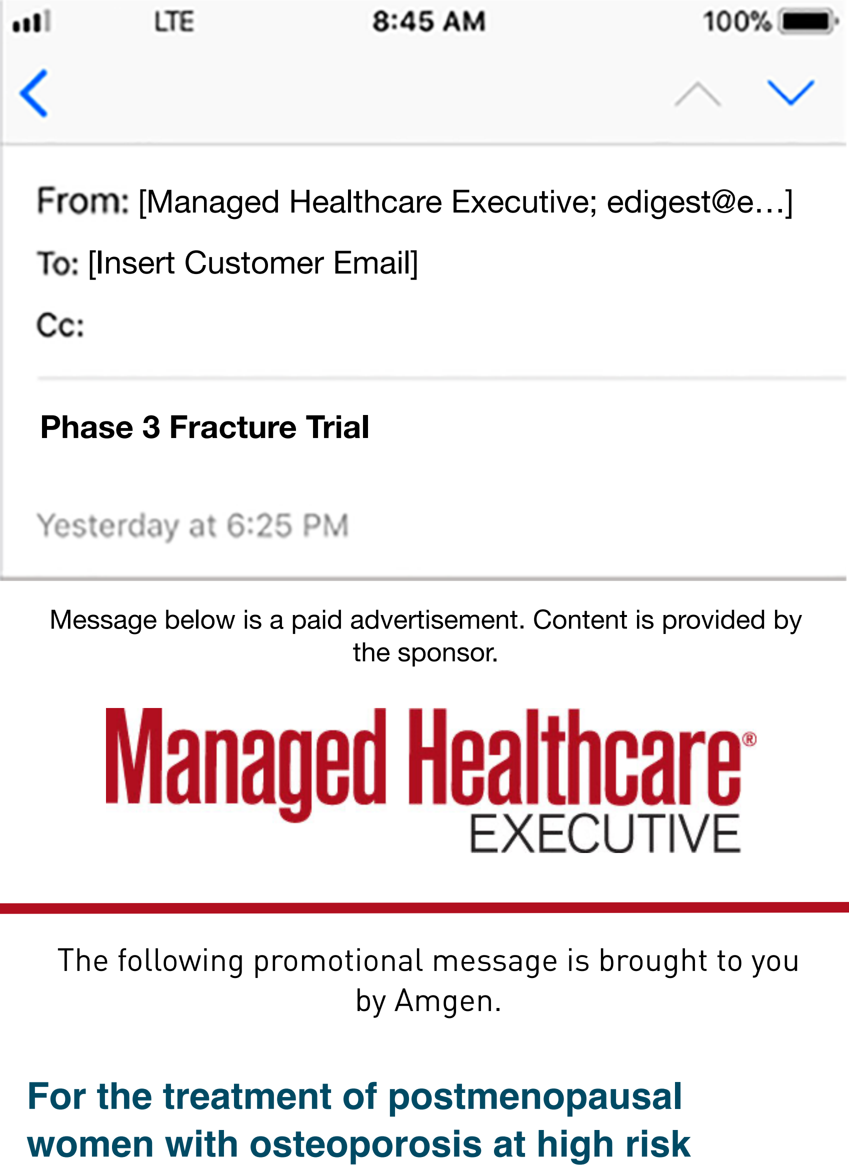


From: [Managed Healthcare Executive; edigest@e…]

To: [Insert Customer Email]

Cc:

Phase 3 Fracture Trial

Yesterday at 6:25 PM

Message below is a paid advertisement. Content is provided by the sponsor.

Managed Healthcare® EXECUTIVE

The following promotional message is brought to you by Amgen.

For the treatment of postmenopausal women with osteoporosis at high risk

for fracture.

Prolia® (denosumab) significantly reduced the risk of new vertebral, hip, and nonvertebral fractures at 3 years.[1,2]

---

prolia®
(denosumab) injection

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, women who are pregnant, and patients with a history of systemic hypersensitivity to any component of the product. Perform pregnancy testing in women of reproductive potential prior to initiating treatment with Prolia®.

Please scroll below for additional
Important Safety Information.

