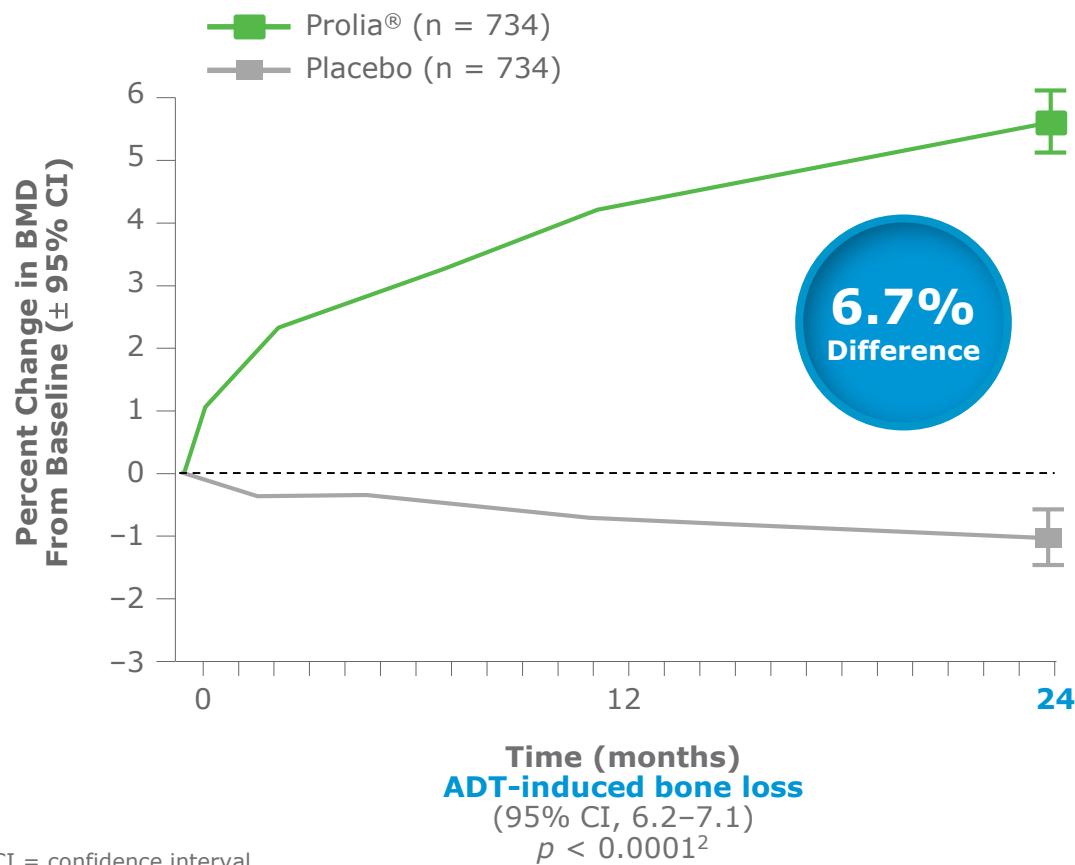
\*Eligible men had baseline spinal, total hip, or femoral neck BMD T-scores between -1.0 and -4.0 or a history of an osteoporotic fracture; †eligible women had baseline spinal, total hip, or femoral neck BMD T-scores between -1.0 to -2.5 and no fracture after age 25; ‡patients were instructed to take ≥ 1,000 mg of calcium and ≥ 400 IU of vitamin D supplementation daily.

1. Smith MR, et al. *N Engl J Med.* 2009;361:745-755; 2. Prolia® (denosumab) prescribing information, Amgen; 3. Ellis GK, et al. *J Clin Oncol.* 2008;26:4875-4882.

