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Denosumab (Prolia & Xgeva) and Associated Biosimilars

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Prolia®/Xgeva® and Associated Biosimilars Continuation Therapy

Continuation of denosumab (Prolia®/Xgeva®) and associated biosimilars (denosumab-bbdz [Jubbonti®] [Wyost®], denosumab-dssb [Ospomyv™] [Xbryk™], denosumab-bmwo [Stoboclo®] [Osenvelt®], and denosumab-bnht [Conexxence®] [Bomyntra®]) therapy **may be considered medically necessary** for members (including new members):

- Who are currently receiving the requested medication; AND
- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Prolia®/Jubbonti®/Ospomyv™/Stoboclo®/Conexxence® Initial Therapy

Denosumab (Prolia®) and associated biosimilars (denosumab-bbdz [Jubbonti®], denosumab-dssb [Ospomyv™], denosumab-bmwo [Stoboclo®], and denosumab-bnht [Conexxence®]) therapy **may be considered medically necessary** for any one of the following indications:

- Postmenopausal osteoporosis when the individual meets **ANY** of the following criteria:
  - A history of fragility fractures; **OR**
  - A pre-treatment T-score less than or equal to -2.5 or the individual has osteopenia (i.e., pre-treatment T-score greater than -2.5 and less than -1) with a high pre-treatment FRAX® fracture probability (See **NOTE 1**) **AND** meets any of the following criteria:
    - Indicators of very high fracture risk (e.g., advanced age, frailty, glucocorticoid use, very low T-score [less than or equal to -3], or increased fall risk); or
    - Has failed prior treatment with or is intolerant to previous injectable osteoporosis therapy (e.g., zoledronic acid [Reclast], teriparatide [Forteo, Bonsity]); or
    - Has had an oral bisphosphonate trial of at least 1-year duration or there is a clinical reason to avoid treatment with an oral bisphosphonate (See **NOTE 2**).
- Osteoporosis in men when **ANY** of the following criteria are met:
  - History of osteoporotic vertebral or hip fracture; **OR**
  - When **BOTH** the following criteria are met:
    - A pre-treatment T-score less than or equal to -2.5 or has osteopenia (i.e., pre-treatment T-score greater than -2.5 and less than -1) with a high pre-treatment FRAX fracture probability (See **NOTE 1**); and
    - Has had an oral or injectable bisphosphonate trial of at least 1-year duration or there is a clinical reason to avoid treatment with a bisphosphonate (See **NOTES 2 and 3**).
- Glucocorticoid-induced osteoporosis when **ALL** the following criteria are met:

- Currently receiving or will be initiating glucocorticoid therapy at an equivalent prednisone dose of greater than or equal to 2.5 mg/day for 3 months or more; **AND**
- Has had an oral or injectable bisphosphonate trial of at least 1-year duration or there is a clinical reason to avoid treatment with a bisphosphonate (See **NOTES 2 & 3**); **AND**
- Meets **ANY** of the following criteria:
  - History of fragility fracture; or
  - Has a pre-treatment T-score less than or equal to -2.5; or
  - Has osteopenia (i.e., pre-treatment T-score greater than -2.5 and less than -1) with a high pre-treatment FRAX fracture probability (See **NOTE 1**).

- Breast cancer when receiving an aromatase inhibitor for breast cancer.
- Prostate cancer when receiving androgen deprivation therapy for prostate cancer.

Xgeva®/Wyost®/Xbryk™/Osenvelt®/Bomyntra® Initial Therapy

Denosumab (Xgeva®) and associated biosimilars (denosumab-bbdz [Wyost®], denosumab-dssb [Xbryk™], denosumab-bmwo [Osenvelt®], and denosumab-bnht [Bomyntra®]) therapy **may be considered medically necessary** for the following indications:

- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone; **OR**
- Patients refractory to (within the past 30 days) or have a clinical reason to avoid (See **NOTE 2**) intravenous (IV) bisphosphonate therapy (e.g., pamidronate, zoledronic acid) for:
  - Prevention of skeletal-related events in patients with multiple myeloma OR bone metastases from a solid tumor; or
  - Treatment of hypercalcemia of malignancy; or
  - Treatment of systemic mastocytosis as second-line therapy for osteopenia or osteoporosis.

Denosumab (Prolia®/Xgeva®) and associated biosimilars (denosumab-bbdz [Jubbonti®] [Wyost®], denosumab-dssb [Ospomyv™] [Xbryk™], denosumab-bmwo [Stoboclo®] [Osenvelt®], and denosumab-bnht [Conexxence®] [Bomyntra®]) therapy **is considered experimental, investigational and/or unproven** for all other indications, including but not limited to:

- Combination therapy of denosumab and intravenous bisphosphonates;
- Patients with uncorrected preexisting hypocalcemia;
- Bone loss associated with hormone-ablation therapy (other than aromatase inhibitors) in breast cancer;
- Cancer pain;
- Central giant cell granuloma;
- Hyper-parathyroidism;
- Immobilization hypercalcemia;
- Osteogenesis imperfecta;
- Osteopenia (other than due to systemic mastocytosis);
- Paget's disease of bone;
- Primary bone sarcomas (e.g., Ewing's sarcoma and osteosarcoma);
- Rheumatoid arthritis.

NOTE 1: World Health Organization (WHO) Fracture Risk Assessment Tool

- High FRAX fracture probability: 10-year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%.
- 10-year probability; calculation tool available at: FRAX – Fracture Risk Assessment Tool (https://www.sheffield.ac.uk/FRAX/).
- The estimated risk score generated with FRAX should be multiplied by 1.15 for major osteoporotic fracture (including fractures of the spine [clinical], hip, wrist, or humerus) and 1.2 for hip fracture if glucocorticoid treatment is greater than 7.5 mg (prednisone equivalent) per day.

NOTE 2: Clinical Reasons to Avoid Oral Bisphosphonate Therapy

- Presence of anatomic or functional esophageal abnormalities that might delay transit of the tablet (e.g., achalasia, stricture, or dysmotility).
- Active upper gastrointestinal problem (e.g., dysphagia, gastritis, duodenitis, erosive esophagitis, ulcers).
- Presence of documented or potential gastrointestinal malabsorption (e.g., gastric bypass procedures, celiac disease, Crohn's disease, infiltrative disorders, etc.).
- Inability to stand or sit upright for at least 30 to 60 minutes.
- Inability to take at least 30 to 60 minutes before first food, drink, or medication of the day.
- Renal insufficiency (creatinine clearance <35 mL/min).
- History of intolerance to an oral bisphosphonate.

NOTE 3: Clinical Reasons to Avoid Intravenous (IV) Bisphosphonate Therapy

- Renal insufficiency (creatinine clearance <35 mL/min).
- Acute renal impairment.
- History of intolerance to an IV bisphosphonate.

Policy Guidelines

None.

Description

Osteoporosis

Osteoporosis is a bone disease that develops when bone mineral density and bone mass decreases, or when the quality or structure of bone changes. This can lead to a decrease in bone strength that can increase the risk of fractures.

Osteoporosis can affect women and men of all races and ethnic groups; it can occur at any age, although the risk for development increases as one ages. For many women, the disease can begin to develop a year or two before menopause. It is most common in non-Hispanic White women and Asian women. African American and Hispanic women have a lower, but still significant, risk of developing osteoporosis. For men, it is more common in non-Hispanic whites.