Dear [Insert Customer Name],

PIVOTAL PHASE 3 STUDY DESIGN:

Multicenter, international, randomized, double-blind, placebo-controlled clinical trial that studied postmenopausal women between 60 years of age with a BMD T-score between -2.5 and -4.0 at the lumbar spine or total hip. 7,808 patients were randomized to receive Prolia(R) 60 mg (n = 3,902) or placebo (n = 3,906) subcutaneously every 6 months. All patients were supplemented with daily calcium and vitamin D,

PRIMARY ENDPOINT[1,2]

- Evaluate incidence of new vertebral fractures at 3 years

SECONDARY ENDPOINTS[1,2]

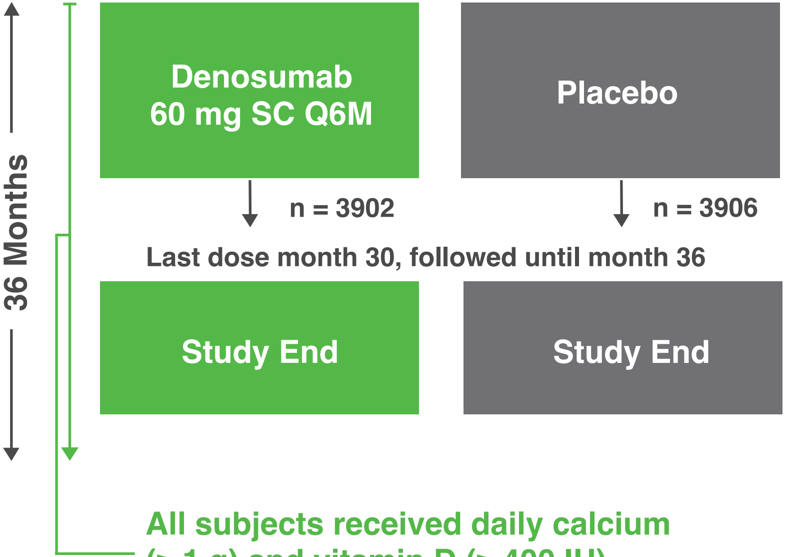
- Evaluate time to nonvertebral fractures and time to the first hip fractures

PIVOTAL STUDY DESIGN DETAILS[1,3]

SCREENING

N = 7808

RANDOMIZATION



Denosumab 60 mg SC Q6M

Placebo

n = 3902

n = 3906

Last dose month 30, followed until month 36

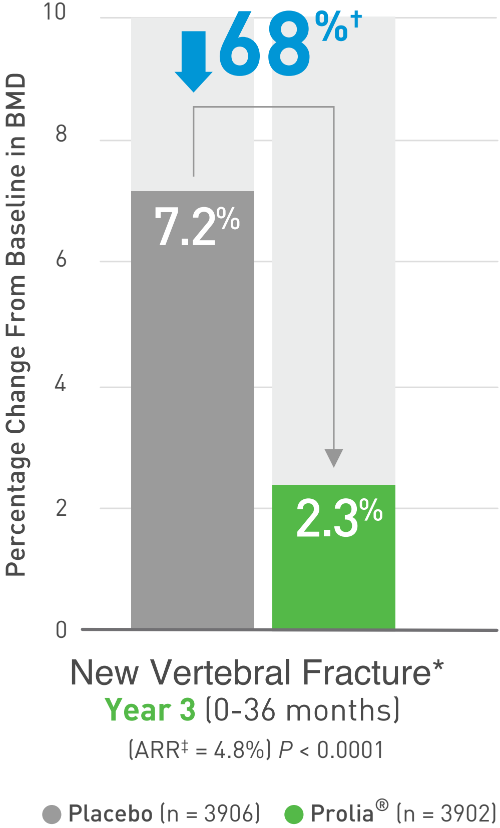
Study End

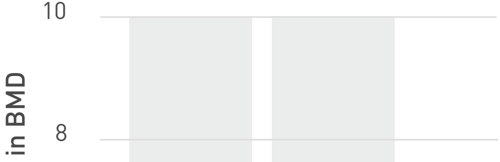
Study End

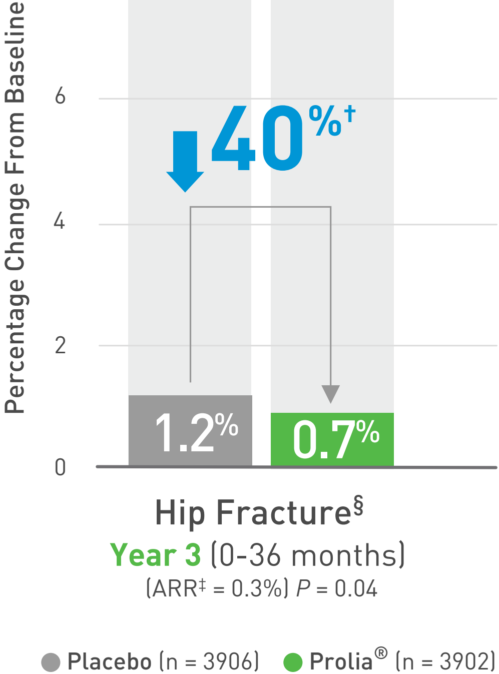
All subjects received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation