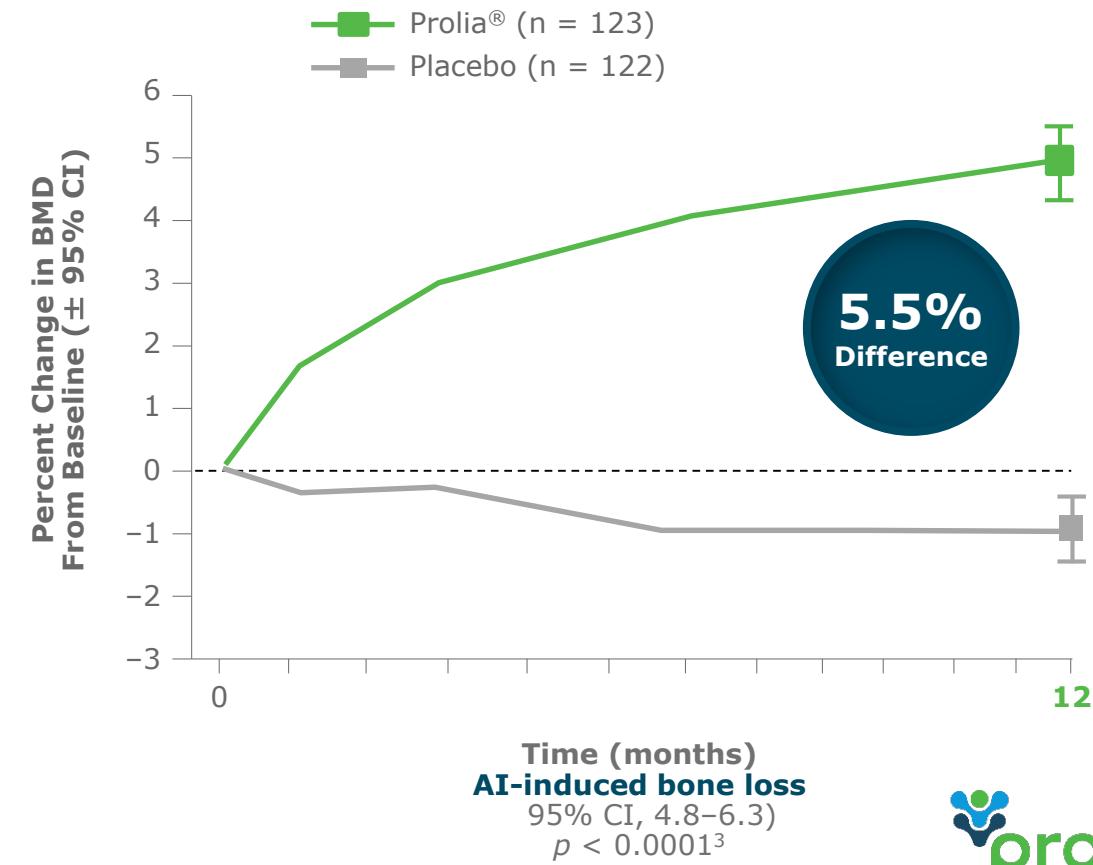
## Primary Endpoints

# Prolia® (denosumab) increased lumbar spine BMD compared with placebo

**Men with prostate cancer on ADT:  
change in lumbar spine BMD over 24 months<sup>1,2</sup>**



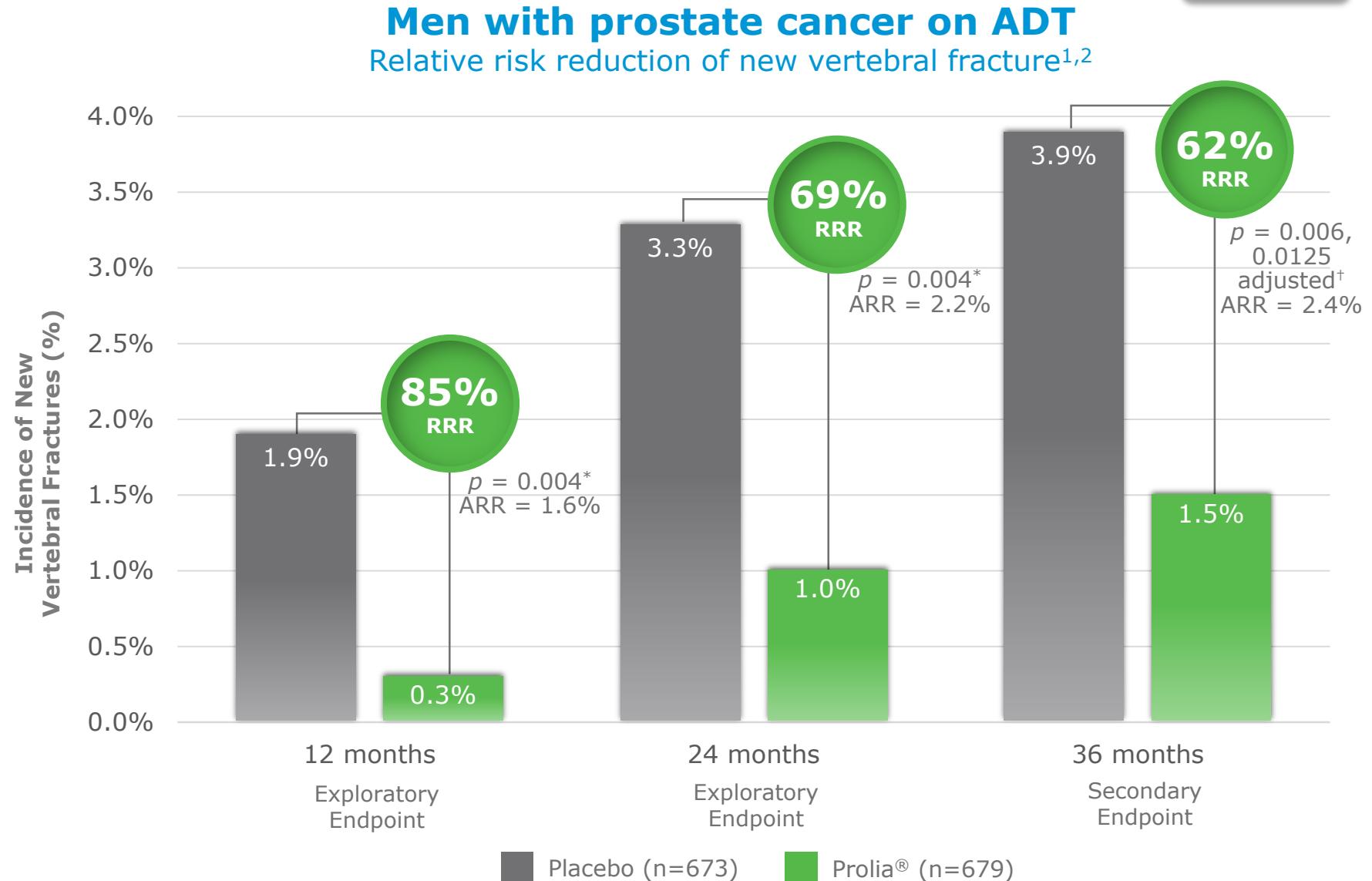
**Women with breast cancer on AI therapy:  
change in lumbar spine BMD over 12 months<sup>1,3</sup>**



1. Prolia® (denosumab) prescribing information, Amgen; 2. Smith MR, et al. *N Engl J Med.* 2009;361:745–755; 3. Ellis GK, et al. *J Clin Oncol.* 2008;26:4875–4882.

Exploratory and Secondary Endpoints

**Prolia® (denosumab) resulted in sustained reduction of new vertebral fractures in men with nonmetastatic prostate cancer at 36 months<sup>1</sup>**



Prolia® significantly decreased the incidence of new vertebral fractures up to 36 months.<sup>1</sup>

1. Smith MR, et al. *N Engl J Med.* 2009;361:745-755; 2. Prolia® (denosumab) prescribing information, Amgen.

# Prolia® (denosumab) helps you treat patients at high risk for fracture with 5 indications<sup>1</sup>



Postmenopausal  
osteoporosis

**Studying the effect  
of transitioning to  
Denosumab or  
Zoledronic Acid on  
BMD**

**Click to view >**



Breast cancer  
treatment-induced  
bone loss due to hormone  
ablation therapy

**Hormone Ablation Therapy  
(HALT) Pivotal Trials**

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Prostate cancer  
treatment-induced  
bone loss due to  
hormone ablation therapy

**FDA-  
APPROVED  
2012<sup>5</sup>**

Osteoporosis in  
men

**Prolia® for treatment  
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**Click to view >**



Glucocorticoid-  
induced  
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**Head-to-Head Study  
of Patients with  
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**Click to view >**

BMD = bone mineral density.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Prolia® (denosumab) FDA approval letter. June 1, 2010; 3. Prolia® (denosumab) FDA approval letter. September 16, 2011; 4. Prolia® (denosumab) FDA approval letter. September 16, 2011; 5. Prolia® (denosumab) FDA approval letter. September 20, 2012; 6. Prolia® (denosumab) FDA approval letter. May 18, 2018.



This concludes our presentation  
**THANK YOU**

Prolia® for  
**treatment of osteoporosis in men**

# Prolia® (denosumab) is approved for osteoporosis in men

**INDICATION:** Prolia® is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

## CONTRAINDICATIONS

---

**Prolia® is contraindicated in patients with hypocalcemia**

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®

---

**Prolia® may cause fetal harm when administered to a pregnant woman**

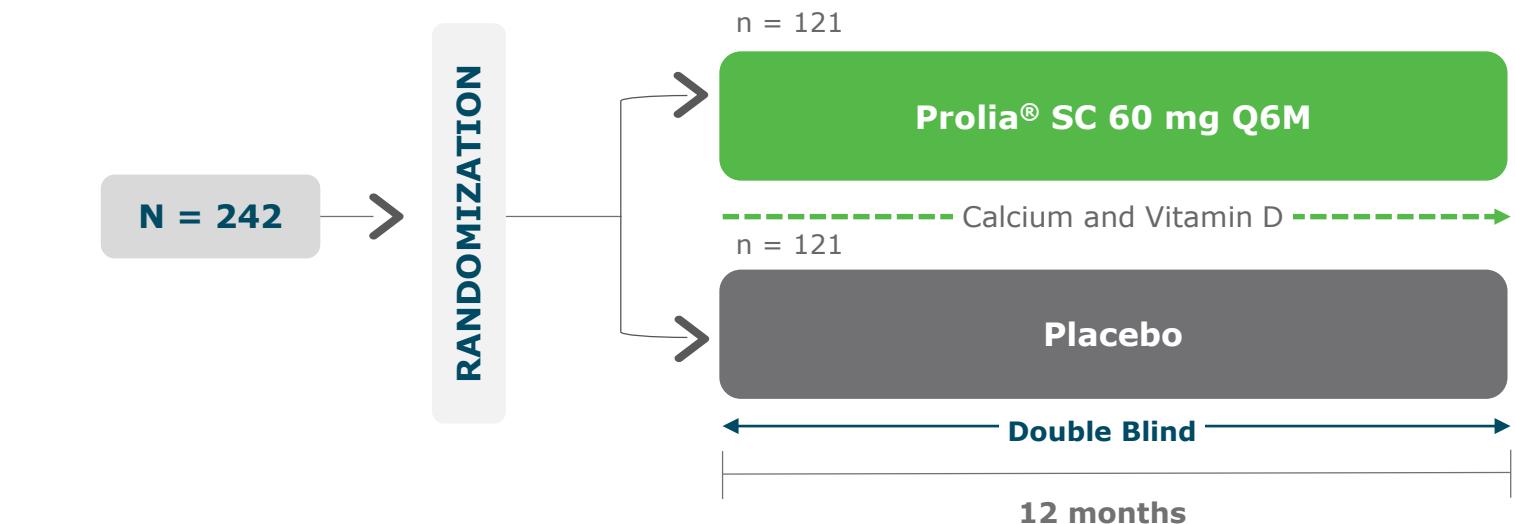
In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®

---

**Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product**

Reactions have included anaphylaxis, facial swelling, and urticaria

Study design  
A pivotal study  
evaluating  
**Prolia®**  
**(denosumab)**  
**in men with**  
**low BMD<sup>1</sup>**



**Key Inclusion Criteria<sup>1</sup>**

- Ambulatory men aged 30 to 85 years
- BMD value corresponding to:
  - T-score  $\leq -2.0$  and  $\geq -3.5$  at the lumbar spine or femoral neck, or
  - T-score  $\leq -1.0$  and  $\geq -3.5$  at the lumbar spine or femoral neck and history of major osteoporotic fracture
- At least 2 lumbar vertebrae, 1 hip, and 1 forearm evaluable by DXA

**Primary Endpoints<sup>1</sup>**

- Percent change from baseline in lumbar spine BMD at 12 months

**Secondary Endpoint<sup>1</sup>**

- Included percent change from baseline in BMD of the total hip and femoral neck

DXA = dual-energy X-ray absorptiometry; Q6M = once every 6 months; SC = subcutaneous.  
1. Orwoll E, et al. *J Clin Endocrinol Metab*. 2012;97:3161-3169.