(1)

Postmenopausal Osteoporosis

Most postmenopausal women with osteoporosis have bone loss related to estrogen deficiency and/or age. A diagnosis can be made in the presence of a fragility fracture (occurring spontaneously or from minor trauma), particularly in the spine, hip, wrist, humerus, rib and pelvis; or with a T-score of ≤-2.5 standard deviations (SDs) at any site based upon bone mineral density measurements by dual-energy x-ray absorptiometry (DXA). The National Bone Health Alliance suggests a clinical diagnosis may be made if there is a clear elevated risk for fracture, such as when the fracture risk assessment tool (FRAX) 10-year probability of major osteoporotic fracture is ≥20 percent or the 10-year probability of hip fracture is ≥3 percent. (2)

T-score

The World Health Organization (WHO) established a classification of bone mineral density by DXA according to the standard deviation difference between a patient's bone mineral density (BMD) and that of a young adult reference population; see Table 1.

Table 1. Diagnostic categories for osteoporosis and low bone mass based on BMD measurement by DXA

Category	Bone Mass
Normal	A value for BMD within 1.0 SD of the young adult female reference mean (T-score greater than or equal to -1.0 SD).
Low bone mass (osteopenia)	A value for BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean (T-score less than -1 and greater than -2.5 SD).
Osteoporosis	A value for BMD 2.5 or more SD below the young adult female reference mean (T-score less than or equal to -2.5 SD).
Severe (established) osteoporosis	A value for BMD more than 2.5 SD below the young adult female reference mean in the presence of one or more fragility fractures.

BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; SD: standard deviation.
Data from: WHO scientific group on the assessment of osteoporosis at the primary health care level: Summary meeting report, 2004. Geneva: World Health Organization, 2007. (2)

The WHO thresholds were chosen based upon fracture risk in postmenopausal White women. Similar diagnostic threshold values for men are less well defined, although for any given BMD, the age-adjusted fracture risk is similar in men and women. The International Society for Clinical Densitometry (ISCD) recommends the application of the WHO classification for men ages 50 years and older. (2)

Fracture Risk Assessment Tool (FRAX)

The Fracture Risk Assessment Tool, or FRAX, is a computer-based calculator that estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) in untreated patients between ages 40 and 90 years using easily

obtainable clinical risk factors for fractures, with or without femoral neck bone mineral density. The FRAX algorithm uses femoral neck BMD (g/cm^2) for calculation of fracture probability. (3)

Androgen-Deprivation Therapy in Prostate Cancer

Androgen-deprivation therapy (ADT) is the main therapeutic approach for individuals with metastatic prostate cancer. ADT is also frequently used: 1) In those whose only manifestation of disseminated disease is a rising or elevated serum prostate-specific antigen (PSA), and 2) In the setting of adjuvant or neoadjuvant therapy in conjunction with initial treatment in those with intermediate- or high-risk prostate cancer. Despite the potential benefits associated with its use, ADT can cause a range of side effects, including osteoporosis. ADT increases bone turnover, decreases bone mineral density, and increases the risk of bone fractures in men with prostate cancer. Loss of bone mineral density can be detected after six to nine months of ADT, and longer therapy confers a higher risk. Osteoporotic skeletal fractures occur in up to 20 percent of men within five years of starting ADT. (4)

Glucocorticoid-Induced Osteoporosis

Glucocorticoids increase the risk of fracture, particularly vertebral fractures, which occur early in treatment during the rapid phase of bone loss and at higher BMD levels than in postmenopausal osteoporosis. Fractures have been reported in as many as 30-50 percent of glucocorticoid users, with the incidence of fracture higher with advanced age, larger doses, and longer duration of therapy. Glucocorticoids increase bone resorption and reduce bone formation. Glucocorticoids stimulate osteoclast proliferation by suppressing synthesis of osteoprotegerin, an inhibitor of osteoclast differentiation from hematopoietic cells of the macrophage lineage, and by stimulating production of the receptor activator of nuclear factor kappa-B (RANK), which is required for osteoclastogenesis. High glucocorticoid levels also stimulate RANK ligand (RANKL) synthesis by pre-osteoblast/stromal cells, supporting osteoclast differentiation and net bone resorption. They also decrease intestinal calcium absorption in part by opposing the action of vitamin D and by decreasing the expression of calcium channels in the duodenum. With long-term use, the predominant effect of glucocorticoids on the skeleton is reduced bone formation. The decline in bone formation is mediated by direct inhibition of osteoblast proliferation and differentiation and by an increase in the apoptosis rates of mature osteoblasts and osteocytes. The reduction in bone formation is associated with a decrease in the mineral apposition rate and in serum and urine biochemical markers of bone formation. (5)

Aromatase Inhibitor-Associated Bone Loss in Breast Cancer

Breast cancer is the most frequent cancer in women, and early diagnosis and improved treatment regimens have increased survival leading to a greater potential for experiencing long term side effects from cancer treatments including bone loss and fractures. The majority of breast malignancies are hormone responsive, and adjuvant endocrine therapy is routinely used to prevent recurrence and death. Aromatase inhibitors (AI) are now the treatment of choice for hormone-responsive breast cancer in post-menopausal women due to better efficacy and fewer serious side effects. However, because AIs prevent peripheral estrogen production, they suppress estrogen levels beyond that attained from a natural menopause, thereby leading to

accelerated bone loss and an increased fracture risk. AI-associated bone loss (AIBL) leads to a marked increase of bone resorption, with a 2–4-fold increased bone loss compared to physiologic postmenopausal BMD loss. As a result, women receiving adjuvant AI therapy for breast cancer are at increased risk for fractures, leading to increased morbidity and mortality. (6)

Skeletal-Related Events in Multiple Myeloma and Bone Metastases

Multiple myeloma (MM), the second most prevalent hematologic malignancy in the adult United States population, is considered a disease of the elderly, with a median age at diagnosis of 69 years and an increasing incidence with age. Destructive bone lesions are one of the classic defining features of MM, which also include hypercalcemia, renal failure, and anemia (i.e., CRAB criteria). It is estimated that 80-90% of patients with MM will develop bone lesions during the course of their disease, with consequent bone destruction a devastating consequence of MM. The severity of bone destruction has been associated with MM disease burden and prognosis. The presence of bone lesions increases the risk for what has been termed skeletal-related events (SREs), which can include pathologic fractures, vertebral compression leading to spinal cord compression, and the need for radiation and surgery to treat bone lesions. SREs, in turn, have been associated with increased mortality, impaired quality of life, and higher healthcare resource utilization and costs for patients with MM. (7)

Bone is one of the most common sites of metastasis from advanced solid cancers. Bone metastases occur in 65-80% of patients with advanced prostate cancer or breast cancer, 40-50% of patients with lung cancer, and in <10% of those with gastrointestinal cancer. Once cancer cells invade the bone tissue, bone remodeling balance is disrupted, leading to destruction of the skeleton. Bone metastases increases the risk of complications of SREs including pathologic fracture, spinal cord compression, palliative radiation to the bone and palliative bone surgery. (8)