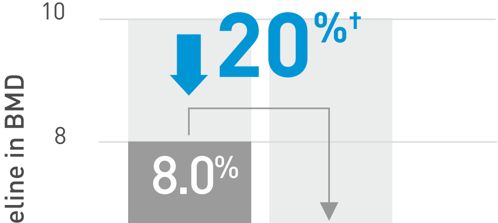
FRACTURE RELATIVE RISK REDUCTION VS PLACEBO[1,3]

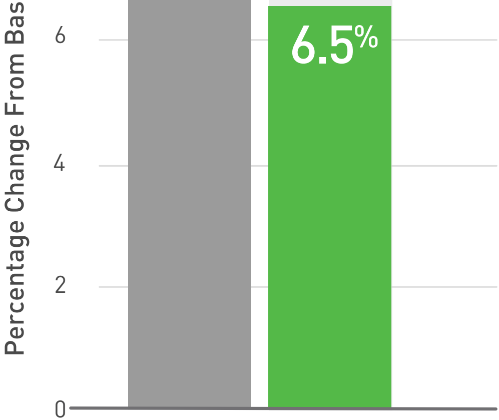
● **Placebo** (n = 3906) ● **Prolia®** (n = 3902)











Nonvertebral Fracture[§,]**
Year 3 (0-36 months)
(ARR[‡] = 1.5%) *P* = 0.01

[*] Includes 7393 patients with a baseline and at least one post-baseline radiograph.[1,3]

[†] Relative risk reduction.

[‡] Absolute risk reduction.

[§] Secondary endpoints were time to first nonvertebral and hip fracture, assessed at 3 years.

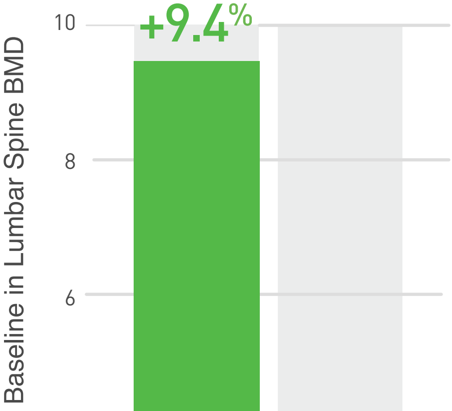
[**] Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.[1,3]

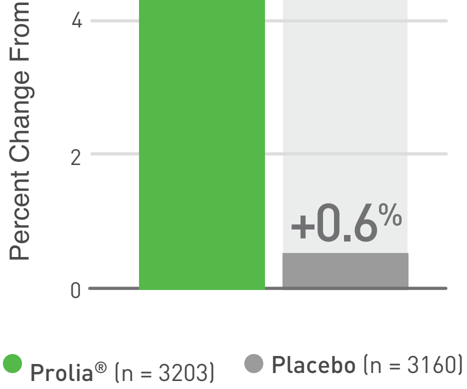
Prolia® is proven to significantly reduce fracture risk at vertebral, hip, and nonvertebral sites at 3 years in female patients with postmenopausal osteoporosis (PMO)[1,3]

PROLIA® SIGNIFICANTLY INCREASED BONE MINERAL DENSITY (BMD) AT KEY SITES AT 3 YEARS[1]

Significant Increase in Lumbar Spine BMD at 3 Years[1,3]

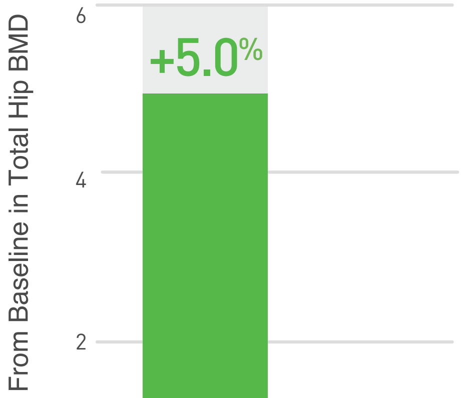
↑ **8.8%††** difference in BMD

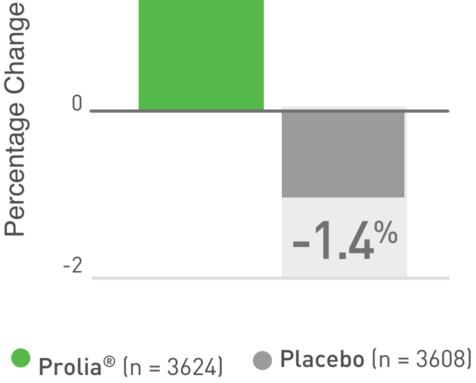




Significant Increase in Total Hip BMD at 3 Years[1,3]