# Demographics and baseline characteristics of men randomized in the study between two treatment groups<sup>1,2</sup>

Wide age range: **30 to 85**

Mean age: **65**

---

Mean BMD T-score from **-1.4 to -2.0** at lumbar spine, total hip, and femoral neck

---

**~39%** with history of any fractures

---

**~25%** had osteoporotic fractures\*, **~15%** had major osteoporotic<sup>†</sup> fractures and **~23%** had prevalent vertebral fracture

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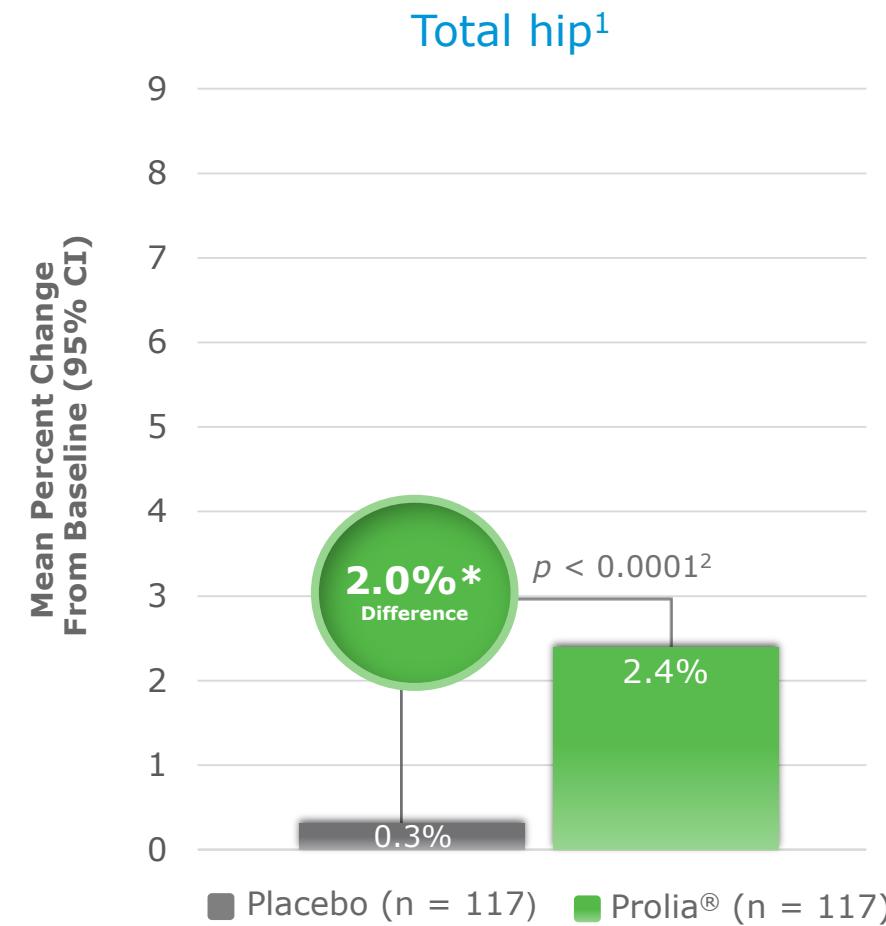
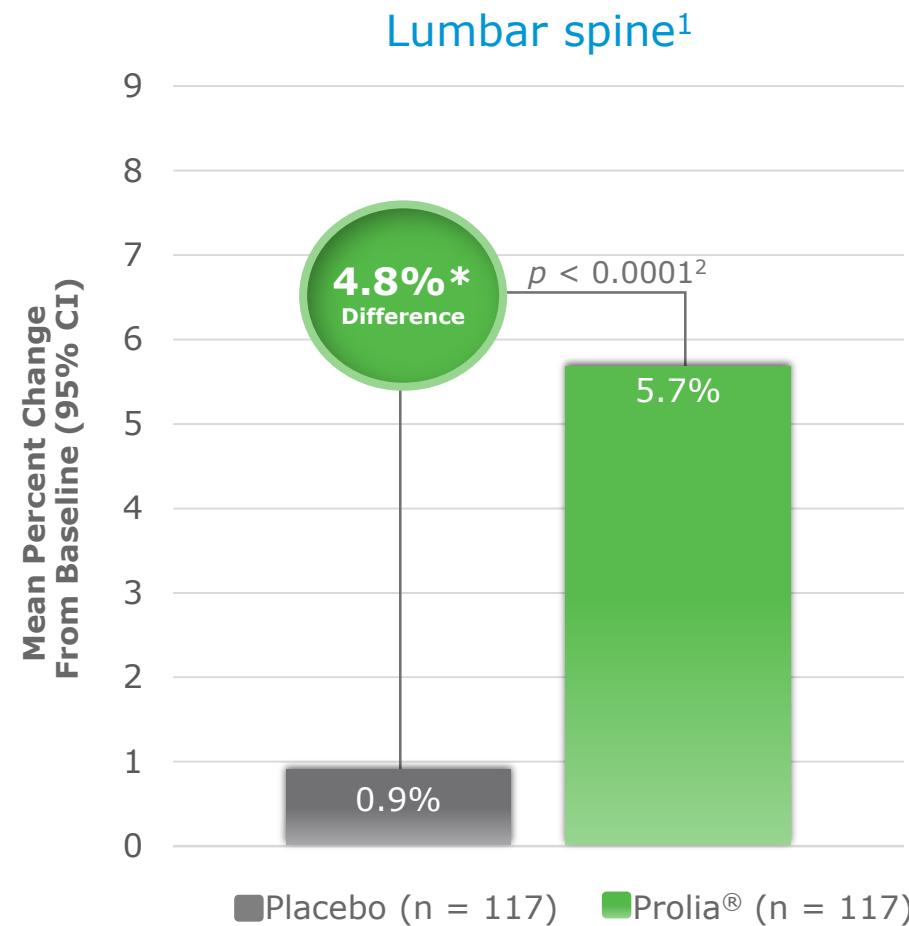
Mean total testosterone level of **362 ng/dL** among men across both treatment groups

\*Defined as either vertebral or nonvertebral fractures with low trauma; <sup>†</sup>Defined as hip, spine, forearm, or humerus fractures with low trauma.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Orwoll E, et al. *J Clin Endocrinol Metab.* 2012;97:3161-3169.

Full baseline characteristics >

# Prolia® (denosumab) resulted in significant increases in BMD at lumbar spine and total hip at 12 months<sup>1,2</sup>



CI = confidence interval.

\*95% CI 4.0% – 5.6%; Difference between Prolia® and placebo is calculated with treatment group as main effect and baseline BMD T-score as covariate.