Hypercalcemia of Malignancy

Hypercalcemia can be produced by a variety of disorders, but primary hyperparathyroidism and malignancy account for most cases. In patients with cancer, hypercalcemia occurs in approximately 20-30% of cases, and in patients with both solid tumors and hematologic malignancies. The most common cancers associated with hypercalcemia in the United States are breast, renal and lung cancer, and multiple myeloma. Patients often have a poor prognosis. There are three major mechanisms by which hypercalcemia of malignancy can occur:

- Tumor secretion of parathyroid hormone-related protein (PTHrP);
- Osteolytic metastases with local release of cytokines (including osteoclast activating factors);
- Tumor production of 1,25-dihydroxyvitamin D (calcitriol). (9)

Patients with mild hypercalcemia (calcium above the upper limit of normal but <12 mg/dL [3 mmol/L]) may be asymptomatic, or they may report nonspecific symptoms, such as constipation, fatigue, and depression. A moderately elevated serum calcium of 12 to 14 mg/dL (3 to 3.5 mmol/L) may be well tolerated chronically, while an acute rise to these concentrations

may cause marked symptoms, including polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness, and changes in sensorium. In patients with severe hypercalcemia (calcium >14 mg/dL [3.5 mmol/L]), there is often progression of these symptoms. (10)

Systemic Mastocytosis

Mastocytosis is a disorder in which abnormal mast cells are increased in one or more organs. The growth of mast cells is poorly controlled, sometimes as the result of mutations that produce clones, or exact copies, of cells. Systemic mastocytosis (SM) is the most common form diagnosed in adults and is characterized by mast cell infiltration of one or more internal organs, with or without skin involvement. Symptoms of mastocytosis include:

- Anaphylaxis;
- Itching, flushing, hives, swelling;
- Wheezing or shortness of breath;
- Sinus congestion and pressure;
- Throat swelling;
- Palpitations, changes in blood pressure, dizziness, fainting;
- Nausea, vomiting, abdominal pain, diarrhea;
- Uterus cramps/bleeding;
- Bone or muscle pain, osteopenia, osteoporosis;
- Headache, brain fog, anxiety, short memory span, depression. (11)

The diagnosis of systemic mastocytosis is determined by criteria established by the World Health Organization (WHO) consensus group and requires meeting the major criterion plus one minor criterion, or alternatively, three of the minor criteria. See Table 2.

T**able 2. Diagnostic Criteria for Systemic Mastocytosis**

Major Criteria	Multifocal dense infiltrates of mast cells (MCs) (≥ 15 MCs in aggregate) detected in sections of bone marrow and/or other extracutaneous organ(s).
Minor Criteria	More than 25% of MCs in bone marrow or other extracutaneous organ(s) show abnormal morphology (i.e., are atypical MC type 1 or are spindle–shaped MCs) in multifocal lesions in histologic examination.
	KIT mutation at codon 816 or other activating *KIT* mutation in extracutaneous organ(s) (in most cases bone marrow) or peripheral blood.
	CD2, CD25, and/or CD30 expression on MCs.
	Serum total tryptase > 20 ng/mL.

Osteoporosis and osteopenia are the most common bone complications in patients with systemic mastocytosis. (12)

Denosumab

Denosumab is a human immunoglobulin - IgG2 - monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). It binds to RANKL, a transmembrane or soluble protein essential for the formation, function and survival

of osteoclasts, the cells responsible for bone resorption. It prevents RANKL from activating is receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. (13, 14)

Regulatory Status
The U.S. Food and Drug Administration (FDA) approved denosumab (Prolia®) for the following indications:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture – June 1, 2010;
- Treatment of bone loss in patients with prostate or breast cancer undergoing hormone ablation therapy – September 19, 2011;
- Treatment of bone loss in men with osteoporosis at high risk for fracture – September 21, 2012;
- Glucocorticoid-induced osteoporosis – May 21, 2018. (15)

The FDA approved denosumab (Xgeva®) for the following indications:

- Prevention of skeletal-related events in patients with bone metastasis from solid tumors – November 19, 2010;
- Treatment of giant cell tumor of the bone – June 13, 2013;
- Hypercalcemia of malignancy refractory to bisphosphonate therapy – December 8, 2014;
- Prevention of skeletal-related events in patients with multiple myeloma – January 5, 2018. (16)

In March 2024, the FDA approved Jubbonti® (denosumab-bbdz) as a biosimilar to Prolia® (denosumab), and Wyost® (denosumab-bbdz) as a biosimilar to Xgeva®. (17, 18)

In February 2025, the FDA approved Ospomyv™ (denosumab-dssb) as a biosimilar to Prolia® (denosumab), and Xbryk™ (denosumab-dssb) as a biosimilar to Xgeva®. (19, 20)

In February 2025, the FDA approved Stoboclo® (denosumab-bmwo) as a biosimilar to Prolia® (denosumab), and Osenvelt® (denosumab-bmwo) as a biosimilar to Xgeva®. (21, 22)

In March 2025, the FDA approved Conexxence® (denosumab-bnht) as a biosimilar to Prolia® (denosumab), and Bomyntra® (denosumab-bnht) as a biosimilar to Xgeva®. (23, 24)

Rationale

Prolia®/Jubbonti®/Ospomyv™/Stoboclo®/Conexxence® (13, 17, 19, 21, 23)
Treatment of Postmenopausal Women with Osteoporosis
The efficacy and safety of denosumab in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled trial. Enrolled women

had a baseline bone mass density (BMD) T-score between -2.5 and -4.0 at either the lumbar spine or total hip. Women with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 7808 enrolled women were aged 60 to 91 years with a mean age of 72 years. Overall, the mean baseline lumbar spine BMD T-score was -2.8, and 23% of women had a vertebral fracture at baseline. Women were randomized to receive subcutaneous injections of either placebo (N = 3906) or denosumab 60 mg (N = 3902) once every 6 months. All women received at least 1000 mg calcium and 400 international units (IU) vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically-diagnosed) vertebral fractures at 3 years. Vertebral fractures were diagnosed based on lateral spine radiographs (T4-L4) using a semiquantitative scoring method. Secondary efficacy variables included the incidence of hip fracture and nonvertebral fracture, assessed at 3 years.

Effect on Vertebral Fractures

Denosumab significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$), as shown in Table 3. The incidence of new vertebral fractures at year 3 was 7.2% in the placebo-treated women compared to 2.3% for the denosumab-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at year 3.

Table 3. The Effect of Denosumab on the Incidence of New Vertebral Fractures in Postmenopausal Women

	Proportion of Women with Fracture (%)[1]		**Absolute Risk of Reduction (%)[2] (95% CI)**	**Relative Risk of Reduction (%)[2] (95% CI)**
	Placebo N=3691 (%)	**Denosumab N=3702 (%)**		
0-1 Year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)
0-2 Years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)
0-3 Years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)

[1] Event rates based on crude rates in each interval.

[2] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group variable.