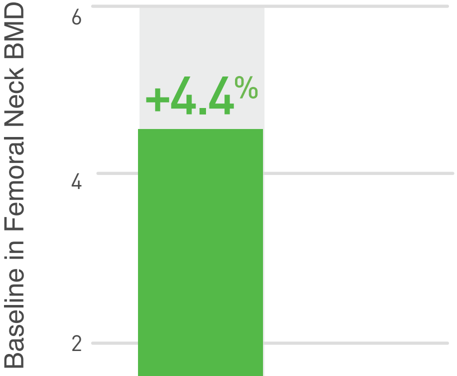
↑6.4%[††] difference in BMD

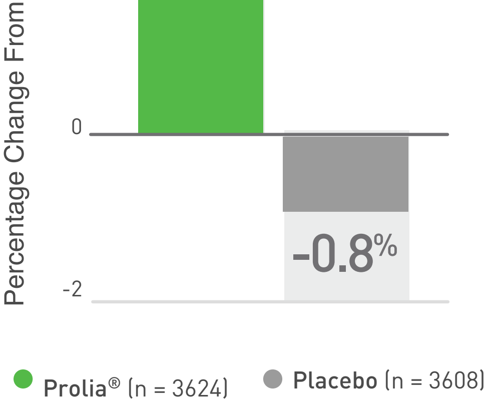




Significant Increase in Femoral Neck BMD at 3 Years[1,3]

5.2%†† difference in BMD





- Prolia® increased bone mass and strength in both cortical and trabecular bone.[1]
- Prolia® patient bone biopsies showed normal bone architecture and quality.[1,‡‡]

[††] $P < 0.0001$, when compared to placebo.
[‡‡] 53 bone biopsy specimens taken from transiliac crest.[1]

Adverse reactions occurring in ≥ 2% of patients with osteoporosis and more frequently than in placebo-treated patients[1]:

Event	Prolia® (n = 3886) n (%)	Placebo (n = 3876) n (%)
Back pain	1347 (34.7)	1340 (34.6)
Pain in extremity	453 (11.7)	430 (11.1)
Musculoskeletal pain	297 (7.6)	291 (7.5)
Hypercholesterolemia	280 (7.2)	236 (6.1)
Cystitis	228 (5.9)	225 (5.8)
Vertigo	195 (5.0)	187 (4.8)
Upper respiratory tract infection	190 (4.9)	167 (4.3)
Edema, peripheral	189 (4.9)	155 (4.0)
Sciatica	178 (4.6)	149 (3.8)
Pneumonia	152 (3.9)	150 (3.9)
Bone pain	142 (3.7)	117 (3.0)

Abdominal pain, upper	129 (3.3)	111 (2.9)
Anemia	129 (3.3)	107 (2.8)
Insomnia	126 (3.2)	122 (3.1)
Myalgia	114 (2.9)	94 (2.4)
Angina pectoris	101 (2.6)	87 (2.2)
Rash	96 (2.5)	79 (2.0)
Pharyngitis	91 (2.3)	78 (2.0)
Asthenia	90 (2.3)	73 (1.9)
Pruritus	87 (2.2)	82 (2.1)
Flatulence	84 (2.2)	53 (1.4)
Spinal osteoarthritis	82 (2.1)	64 (1.7)
Gastroesophageal reflux disease	80 (2.1)	66 (1.7)
Atrial fibrillation	79 (2.0)	77 (2.0)
Herpes zoster	79 (2.0)	72 (1.9)

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.[1]

The efficacy and safety of Prolia® in female patients with PMO were further evaluated in a 7-year open-label extension study.[1-4]

REVIEW STUDY ONLINE

Help lead your members to stronger bones with access to Prolia®.[1,5]

Please visit proliapayerresources.com for more information.

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.

Osteonecrosis of the Jaw (ONJ): 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 (e.g. 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.

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 antiresorptive 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.

Serious Infections: In a clinical trial (N = 7808), 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: 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.

Suppression of Bone Turnover: 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 consequences, including ONJ, atypical fractures, and delayed fracture healing.

Adverse Reactions: The most common adverse reactions (>5% and more common than placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has been reported with Prolia®.

The overall incidence of new malignancies was 4.3% in the placebo group and 4.8% in the Prolia® group. A causal relationship to drug exposure has not been established. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

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

References: **1.** Prolia® (denosumab) prescribing information, Amgen. **2.** Data on File, Amgen. 2008. **3.** Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;36:756-765. **4.** Bone HG, Brandi ML, Brown JP, et al. Ten years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM extension trial. Presented at: American Society of Bone and Mineral Research; October 9-12, 2015; Seattle, WA. **5.** Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Mineral Res*. 2010;25:72-81.

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