1. Orwoll E, et al. *J Clin Endocrinol Metab*. 2012;97:3161-3169; 2. Prolia® (denosumab) prescribing information, Amgen.

Pivotal study in men  
 Prolia® (denosumab)  
**adverse  
 event (AE)  
 profile<sup>1</sup>**

<b>Event</b>	<b>Prolia®  (N = 120) n (%)</b>	<b>Placebo  (N = 120) n (%)</b>
<b>AEs regardless of relationship to treatment</b>		
All	86 (71.1)	84 (70.0)
Serious	11 (9.2)	10 (8.3)
Fatal	1 (0.8)	1 (0.8)
Leading to investigational product discontinuation	4 (3.3)	0 (0)
<b>AEs with ≥5% incidence</b>		
Back pain	10 (8.3)	8 (6.7)
Arthralgia	8 (6.7)	7 (5.8)
Nasopharyngitis	8 (6.7)	7 (5.8)
Constipation	0 (0)	7 (5.8)
AE of new vertebral fractures	0 (0)	1 (0.8)
AE of any clinical fracture	1 (0.8)	2 (1.7)
ONJ	0 (0)	0 (0)
Fracture healing complications	0 (0)	0 (0)
Atypical femoral fracture	0 (0)	0 (0)

1. Orwoll E, et al. *J Clin Endocrinol Metab.* 2012;97:3161-3169.

# Prolia® (denosumab) helps you treat patients at high risk for fracture with 5 indications<sup>1</sup>



Postmenopausal  
osteoporosis

**Studying the effect  
of transitioning to  
Denosumab or  
Zoledronic Acid on  
BMD**

**Click to view >**



Breast cancer  
treatment-induced  
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**Hormone Ablation Therapy  
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Prostate cancer  
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**Prolia® for treatment  
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**Click to view >**



Osteoporosis in  
men



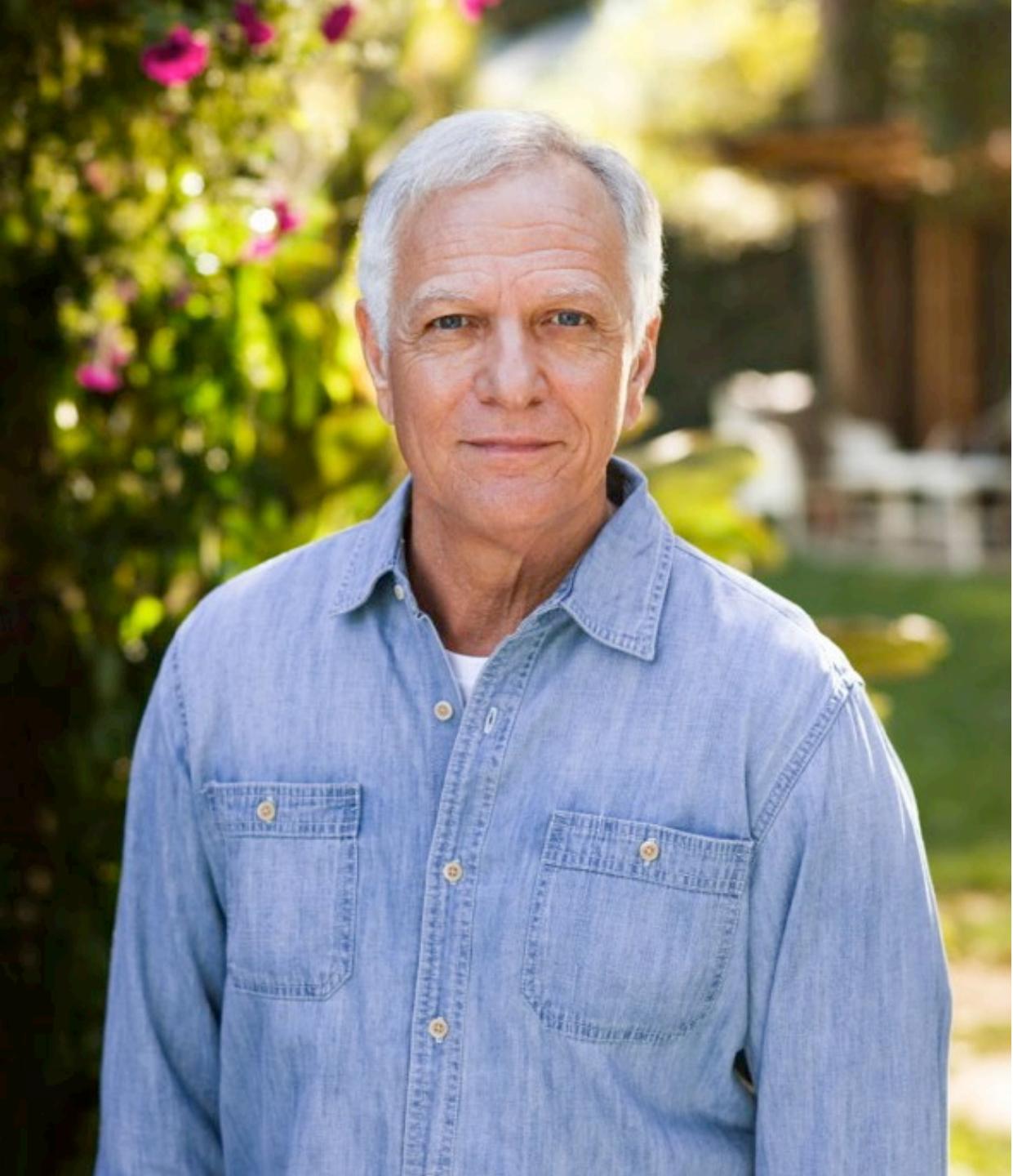
Glucocorticoid-  
induced  
osteoporosis

**Head-to-Head Study  
of Patients with  
Glucocorticoid-  
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**Click to view >**

BMD = bone mineral density.

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This concludes our presentation  
**THANK YOU**

Prolia® in a head-to-head study of  
**patients with glucocorticoid-  
induced osteoporosis**

# Prolia® (denosumab) is approved in glucocorticoid-induced osteoporosis

**INDICATION:** Prolia® is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

## CONTRAINDICATIONS

---

**Prolia® is contraindicated in patients with hypocalcemia**

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®

---

**Prolia® may cause fetal harm when administered to a pregnant woman**

In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®

---

**Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product**

Reactions have included anaphylaxis, facial swelling, and urticaria

# Prolia® (denosumab) in a head-to- head study of patients with glucocorticoid- induced osteoporosis<sup>1</sup>

## Study subpopulations

- Glucocorticoid initiated (GC-I)**  
Initiated glucocorticoids < 3 months prior
- Glucocorticoid continuing (GC-C)**  
Initiated glucocorticoids ≥ 3 months prior

Some patients were also taking biologic or nonbiologic immunosuppressants<sup>2</sup>

# Prolia® (denosumab) in a head-to- head study of patients with glucocorticoid- induced osteoporosis<sup>1</sup>

## Study subpopulations

- Glucocorticoid initiated (GC-I)**  
Initiated glucocorticoids < 3 months prior
- Glucocorticoid continuing (GC-C)**  
Initiated glucocorticoids ≥ 3 months prior

Some patients were also taking biologic or nonbiologic immunosuppressants<sup>2</sup>

## Key Inclusion Criteria

- Women and men treated with ≥ 7.5 mg/day oral prednisone or (equivalent) and planning to continue glucocorticoid therapy for a total of at least 6 months
- Enrolled patients < 50 years of age were required to have a history of osteoporotic fracture
- Enrolled patients ≥ 50 years of age who were in the GC-C subpopulation were required to have:
  - BMD < -2.0 at the lumbar spine, total hip, or femoral neck; or
  - BMD < -1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture

## Primary Endpoint

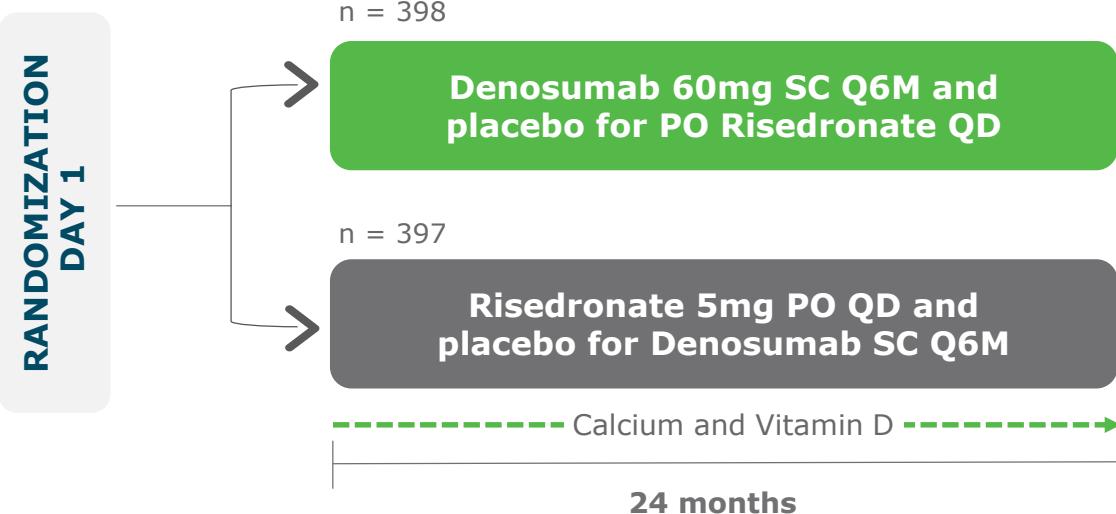
- Percent change from baseline in lumbar spine BMD at 12 months

## Select Endpoints

- Secondary:** Percent change from baseline in lumbar spine and total hip BMD at 12 months
- Exploratory:** Percent change from baseline in lumbar spine BMD at 6 months

PO = by mouth; QD = once daily; Q6M = once every 6 months; SC = subcutaneous.