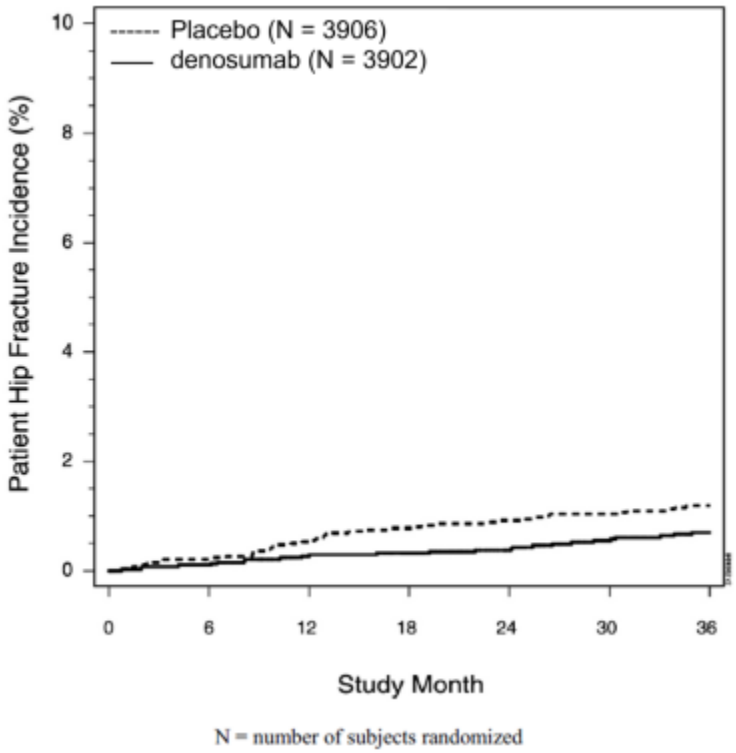
CI: confidence interval.

Denosumab was effective in reducing the risk for new morphometric vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis.

Effect on Hip Fractures

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for denosumab-treated women at year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years ($p = 0.04$) (Figure 1).

Figure 1. Cumulative Incidence of Hip Fractures Over 3 Years



Effect on Nonvertebral Fractures

Treatment with denosumab resulted in a significant reduction in the incidence of nonvertebral fractures (Table 4).

Table 4. The Effect of Denosumab on the Incidence of Nonvertebral Fractures at Year 3

	Proportion of Women with Fracture (%)[1]		**Absolute Risk Reduction (%) (95% CI)**	**Relative Risk Reduction (%) (95% CI)**
	Placebo N=3906 (%)	**Denosumab N=3902 (%)**		
Nonvertebral fracture[2]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)[3]

CI: confidence interval.

[1] Event rates based on Kaplan-Meier estimates at 3 years.

[2] Excluding those of the vertebrae (cervical, thoracic, and lumbar) skull, facial, mandible, metacarpus, and finger and toe phalanges.

[3] p-value = 0.01.

Effect on Bone Mineral Density (BMD)

Treatment with denosumab significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck. Consistent effects on BMD were observed at the

lumbar spine, regardless of baseline age, race, weight/body mass index (BMI), baseline BMD, and level of bone turnover.

After denosumab discontinuation, BMD returned to approximately baseline levels within 12 months.

Bone Histology and Histomorphometry
A total of 115 transiliac crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either month 24 and/or month 36 (53 specimens in denosumab group, 62 specimens in placebo group). Of the biopsies obtained, 115 (100%) were adequate for qualitative histology and 7 (6%) were adequate for full quantitative histomorphometry assessment.

Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with denosumab.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with denosumab, 35% had no tetracycline label present at the month 24 biopsy and 38% had no tetracycline label present at the month 36 biopsy, while 100% of placebo-treated patients had double label present at both time points. When compared to placebo, treatment with denosumab resulted in virtually absent activation frequency and markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

<u>Treatment to Increase Bone Mass in Men with Osteoporosis</u>
The efficacy and safety of denosumab in the treatment to increase bone mass in men with osteoporosis was demonstrated in a 1-year, randomized, double-blind, placebo-controlled trial. Enrolled men had a baseline BMD T-score between -2.0 and -3.5 at the lumbar spine or femoral neck. Men with a BMD T-score between -1.0 and -3.5 at the lumbar spine or femoral neck were also enrolled if there was a history of prior fragility fracture. Men with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that may affect bone were excluded from this study. The 242 men enrolled in the study ranged in age from 31 to 84 years with a mean age of 65 years. Men were randomized to receive SC injections of either placebo (n = 121) or denosumab 60 mg (n = 121) once every 6 months. All men received at least 1000 mg calcium and at least 800 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to 1-year. Secondary efficacy variables included percent change in total hip, and femoral neck BMD from baseline to 1-year.

Treatment with denosumab significantly increased BMD at 1-year. The treatment differences in BMD at 1-year were 4.8% (+0.9% placebo, +5.7% denosumab; (95% CI: 4.0, 5.6); $p < 0.0001$) at

the lumbar spine, 2.0% (+0.3% placebo, +2.4% denosumab) at the total hip, and 2.2% (0.0% placebo, +2.1% denosumab) at femoral neck. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, BMD, testosterone concentrations, and level of bone turnover.

Bone Histology and Histomorphometry
A total of 29 transiliac crest bone biopsy specimens were obtained from men with osteoporosis at 12 months (17 specimens in denosumab group, 12 specimens in placebo group). Of the biopsies obtained, 29 (100%) were adequate for qualitative histology and, in denosumab patients, 6 (35%) were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with denosumab. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with denosumab, 6% had no tetracycline label present at the month 12 biopsy, while 100% of placebo-treated patients had double label present. When compared to placebo, treatment with denosumab resulted in markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

<u>Treatment of Glucocorticoid-Induced Osteoporosis</u>
The efficacy and safety of denosumab in the treatment of patients with glucocorticoid-induced osteoporosis was assessed in the 12-month primary analysis of a 2-year, randomized, multicenter, double-blind, parallel-group, active-controlled study (NCT 01575873) of 795 patients (70% women and 30% men) aged 20 to 94 years (mean age of 63 years) treated with greater than or equal to 7.5 mg/day oral prednisone (or equivalent) for < 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (glucocorticoid-initiating subpopulation; n = 290) or ≥ 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (glucocorticoid-continuing subpopulation, n = 505). 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 glucocorticoid-continuing subpopulation were required to have a baseline BMD T-score of ≤ -2.0 at the lumbar spine, total hip, or femoral neck; or a BMD T-score ≤ -1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture.

Patients were randomized (1:1) to receive either an oral daily bisphosphonate (active-control, risedronate 5 mg once daily) (n = 397) or denosumab 60 mg subcutaneously once every 6 months (n = 398) for one year. Randomization was stratified by gender within each subpopulation. Patients received at least 1000 mg calcium and 800 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
In the glucocorticoid-initiating subpopulation, denosumab significantly increased lumbar spine BMD compared to the active-control at one year (Active-control 0.8%, denosumab 3.8%) with a

treatment difference of 2.9% ($p < 0.001$). In the glucocorticoid-continuing subpopulation, denosumab significantly increased lumbar spine BMD compared to active-control at 1 year (Active-control 2.3%, denosumab 4.4%) with a treatment difference of 2.2% ($p < 0.001$). Consistent effects on lumbar spine BMD were observed regardless of gender; race; geographic region; menopausal status; and baseline age, lumbar spine BMD T-score, and glucocorticoid dose within each subpopulation.