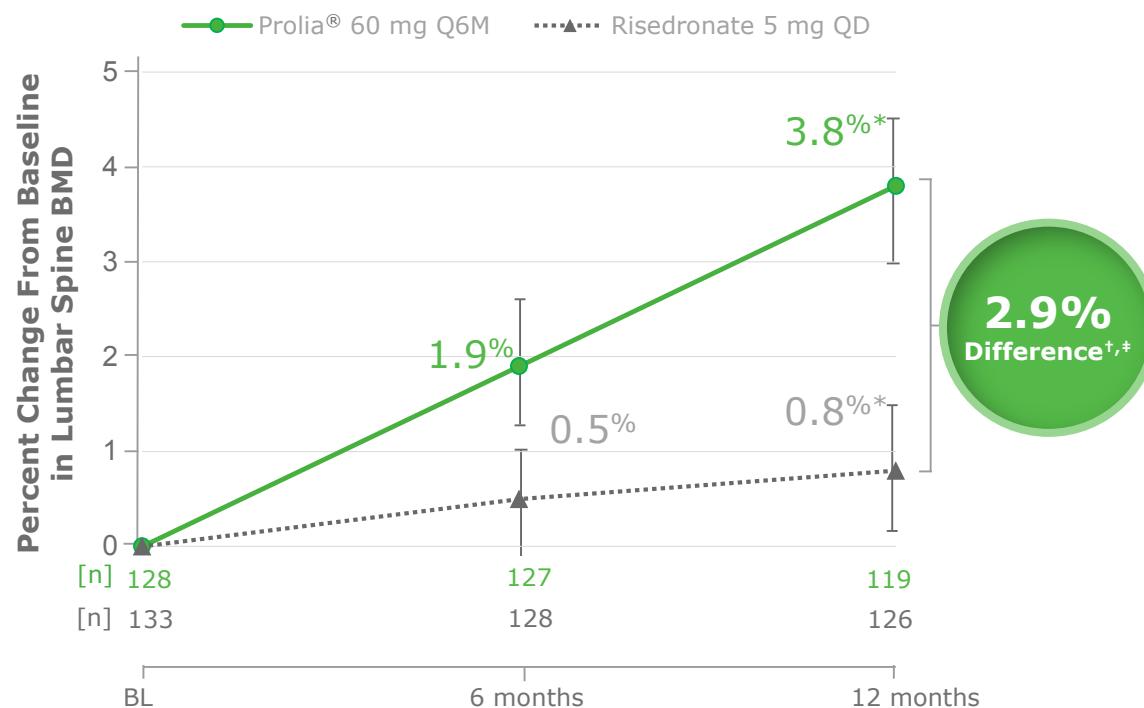
1. Data on file, Amgen; 2016; 2. Saag KG, et al. *Lancet Diabetes Endocrinol.* 2018;6:445-454.



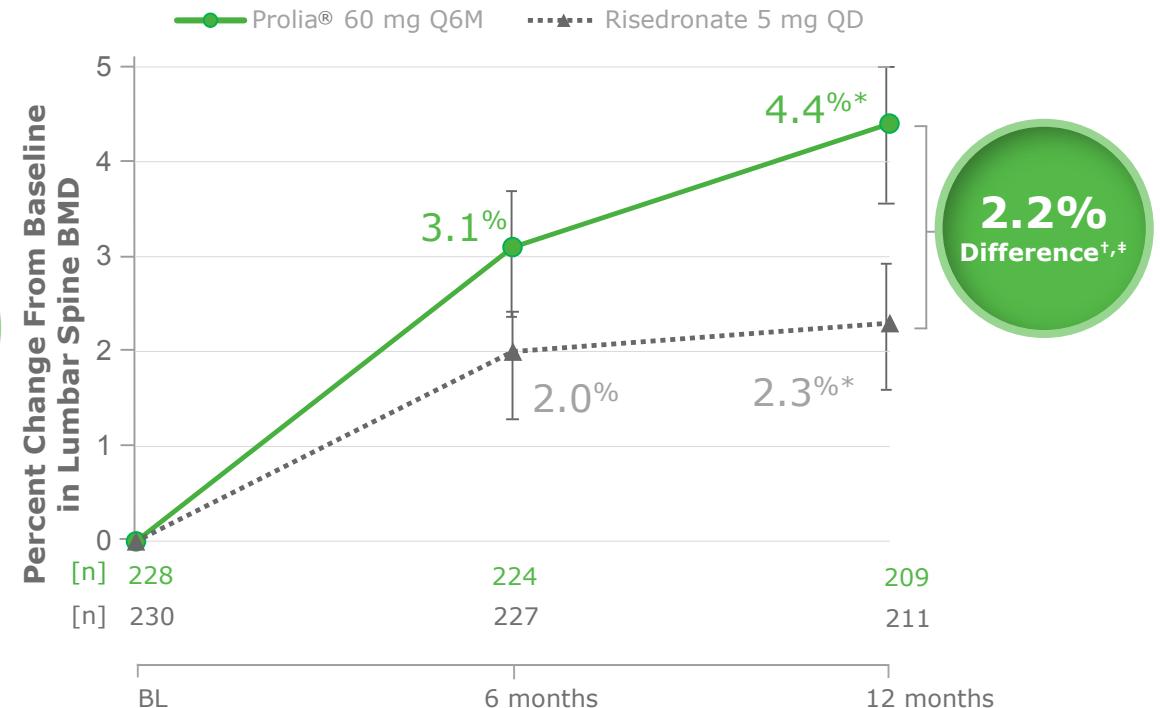
# Prolia® (denosumab) demonstrated noninferiority and superiority in lumbar spine BMD at 12 months vs risedronate<sup>1</sup>

**Prolia® delivered significantly greater improvements in lumbar spine BMD as early as 6 months<sup>1</sup>**

## Initiating Glucocorticoid Therapy [GC-I]



## Continuing Glucocorticoid Therapy [GC-C]



BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy. Head-to-head fracture studies have not been conducted.

\*Primary endpoint.

†(95% CI 2.0% - 3.9%),  $p < 0.001$ ; ‡Based on ANCOVA model adjusting for treatment, gender, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction; additionally, includes duration of prior glucocorticoid use (< 12 months vs ≥ 12 months) for GC-C subpopulation; § (95% CI 1.4% - 3.0%),  $p < 0.001$ .

1. Saag KG, et al. *Lancet Diabetes Endocrinol.* 2018;6:445-454.

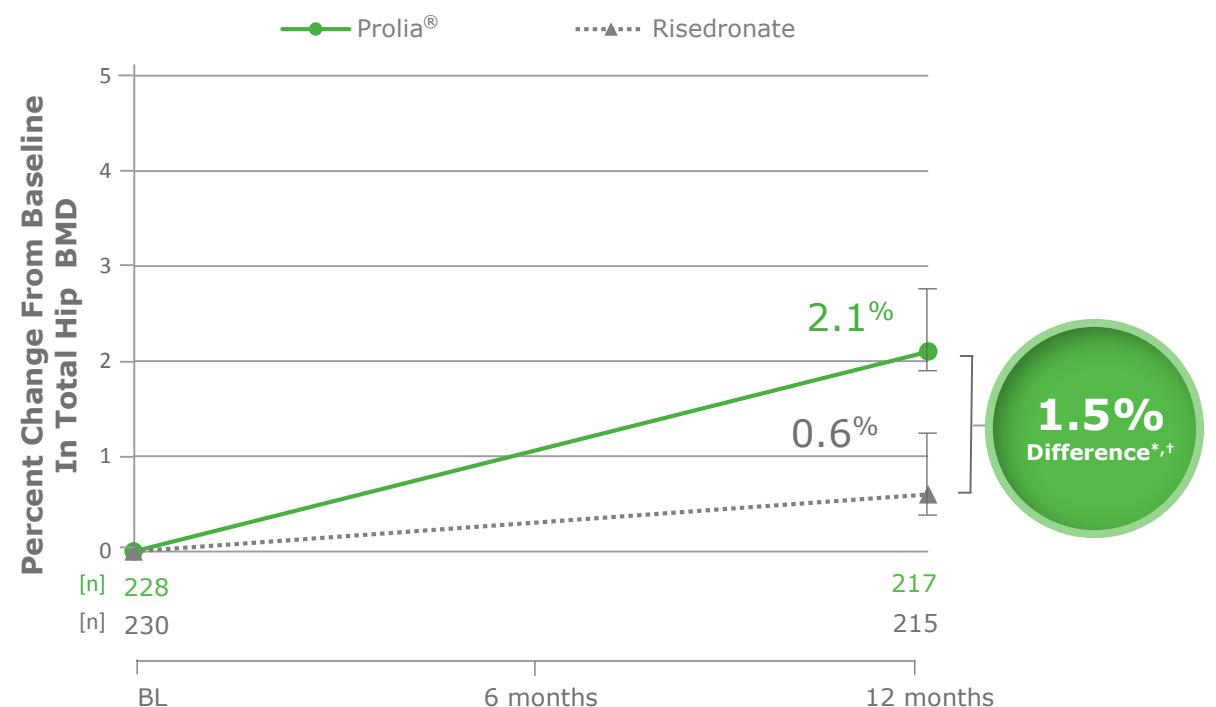
# Prolia® (denosumab) demonstrated superiority in total hip BMD at 12 months vs risedronate<sup>1</sup>

## Total Hip BMD Increase

### Initiating Glucocorticoid Therapy [GC-I]



### Continuing Glucocorticoid Therapy [GC-C]



BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy. Head-to-head fracture studies have not been conducted.

*p* < 0.001.

\*Based on ANCOVA model adjusting for treatment, gender, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction; additionally, includes duration of prior glucocorticoid use (< 12 months vs ≥ 12 months) for GC-C subpopulation.

†95% CI 1.4% - 3.0%, *p* < 0.001.

1. Saag KG, et al. *Lancet Diabetes Endocrinol.* 2018;6:445-454.

**The incidence of serious adverse events was similar for both Prolia® (denosumab) and risedronate groups (16% vs 17%)<sup>1</sup>**

**Adverse reactions in ≥ 2% of patients with glucocorticoid-induced osteoporosis and more frequently with Prolia®<sup>1</sup>**

Event	Prolia® (N = 394) n (%)	Risedronate (N = 384) n (%)
<b>Most common adverse events</b>		
Back pain	18 (4.6)	17 (4.4)
Hypertension	15 (3.8)	13 (3.4)
Bronchitis	15 (3.8)	11 (2.9)
Headache	14 (3.6)	7 (1.8)
Dyspepsia	12 (3.0)	10 (2.6)
Urinary tract infection	12 (3.0)	8 (2.1)
Abdominal pain, upper	12 (3.0)	7 (1.8)
Upper respiratory tract infection	11 (2.8)	10 (2.6)
Constipation	11 (2.8)	6 (1.6)
Vomiting	10 (2.5)	6 (1.6)
Dizziness	9 (2.3)	8 (2.1)
Fall	8 (2.0)	7 (1.8)
Polymyalgia rheumatica*	8 (2.0)	1 (0.3)

**Osteonecrosis of the Jaw (ONJ)**

No cases of ONJ were reported<sup>1</sup>

**Atypical Femoral Fractures (AFF)**

AFF were reported in 1 patient treated with Prolia®. The duration of Prolia® exposure to time of AFF diagnosis was 8.0 months<sup>1</sup>

**Serious Infections**

Serious infections were reported in 15 patients (3.9%) in the active-control group and 17 patients (4.3%) in the Prolia® group<sup>1</sup>

**Dermatologic Reactions**

Epidermal and dermal adverse events (such as dermatitis, eczema, and rashes) were reported in 16 patients (4.2%) in the active-control group and 15 patients (3.8%) in the Prolia® group<sup>1</sup>

\*Events of worsening of underlying polymyalgia rheumatica.

1. Prolia® (denosumab) prescribing information, Amgen.

# Prolia® (denosumab) helps you treat patients at high risk for fracture with 5 indications<sup>1</sup>



Postmenopausal  
osteoporosis

**Studying the effect  
of transitioning to  
Denosumab or  
Zoledronic Acid on  
BMD**

**Click to view >**



Breast cancer  
treatment-induced  
bone loss due to hormone  
ablation therapy

**Hormone Ablation Therapy  
(HALT) Pivotal Trials**

**Click to view >**



Prostate cancer  
treatment-induced  
bone loss due to  
hormone ablation therapy

**Prolia® for treatment  
of osteoporosis  
in men**

**Click to view >**



Osteoporosis in  
men



Glucocorticoid-  
induced  
osteoporosis

**Head-to-Head Study  
of Patients with  
Glucocorticoid-  
Induced Osteoporosis**

**Click to view >**

BMD = bone mineral density.

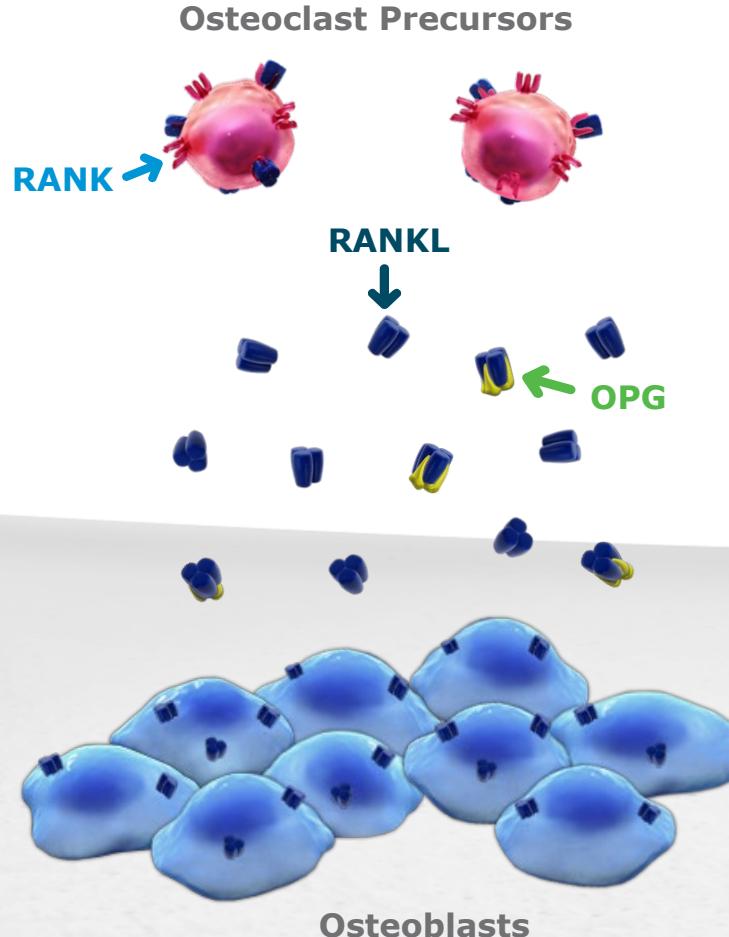
1. Prolia® (denosumab) prescribing information, Amgen; 2. Prolia® (denosumab) FDA approval letter. June 1, 2010; 3. Prolia® (denosumab) FDA approval letter. September 16, 2011; 4. Prolia® (denosumab) FDA approval letter. September 16, 2011; 5. Prolia® (denosumab) FDA approval letter. September 20, 2012; 6. Prolia® (denosumab) FDA approval letter. May 18, 2018.