Bone Histology

Bone biopsy specimens were obtained from 17 patients (11 in the active-control treatment group and 6 in the denosumab treatment group) at Month 12. Of the biopsies obtained, 17 (100%) were adequate for qualitative histology. Qualitative assessments showed bone of normal architecture and quality without mineralization defects or bone marrow abnormality. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with active-control, 100% of biopsies had tetracycline label. In patients treated with denosumab, 1 (33%) had tetracycline label and 2 (67%) had no tetracycline label present at the 12-month biopsy. Evaluation of full quantitative histomorphometry including bone remodeling rates was not possible in the glucocorticoid-induced osteoporosis population treated with denosumab. The long-term consequences of this degree of suppression of bone remodeling in glucocorticoid-treated patients is unknown.

<u>Treatment of Bone Loss in Men with Prostate Cancer</u>

The efficacy and safety of denosumab in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) were demonstrated in a 3-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Men less than 70 years of age had either a BMD T-score at the lumbar spine, total hip, or femoral neck between -1.0 and -4.0, or a history of an osteoporotic fracture. The mean baseline lumbar spine BMD T-score was -0.4, and 22% of men had a vertebral fracture at baseline. The 1468 men enrolled ranged in age from 48 to 97 years (median 76 years). Men were randomized to receive subcutaneous injections of either placebo (n = 734) or denosumab 60 mg (n = 734) once every 6 months for a total of 6 doses. Randomization was stratified by age (< 70 years vs. ≥ 70 years) and duration of ADT at trial entry (≤ 6 months vs. > 6 months). Seventy-nine percent of patients received ADT for more than 6 months at study entry. All men received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)

The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 24. An additional key secondary efficacy variable was the incidence of new vertebral fracture through month 36 diagnosed based on x-ray evaluation by two independent radiologists. Lumbar spine BMD was higher at 2 years in denosumab-treated patients as compared to placebo-treated patients [-1.0% placebo, +5.6% denosumab; treatment difference 6.7% (95% CI: 6.2, 7.1); $p < 0.0001$].

With approximately 62% of patients followed for 3 years, treatment differences in BMD at 3 years were 7.9% (-1.2% placebo, +6.8% denosumab) at the lumbar spine, 5.7% (-2.6% placebo, +3.2% denosumab) at the total hip, and 4.9% (-1.8% placebo, +3.0% denosumab) at the femoral neck. Consistent effects on BMD were observed at the lumbar spine in relevant subgroups defined by baseline age, BMD, and baseline history of vertebral fracture.

Effect on Vertebral Fractures
Denosumab significantly reduced the incidence of new vertebral fractures at 3 years (p = 0.0125), as shown in Table 5.

Table 5. The Effect of Denosumab on the Incidence of New Vertebral Fractures in Men with Nonmetastatic Prostate Cancer

	Proportion of Men with Fracture (%)[1]		**Absolute Risk Reduction (%)[2] (95% CI)**	**Relative Risk of Reduction (%)[2] (95% CI)**
	Placebo N=673 (%)	**Denosumab N=679 (%)**		
0-1 Year	1.9	0.3	1.6 (0.5, 2.8)	85 (33, 97)
0-2 Years	3.3	1.0	2.2 (0.7, 3.8)	69 (27, 86)
0-3 Years	3.9	1.5	2.4 (0.7, 4.1)	62 (22, 81)

[1] Event rates based on crude rates in each interval.
[2] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group and androgen deprivation therapy (ADT) duration variables.
CI: confidence interval.

Treatment of Bone Loss in Women with Breast Cancer
The efficacy and safety of denosumab in the treatment of bone loss in women receiving adjuvant aromatase inhibitor (AI) therapy for breast cancer was assessed in a 2-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25. The mean baseline lumbar spine BMD T-score was -1.1, and 2.0% of women had a vertebral fracture at baseline. The 252 women enrolled ranged in age from 35 to 84 years (median 59 years). Women were randomized to receive subcutaneous injections of either placebo (n = 125) or denosumab 60 mg (n = 127) once every 6 months for a total of 4 doses. Randomization was stratified by duration of adjuvant AI therapy at trial entry (≤ 6 months vs. > 6 months). Sixty-two percent of patients received adjuvant AI therapy for more than 6 months at study entry. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 12. Lumbar spine BMD was higher at 12 months in denosumab -treated patients as compared to placebo-treated patients [-0.7% placebo, +4.8% denosumab; treatment difference 5.5% (95% CI: 4.8, 6.3); p < 0.0001].

With approximately 81% of patients followed for 2 years, treatment differences in BMD at 2 years were 7.6% (-1.4% placebo, +6.2% denosumab) at the lumbar spine, 4.7% (-1.0% placebo, +3.8% denosumab) at the total hip, and 3.6% (-0.8% placebo, +2.8% denosumab) at the femoral neck.

Xgeva/Wyost®/Xbryk™/Osenvelt®/Bomyntra® (14, 18, 20, 22, 24)

Bone Metastasis from Solid Tumors

The safety and efficacy of denosumab for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials comparing denosumab with zoledronic acid. In all three trials, patients were randomized to receive 120 mg denosumab subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE; testing for these outcome measures occurred if the main outcome measure was statistically significant. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Study 20050136 (NCT00321464) enrolled 2046 patients with advanced breast cancer and bone metastasis. Randomization was stratified by a history of prior SRE (yes or no), receipt of chemotherapy within 6 weeks prior to randomization (yes or no), prior oral bisphosphonate use (yes or no), and region (Japan or other countries). Forty percent of patients had a previous SRE, 40% received chemotherapy within 6 weeks prior to randomization, 5% received prior oral bisphosphonates, and 7% were enrolled from Japan. Median age was 57 years, 80% of patients were White, and 99% of patients were women. The median number of doses administered was 18 for denosumab and 17 for zoledronic acid.

Study 20050244 (NCT00330759) enrolled 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer with bone metastasis and multiple myeloma. Randomization was stratified by previous SRE (yes or no), systemic anticancer therapy at time of randomization (yes or no), and tumor type (non-small cell lung cancer, myeloma, or other). Eighty-seven percent were receiving systemic anticancer therapy at the time of randomization, 52% had a previous SRE, 64% of patients were men, 87% were White, and the median age was 60 years. A total of 40% of patients had non-small cell cancer, 10% had multiple myeloma, 9% had renal cell carcinoma, and 6% had small cell lung cancer. Other tumor types each comprised less than 5% of the enrolled population. The median number of doses administered was 7 for both denosumab and zoledronic acid.

Study 20050103 (NCT00321620) enrolled 1901 men with castrate-resistant prostate cancer and bone metastasis. Randomization was stratified by previous SRE, PSA level (less than 10 ng/mL or 10 ng/mL or greater) and receipt of chemotherapy within 6 weeks prior to randomization (yes or no). Twenty-six percent of patients had a previous SRE, 15% of patients had PSA less

than 10 ng/mL, and 14% received chemotherapy within 6 weeks prior to randomization. Median age was 71 years and 86% of patients were White. The median number of doses administered was 13 for denosumab and 11 for zoledronic acid.

Denosumab delayed the time to first SRE following randomization as compared to zoledronic acid in patients with breast or castrate-resistant prostate cancer (CRPC) with osseous metastases (Table 6). In patients with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, denosumab was noninferior to zoledronic acid in delaying the time to first SRE following randomization.

Overall survival and progression-free survival were similar between arms in all three trials.