This concludes our presentation  
**THANK YOU**

## **Additional Modules/Slides**

# In premenopausal women, bone resorption and bone formation is balanced<sup>1,2</sup>



- ❖ RANKL is a protein that is expressed by osteoblasts which binds to RANK receptor on osteoclast precursor and mature osteoclasts cell. This binding regulates osteoclast differentiation and activation.<sup>1</sup>
- ❖ OPG, also expressed by osteoblasts, is a cytokine receptor that inhibits bone resorption by binding to RANKL and preventing it from interacting with RANK<sup>2</sup>
- ❖ Osteoclast precursors appear and RANKL binds to the osteoclast precursors<sup>2</sup>



RANK<sup>1</sup>

[Receptor Activator of Nuclear Factor Kappa-B]



RANKL<sup>1</sup>

[RANK Ligand]

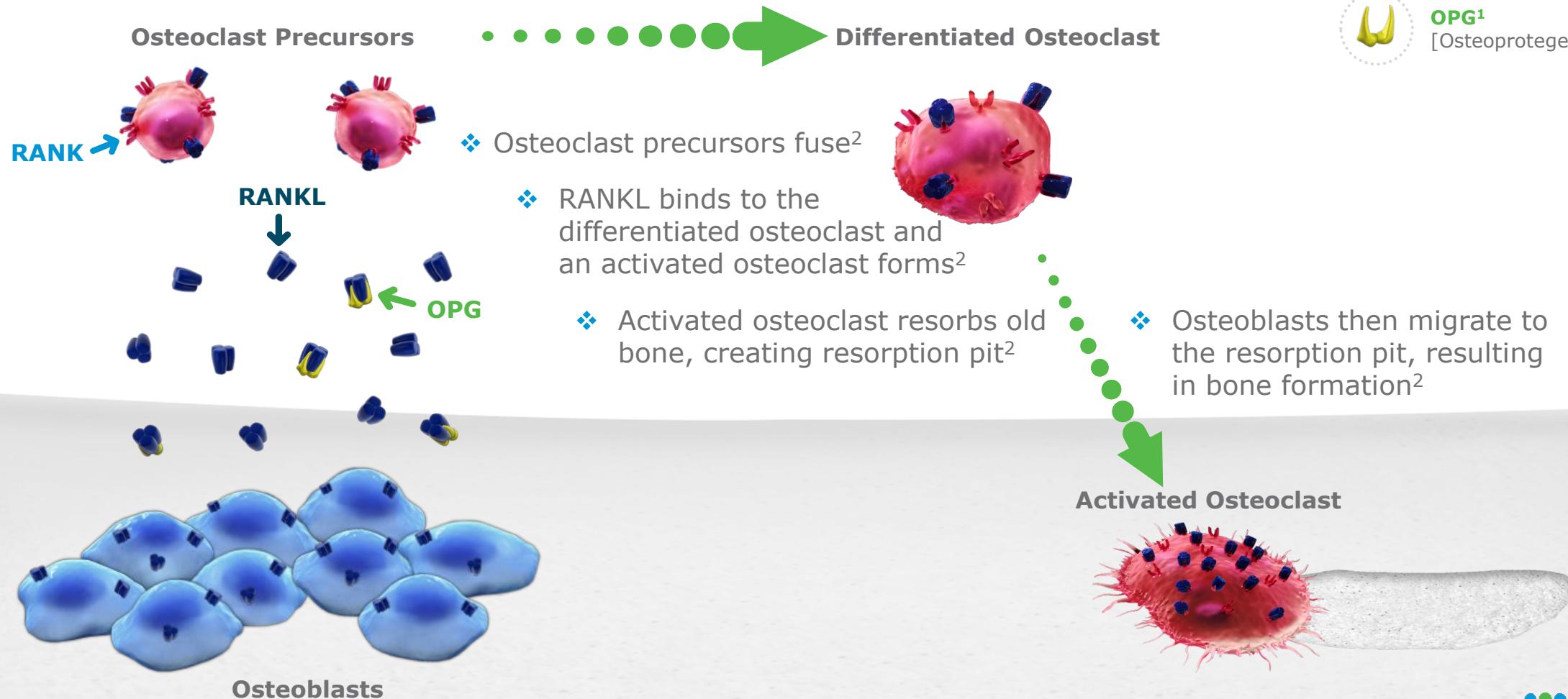


OPG<sup>1</sup>

[Osteoprotegerin]

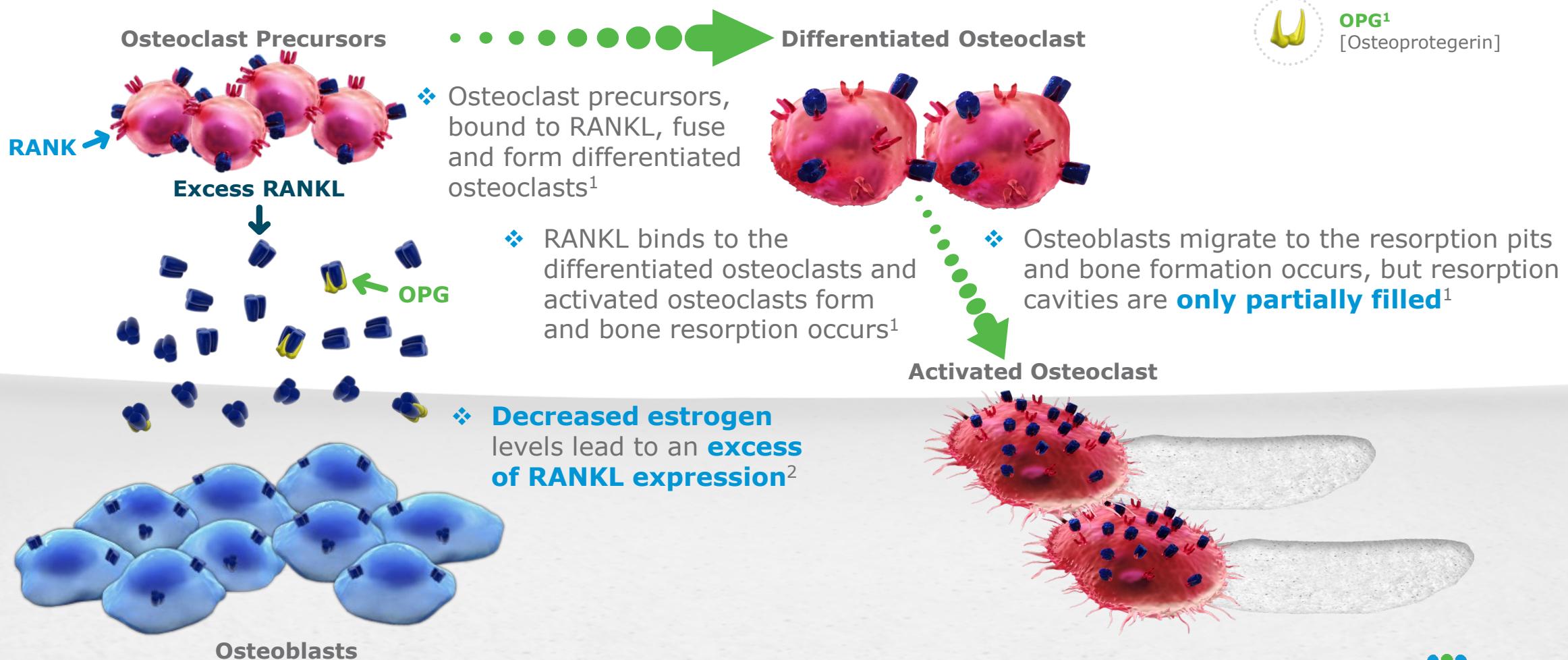
1. Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342. 2. Kostenuik PJ, et al. *Curr Opin Pharmacol*. 2005;5:618-625.