Table 6. Efficacy Results for Denosumab Compared to Zoledronic Acid

	Study 20050139 Metastatic Breast Cancer		**Study 20050244 Metastatic Solid Tumors or Multiple Myeloma**		**Study 20050103 Metastatic Castrate-Resistant Prostate Cancer**	
	Denosumab N=1026	**Zoledronic Acid N=1020**	**Denosumab N=886**	**Zoledronic Acid N=890**	**Denosumab N=950**	**Zoledronic Acid N=951**
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
• Radiation to bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
• Pathological fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
• Surgery to bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
• Spinal cord compression	9 (0.9)	7 (0.7)	24 (2.7)	21 (2.4)	26 (2.7)	36 (3.8)
Meant time to SRE (months)	NR	26.4	20.5	16.3	20.7	17.1
Hazard ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	<0.001		<0.001		<0.001	
Superiority p-value[1]	0.010		0.060		0.008	
First and Subsequent SRE[2]						
Mean number/Patient	0.49	0.60	0.44	0.49	0.52	0.61
Rate ratio (95% CI)	0.77		0.90		0.82	

	(0.66, 0.89)	(0.77, 1.04)	(0.71, 0.94)
Superiority p-value[3]	0.001	0.145	0.009

[1] Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid within trial.
[2] All skeletal events post-randomization; new events defined by occurrence ≥21 days after preceding event.
[3] Adjusted p-values are presented.
SRE: skeletal-related event; CI: confidence interval.

Multiple Myeloma
The efficacy of denosumab for the prevention of skeletal-related events in newly diagnosed multiple myeloma patients with treatment through disease progression, was evaluated in Study 20090482 (NCT01345019), an international, randomized (1:1), double-blind, active-controlled, noninferiority trial comparing denosumab with zoledronic acid. In this trial, patients were randomized to receive 120 mg denosumab subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In this trial, the main efficacy outcome measure was noninferiority of time to first skeletal-related event (SRE). Additional efficacy outcome measures were superiority of time to first SRE, time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Study 20090482 enrolled 1718 newly diagnosed multiple myeloma patients with bone lesions. Randomization was stratified by a history of prior SRE (yes or no), the anti-myeloma agent being utilized/planned to be utilized in first-line therapy (novel therapy-based or non-novel therapy-based [novel therapies include bortezomib, lenalidomide, or thalidomide]), intent to undergo autologous PBSC transplantation (yes or no), stage at diagnosis (International Staging System I or II or III) and region Japan (yes or no). At study enrollment, 96% of the patients were receiving or planning to receive novel therapy-based first-line anti-myeloma therapy, 55% of the patients intended to undergo autologous PBSC transplantation, 61% of patients had a previous SRE, 32% were at ISS stage I, 38% were at ISS stage II and 29% were at ISS Stage III, and 2% were enrolled from Japan. Median age was 63 years, 82% of patients were White, and 46% of patients were women. The median number of doses administered was 16 for denosumab and 15 for zoledronic acid.

Denosumab was noninferior to zoledronic acid in delaying the time to first SRE following randomization (HR = 0.98, 95% CI, 0.85-1.14). The results for overall survival (OS) were comparable between denosumab and zoledronic acid treatment groups with a hazard ratio of 0.90 (95% CI: 0.70, 1.16).

Table 7. Efficacy Results for Denosumab Compared to Zoledronic Acid

	Study 20090482 Multiple Myeloma	
	Denosumab N=859	**Zoledronic Acid N=859**
First On-Study SRE		

Number of Patients who had SREs (%)	376 (43.8)	383 (44.6)
Components of First SRE		
Radiation to bone	47 (5.5)	62 (7.2)
Pathological fracture	342 (39.8)	338 (39.3)
Surgery to bone	37 (4.3)	48 (5.6)
Spinal cord compression	6 (0.7)	4 (0.5)
Median time to SRE (months) (95% CI)	22.8 (14.7, NE)	24 (16.6, 33.3)
Hazard ration (95% CI)	0.98 (0.85, 1.14)	

SRE: skeletal-related event; NE: not estimable.

Giant Cell Tumor of Bone

The safety and efficacy of denosumab for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials [Study 20040215 (NCT00396279) and Study 20062004 (NCT00680992)] that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. Patients received 120 mg denosumab subcutaneously every 4 weeks with additional doses on Days 8 and 15 of the first cycle of therapy.

Study 20040215 was a single-arm, pharmacodynamic, and proof of concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic resonance imaging (MRI) obtained within 28 days prior to study enrollment. Patients enrolled in Study 20040215 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during denosumab treatment.

Study 20062004 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Study 20062004 enrolled 10 patients who were 13-17 years of age. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease (e.g., sacral or spinal sites of disease, or pulmonary metastases); Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); Cohort 3 enrolled 11 patients who previously participated in Study 20040215. Patients underwent imaging assessment of disease status at intervals determined by their treating physician.

A retrospective interim analysis concluded by an independent review committee evaluated objective response in 187 patients enrolled and treated in Study 20040215 and Study 20062004 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Study 20040215 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Study 20062004). The primary efficacy outcome measure was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

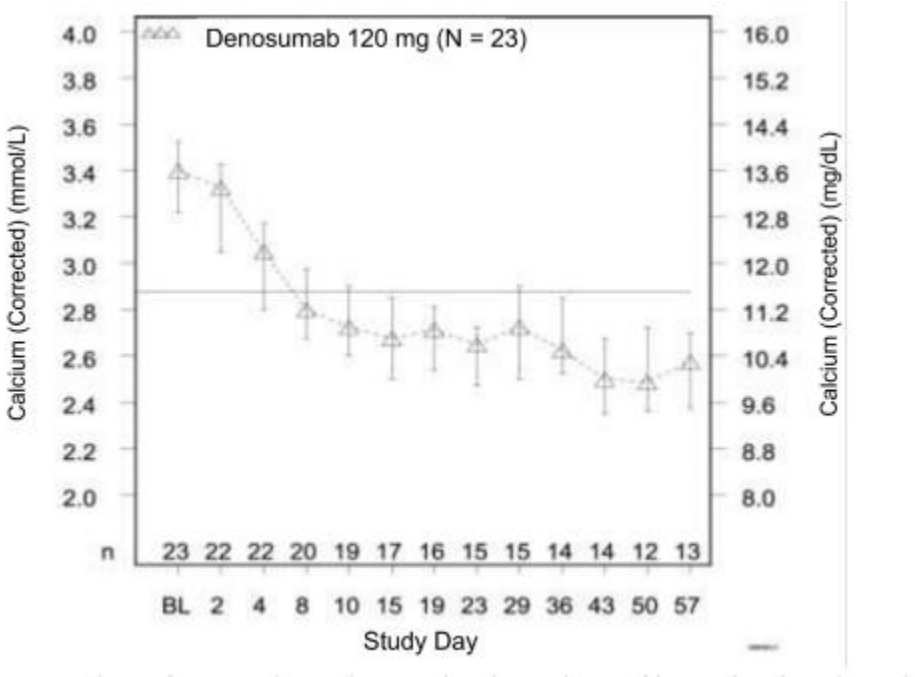
The overall objective response rate (RECIST 1.1) was 25% (95% CI: 19, 32). All responses were partial responses. The estimated median time to response was 3 months. In the 47 patients with an objective response, the median duration of follow-up was 20 months (range: 2-44 months), and 51% (24/47) had a duration of response lasting at least 8 months. Three patients experienced disease progression following an objective response.