# In premenopausal women, bone resorption and bone formation is balanced<sup>1,2</sup>

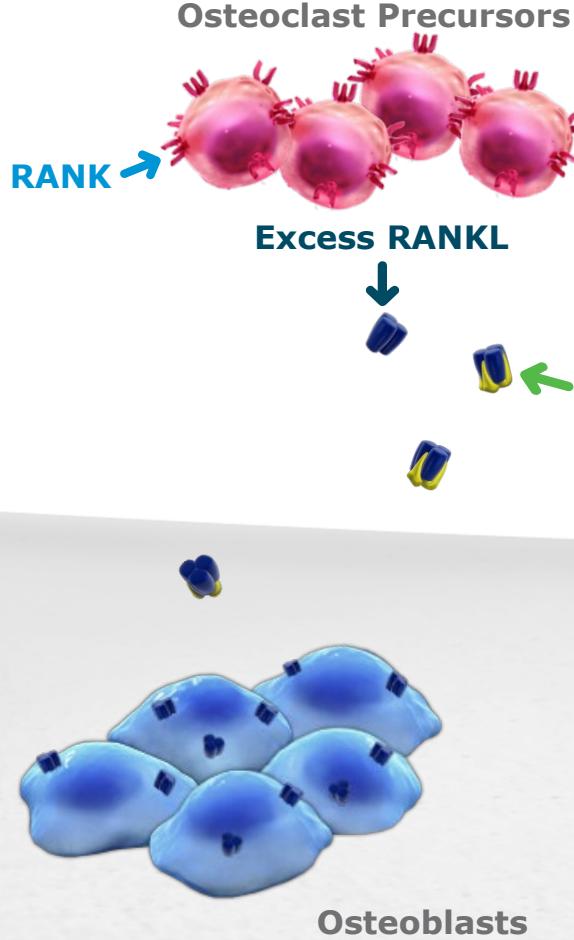


1. Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342; 2. Kostenuik PJ, et al. *Curr Opin Pharmacol*. 2005;5:618-625.

# In postmenopausal women, bone resorption is increased<sup>1</sup>



1. Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342; 2. Kostenuik PJ. *Curr Opin Pharmacol*. 2005;5:618-625.



**RANKL is an essential mediator  
for osteoclast formation,  
function, and survival<sup>1,2</sup>**

**Increased RANKL in  
postmenopausal women leads  
to increased bone resorption<sup>1,3</sup>**

-  **RANK<sup>1</sup>**  
[Receptor Activator of Nuclear Factor Kappa-B]
-  **RANKL<sup>1</sup>**  
[RANK Ligand]
-  **OPG<sup>1</sup>**  
[Osteoprotegerin]

**BACK TO  
SECTION >**

1. Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342; 2. Kostenuik PJ. *Curr Opin Pharmacol.* 2005;5:618-625; 3. Eghbali-Fatourechi G, et al. *J Clin Invest.* 2003;111:1221-1230;

Pivotal phase 3 trial  
**Baseline characteristics**  
of the patients<sup>1,\*</sup>

	<b>PROLIA® (denosumab) (N = 3,902)</b>	<b>PLACEBO (N = 3,906)</b>
<b>Age</b>		
Mean—years	72.3 ± 5.2	72.3 ± 5.2
Group—number (%)		
< 70 years	1,030 (26.4)	1,028 (26.3)
70–74 years	1,637 (42.0)	1,642 (42.0)
≥ 75 years	1,235 (31.7)	1,236 (31.6)
<b>BMI<sup>†</sup></b>	26.0 ± 4.1	26.0 ± 4.2
<b>Region<sup>‡</sup></b>		
Western Europe	1,761 (44.8)	1,773 (45.1)
Eastern Europe	1,374 (34.9)	1,355 (34.4)
Latin America	472 (12.0)	462 (11.7)
North America	282 (7.2)	297 (7.5)
Australia and New Zealand	44 (1.1)	48 (1.2)
<b>T-score</b>		
Lumbar spine	-2.82 ± 0.70	-2.84 ± 0.69
Total hip	-1.89 ± 0.81	-1.91 ± 0.81
Femoral neck	-2.15 ± 0.72	-2.17 ± 0.71
<b>Prevalent vertebral fracture—number (%)</b>		
Yes	929 (23.8)	915 (23.4)
No	2,864 (73.4)	2,854 (73.1)
Unreadable or missing data	109 (2.8)	137 (3.5)

BMI = body mass index; SD = standard deviation.

\*Plus-minus values are means ± SD. A total of 60 subjects at 1 center (31 in the Prolia® group and 29 in the placebo group) were excluded from all analyses because of issues with respect to study procedures and the reliability of data; <sup>†</sup>the BMI is the weight in kilograms divided by the square of the height in meters; <sup>‡</sup>percentages for region are based on all subjects enrolled in the study: 3,933 in the Prolia® group and 3,935 in the placebo group.

1. Cummings SR, et al. *N Engl J Med.* 2009;361:756-765.

Pivotal phase 3 trial  
**Baseline characteristics**  
of the patients<sup>1,2</sup>

	<b>PROLIA® (denosumab) (N = 3,902)</b>	<b>PLACEBO (N = 3,906)</b>
<b>Serum 25-hydroxyvitamin D—ng/mL*</b>	23.1 ± 11.7	22.9 ± 11.3
<b>No prior use of osteoporosis medications</b>	2,713 (69.5)	2,628 (67.3)
<b>Prior osteoporosis medication<sup>†</sup></b>	1,189 (30.5)	1,278 (32.7)
Bisphosphonate (oral)	456 (11.7)	505 (12.9)
Calcitriol	334 (8.6)	352 (9.0)
Hormone-replacement therapy	97 (2.5)	88 (2.3)
Estrogens	92 (2.4)	80 (2.0)
Calcitonin	88 (2.3)	97 (2.5)
SERM	84 (2.2)	91 (2.3)
PTH or PTH derivatives	13 (0.3)	18 (0.5)
Bisphosphonate (IV)	11 (0.3)	11 (0.3)
Fluoride	1 (< 0.1)	0 (0.0)

SERM = selective estrogen receptor modulator; PTH = parathyroid hormone; IV = intravenous.

\*Subjects with outlier values of more than 200 ng per mL were excluded from this analysis; <sup>†</sup>women were excluded if they had conditions that influence bone metabolism or had taken oral bisphosphonates for more than 3 years. If they had taken bisphosphonates for less than 3 years, they were eligible after 12 months without treatment. Women were also excluded if they had used IV bisphosphonates, fluoride, or strontium for osteoporosis within the past 5 years; or PTH or its derivatives, corticosteroids, systemic hormone-replacement therapy, SERMs, or tibolone, calcitonin, or calcitriol within 6 weeks before study enrollment.

1. Cummings SR, et al. *N Engl J Med.* 2009;361:756-765; 2. Data on file, Amgen; 2008.

**BACK TO  
SECTION >**

Pivotal study in men  
**Demographics and baseline characteristics of men**  
 randomized in the study<sup>1,2</sup>

**BACK TO SECTION >**

	<b>PROLIA® (denosumab) (N = 121)</b>	<b>PLACEBO (N = 121)</b>
<b>Age—mean years (SD)</b>	64.9 (10.5)	65.0 (9.1)
<b>Age group (years)—number (%)</b>		
< 50	9 (7.4)	5 (4.1)
50–59	22 (18.2)	26 (21.5)
60–69	44 (36.4)	49 (40.5)
70–79	39 (32.2)	35 (28.9)
≥ 80	7 (5.8)	6 (5.0)
<b>BMD T-score—mean (SD), range</b>		
Lumbar spine	-2.0 (1.1), -3.6 to 2.1	-2.0 (1.0), -3.6 to 2.3
Total hip	-1.5 (0.6), -3.5 to 0.2	-1.4 (0.7), -2.8 to 0.1
Femoral neck	-1.9 (0.6), -3.8 to 0.7	-1.9 (0.6), -3.4 to -0.3
Trochanter	-1.2 (0.7), -2.7 to 0.6	-1.3 (0.7), -2.9 to 0.6
1/3R	-1.4 (1.3), -5.1 to 1.5	-1.7 (1.2), -5.0 to 1.2
<b>sCTx (ng/mL)—mean (SD)</b>	0.40 (0.18)	0.41 (0.2)
<b>History of fracture—number (%)</b>		
Any	47 (38.8)	48 (39.7)
Osteoporotic*	23 (19.0)	37 (30.6)
Major osteoporotic†	16 (13.2)	20 (16.5)
Prevalent vertebral fracture	30 (24.8)	25 (20.7)
<b>Total testosterone—number (%)</b>		
< 230 ng/dL	14 (11.6)	14 (11.6)
< 250 ng/dL‡	17 (14.0)	19 (15.7)
< 350 ng/dL	53 (43.8)	44 (44.6)

\*Defined as either vertebral or nonvertebral fractures with low trauma; †defined as hip, spine, forearm, or humerus fractures with low trauma; ‡testosterone threshold prespecified by the study.

1. Prolia® (denosumab) prescribing information, Amgen; 2. Orwoll E, et al. *J Clin Endocrinol Metab*. 2012;97:3161-3169.