Hypercalcemia of Malignancy

The safety and efficacy of denosumab was demonstrated in an open-label, single-arm trial [Study 20070315 (NCT00896454)] that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy. Patients received denosumab subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

In this trial, refractory hypercalcemia of malignancy was defined as an albumin-corrected calcium of > 12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate therapy in 7-30 days prior to initiation of denosumab therapy. The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium (CSC) ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after denosumab administration. Efficacy data are summarized in Figure 2 and Table 8. Concurrent chemotherapy did not appear to affect response to denosumab.

Figure 2. Corrected Serum Calcium by Visit in Responders (Median and Interquartile Range)



N = Number of responders who received ≥ 1 dose of investigational product.
n = Number of responders who had no missing data at baseline and the time point of interest.

Table 8. Efficacy in Patients with Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy

	N=33	Proportion (%) (95% CI)
All Responders (CSC ≤ 11.5 mg/dL) by Day 10	21	63.6 (45.1, 79.6)
All Responders by Day 57	23	69.7 (51.3, 84.4)
Complete Responders (CSC ≤ 10.8 mg/dL) by Day 10	12	36.4 (20.4, 54.9)
All Complete Responders by Day 57	21	63.6 (45.1, 79.6)

CSC: corrected serum calcium; CI: confidence interval.

Median time to response (CSC ≤ 11.5 mg/dL) was 9 days (95% CI: 8, 19), and the median duration of response was 104 days (95% CI: 7, not estimable). Median time to complete response (CSC ≤ 10.8 mg/dL) was 23 days (95% CI: 9, 36), and the median duration of complete response was 34 days (95% CI: 1, 134).

National Comprehensive Cancer Network® Drugs and Biologics Compendium®
The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium lists the following 2A or higher recommendations for denosumab. (25)

Prolia®:
- Prostate cancer:
  - For treatment-related bone loss in those receiving androgen deprivation therapy (ADT) when the absolute fracture risk warrants drug therapy.
- Invasive breast cancer:
  - Consider in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce risk of fractures.
- Inflammatory breast cancer (special consideration):
  - Consider in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce risk of fractures.
- Ductal carcinoma in situ (DCIS)
  - Consider in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce risk of fractures.

Xgeva®:
- Systematic mastocystosis:
  - As second-line therapy for osteopenia/osteoporosis in patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency.
- Giant cell tumor of bone:

    - Therapy as a single agent (preferred) or combined with serial embolization (preferred), and/or radiation therapy for resectable disease with unacceptable morbidity and/or unresectable axial lesions for patients with:
        - Localized disease;
        - Metastases at presentation;
        - Disease recurrence.
    - Preferred therapy as a single agent for:
        - Unresectable metastatic disease at presentation;
        - Unresectable metastatic recurrence;
        - Considered prior to surgery for resectable local recurrence.
- Papillary carcinoma:
    - Consider for bone metastases.
- Follicular carcinoma:
    - Consider for bone metastases.
- Medullary carcinoma:
    - Consider for bone metastases.
- Anaplastic carcinoma:
    - Consider as palliative care for bone metastases.
- Multiple myeloma:
    - Used in combination with primary myeloma therapy (preferred agent in patients with renal insufficiency).
- Kidney cancer:
    - Used as a component of best supportive care for bony metastases.
- Prostate cancer:
    - Prevention of skeletal-related events in M1 castration-resistant prostate cancer if bone metastases present (preferred).
- Invasive breast cancer:
    - Used with calcium and vitamin D supplementation in addition to systemic therapy or endocrine therapy for bone metastasis in patients with expected survival of ≥3 months and adequate renal function.
- Inflammatory breast cancer (special consideration):
    - Used with calcium and vitamin D supplementation in addition to systemic therapy or endocrine therapy for bone metastasis in patients with expected survival of ≥3 months and adequate renal function.
- Non-small cell lung cancer:
    - Consider in patients with bone metastases.
- Oncocytic carcinoma:
    - Consider for bone metastases.

Practice Guidelines and Position Statements

The International Osteoporosis Foundation, the Cancer and Bone Society, the International Expert Group for Aromatase Inhibitor–Associated Bone Loss, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, the

European Calcified Tissue Society, the International Menopause Society; and the International Society for Geriatric Oncology

A joint position statement was published in 2017 to identify fracture-related risk factors in patients treated with aromatase inhibitors and to outline key management strategies to help prevent bone loss and related fractures. The position statement offers the following guidance (6) In all patients initiating aromatase inhibitor treatment, fracture risk should be assessed, and recommendations given in regard to exercise and calcium/vitamin D supplementation.

- Bone-directed therapy should be recommended for the duration of aromatase inhibitor treatment to all patients with a T score less than –2.0 standard deviations (SD), or with a T score less than –1.5 SD with 1 additional risk factor, or with 2 or more risk factors (without bone mineral density).
- Patients with a T score greater than –1.5 SD and no risk factors should be managed based on bone mineral density loss during the first year and based on local guidelines for postmenopausal osteoporosis.
- Based on current evidence, 6-monthly denosumab (Xgeva®) or yearly zoledronic acid for the duration of aromatase inhibitor therapy is recommend for the prevention of aromatase inhibitor–associated bone loss in postmenopausal women receiving adjuvant aromatase inhibitor therapy, with zoledronic acid recommended when effects on disease recurrence are the priority and denosumab recommended when fracture risk is the dominant concern.
- Because of the decreased incidence of bone recurrence and breast cancer–specific mortality associated with bisphosphonate use, adjuvant bisphosphonates are recommended for all postmenopausal women at significant risk of disease recurrence.
- Compliance should be regularly assessed as well as bone mineral density after 12 to 24 months on treatment.

The North American Menopause Society

In 2021, the North American Menopause Society (NAMS) updated their 2010 position statement regarding the management of osteoporosis in postmenopausal women. (26) The position statement recommendations include in part:

- Evaluate bone mineral density (BMD) in all women:
  - Aged 65 years and older;
  - With a history of fracture (other than skull, facial bone, ankle, finger, and toe) after menopause;
  - With medical causes of bone loss such as adverse event (AE) therapy and systemic glucocorticoid therapy of more than 3 months.
- Consider BMD testing for postmenopausal women aged younger than 65 years who have 1 or more of more of these risk factors:
  - Discontinued estrogen with additional risk factors for fracture;
  - Thinness (body weight <127 lb. [57.7 kg] or body mass index [BMI] <21 kg/m^2);
  - History of hip fracture in a parent;
  - Current smoking;
  - Excessive alcohol intake;

- Long-term use of medications associated with bone loss such as prednisone or an aromatase inhibitor (AI).

- Drug therapy is recommended to prevent bone loss in postmenopausal women with:
  - Premature menopause, at least until the average age of natural menopause;
  - Low BMD (T-score < -1.0) and experiencing relatively rapid bone loss because of acute estrogen deficiency in the menopause transition or on discontinuing estrogen therapy;
  - Low BMD (T-score < -1.0) and other risk factors for fracture (e.g., family history) but who do not meet the criteria for osteoporosis treatment.
- Drug therapy is recommended to treat osteoporosis in these populations:
  - All postmenopausal women who have had a vertebral or hip fracture.
  - All postmenopausal women who have BMD values consistent with osteoporosis (i.e., T-scores <-2.5) at the lumbar spine, femoral neck, or total hip (LS, FN, or TH) region.
  - All postmenopausal women who have T-scores from-1.0 to -2.5 and any one of:
    - History of fracture of proximal humerus, pelvis, or distal forearm.
    - History of multiple fractures at other sites (excluding face, feet, and hands).
    - Increased fracture risk according to country-specific thresholds using FRAX. In the United States, those thresholds are a 10-year risk of major osteoporotic fracture (spine, hip, shoulder, and wrist) of at least 20% or of hip fracture of at least 3%.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J0897, J3490, J3590, J9999, Q5136

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. NIH. Osteoporosis Overview. NIH Osteoporosis and Related Bone Diseases National Resource Center. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Available at: <https://www.niams.nih.gov> (accessed January 29, 2025).
2. Rosen HN, Drake MT. Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women. In: UpToDate, Rosen CJ, Schmader KE (Eds), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed January 29, 2025).

3. Lewiecki EM. Osteoporotic fracture risk assessment. In: UpToDate, Rosen CJ, Schmader KE (Eds), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed January 29, 2025).
4. Smith MR. Side effects of androgen deprivation therapy. In: UpToDate. Lee WR, Richie JP (Eds), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed January 30, 2025).
5. Rosen HN. Clinical features and evaluation of glucocorticoid-induced osteoporosis. In: UpToDate. Rosen CJ (Ed), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed January 30, 2025).
6. Hadji P, Aapro MS, Body JJ, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO, IMS and SIOG. Journal of Bone Oncology. 2017; 7(1):1-12. PMID 28413771
7. Kim C, Bhatta S, Cyprien L, et al. Incidence of skeletal-related events among multiple myeloma patients in the United States at oncology clinics: Observations from real-world data. J Bone Oncol. Dec 2018; 14:100215. PMID 30666288
8. Hong S, Youk T, Lee SJ, et al. Bone metastases and skeletal-related events in patients with solid cancer: A Korean nationwide health insurance database study. PLoS ONE. 2020; 15(7):e0234927. PMID 32678818
9. Howritz MJ. Hypercalcemia of malignancy: Mechanisms. In: UpToDate. Rosen CJ (Ed), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed January 30, 2025).
10. Shane E. Clinical manifestations of hypercalcemia. In: UpToDate. Rosen CJ (Ed), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed January 30, 2025).
11. American Academy of Allergy Asthma & Immunology. Systemic Mastocytosis. Available at: <https://www.aaaai.org> (accessed January 30, 2025).
12. NCCN - Systemic Mastocytosis. NCCN Clinical Practice Guidelines in Oncology, Version 3, 2024 (April 24, 2024). National Comprehensive Cancer Network. Available at: <https://www.nccn.org> (accessed January 30, 2025).
13. Highlights of Prescribing Information: Prolia® (denosumab) (March 2024). Available at: <https://www.pi.amgen.com> (accessed January 29, 2025).
14. Highlights of Prescribing Information: Xgeva® (denosumab) (June 2020). Available at: <https://www.pi.amgen.com> (accessed January 29, 2025).
15. Prolia FDA Approval History. Available at: <https://www.drugs.com> (accessed January 29, 2025).
16. Xgeva FDA Approval History. Available at: <https://www.drugs.com> (accessed January 29, 2025).
17. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Jubbonti® (denosumab-bbdz) (March 2024). Available at: <https://www.accessdata.fda.gov> (accessed January 30, 2025).
18. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Wyost® (denosumab-bbdz) (March 2024). Available at: <https://www.accessdata.fda.gov> (accessed January 30, 2025).

19. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Ospomyv™ (denosumab-dssb) (February 2025). Available at: <https://www.accessdata.fda.gov> (accessed March 6, 2025).
20. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Xbryk™ (denosumab-dssb) (February 2025). Available at: <https://www.accessdata.fda.gov> (accessed March 6, 2025).
21. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Stoboclo® (denosumab-bmwo) (February 2025). Available at: <https://www.accessdata.fda.gov> (accessed July 1, 2025).
22. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Osenvelt® (denosumab-bmwo) (February 2025). Available at: <https://www.accessdata.fda.gov> (accessed July 1, 2025).
23. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Conexxence® (denosumab-bnht) (March 2025). Available at: <https://www.accessdata.fda.gov> (accessed July 1, 2025).
24. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Bomyntra® (denosumab-bnht) (March 2025). Available at: <https://www.accessdata.fda.gov> (accessed July 1, 2025).
25. NCCN Drugs and Biologics Compendium®. Denosumab. National Comprehensive Cancer Network. Available at: <https://www.nccn.org> (accessed January 30, 2025).
26. NAMS. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause. Sep 2021; 28(9):973-997. PMID 34448749

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
10/01/2025	Document updated. The following change was made to Coverage: Updated coverage criteria to include the biosimilars denosumab-bmwo (i.e., Stoboclo®/Osenvelt®) and denosumab-bnht (i.e., Conexxence®/Bomyntra®). Added references 21-24.

07/01/2025	Document updated. The following change was made to Coverage: Updated coverage criteria to include the biosimilar denosumab-dssb (i.e., Ospomyv™ and Xbryk™). Added references 19 and 20.
06/01/2025	Document updated with literature review. The following change was made to Coverage: Modified Prolia criteria specific to breast cancer to replace "adjuvant endocrine therapy" with "an aromatase inhibitor". Added references 3, 10, 11, 15, and 16; others updated.
10/01/2024	Document updated. The following change was made to Coverage: Updated coverage criteria to include the biosimilar denosumab-bbdz (i.e., Jubbonti® and Wyost®). Added references 14 and 15. Title changed from "Denosumab (Prolia & Xgeva)".
06/01/2024	Document updated. The following change was made to Continuation Therapy in Coverage: removed "through a previously authorized pharmacy or medical benefit" in the statement "Continuation of Prolia/Xgeva may be considered medically necessary for all members (including new members…" Now reads: Continuation of Prolia/Xgeva may be considered medically necessary for all Members (including new members): who are currently receiving the requested medication for an indication listed below, AND who are experiencing benefit from therapy as evidenced by disease stability or disease improvement, AND when dosing is in accordance with an authoritative source." No new references added.
04/01/2024	New medical document. Denosumab (Prolia® and Xgeva®) may be considered medically necessary based on the indications listed in the coverage. Continuation of denosumab (Prolia/Xgeva) therapy is considered medically necessary for all members (including new members) who are currently receiving the requested medication through a previously authorized pharmacy or medical benefit, when dosing is in accordance with an authoritative source, and who are experiencing benefit from therapy as evidenced by disease stability or disease improvement. Denosumab (Prolia or Xgeva) is considered experimental, investigational and/or unproven for all other indications, including but not limited to combination therapy of denosumab and intravenous bisphosphonates; patients with uncorrected preexisting hypocalcemia; bone loss associated with hormone-ablation therapy (other than aromatase inhibitors) in breast cancer; cancer pain; central giant cell granuloma; hyper-parathyroidism; immobilization hypercalcemia; osteogenesis imperfecta; osteopenia (other than due to systemic mastocytosis); Paget's disease of bone; primary bone sarcomas (e.g., Ewing's sarcoma and osteosarcoma); rheumatoid arthritis.