



## Bone Resorption Suppression and Related Agents Therapeutic Class Review (TCR)

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June 4, 2020

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June 2020

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
<b>Bisphosphonates</b>		
alendronate (Binosto®) <sup>1</sup>	Mission, Ascend*	Treatment and prevention of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis
alendronate (Fosamax®) <sup>2</sup>	generic, Merck	Treatment and prevention of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent of 7.5 mg or greater of prednisone and who have low bone mineral density Treatment of Paget's disease of bone in men and women
alendronate/ vitamin D (Fosamax® Plus D) <sup>3</sup>	Merck	Treatment of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis
ibandronate (Boniva®) <sup>4</sup>	generic, Roche	Treatment and prevention of osteoporosis in postmenopausal women
risedronate (Actonel®) <sup>5</sup>	generic, Actavis/Allergan	Treatment and prevention of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis Prevention and treatment of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent of 7.5 mg or greater of prednisone for chronic diseases Treatment of Paget's disease of bone in men and women
risedronate delayed-release (Atelvia®) <sup>6</sup>	generic, Actavis/Allergan	Treatment of osteoporosis in postmenopausal women
<b>Calcitonins</b>		
calcitonin-salmon <sup>7</sup>	generic	Treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause when alternative treatments are not suitable. Fracture reduction efficacy has not been demonstrated.

\* Ascend Therapeutics has launched a Binosto tablet, and Mission's Binosto will be discontinued in the future.

**FDA-Approved Indications (continued)**

Drug	Manufacturer	Indication(s)
<b>Others</b>		
abaloparatide (Tymlos®) <sup>8</sup>	Radius Health	Treatment of osteoporosis in postmenopausal women who are at high risk for fractures
denosumab (Prolia®) <sup>9</sup>	Amgen	Treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or in patients who have failed or are intolerant to other available osteoporosis therapy Treatment of osteoporosis associated with newly initiated or sustained systemic glucocorticoid therapy in men and women at high risk for fracture. Treatment of bone loss in men with prostate cancer on androgen deprivation therapy Treatment of bone loss in women undergoing breast cancer therapy with adjuvant aromatase therapy Treatment to increase bone mass in men diagnosed with osteoporosis and a high fracture risk who have failed or are intolerant to other potential therapies
raloxifene (Evista®) <sup>10</sup>	generic, Eli Lilly	Treatment and prevention of osteoporosis in postmenopausal women Reduction in risk of invasive breast cancer in postmenopausal women who either have osteoporosis or are at high risk for invasive breast cancer
romosozumab-aqqg (Evenity®) <sup>11</sup>	Amgen	Treatment of osteoporosis in postmenopausal women 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
teriparatide* <sup>12</sup>	Alvogen	Treatment of osteoporosis in postmenopausal women who are at high risk for fracture Increase of bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
teriparatide (Forteo®) <sup>13</sup>	Eli Lilly	Treatment of osteoporosis in postmenopausal women who are at high risk for fractures Increase of bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fractures Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

\* Approved via an abbreviated approval pathway under a 505(b)(2) application that relied, in part, on safety and efficacy data for Eli Lilly's teriparatide (Forteo). Notably, this was approved under the trade name Bonsity, but it has been marketed without the trade name.<sup>14</sup>

Amgen manufactures denosumab (Xgeva®), indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors, treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, and treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. It is administered as a 120 mg subcutaneous (SC) injection every 4 weeks.<sup>15</sup> Xgeva will not be addressed in this therapeutic class review.

## OVERVIEW

Osteoporosis is characterized by the deterioration of bone tissue and low bone mass. Approximately 10 million Americans have the diagnosis of osteoporosis, and an additional 43 million have low bone mass, placing them at increased risk for this disease.<sup>16</sup> Approximately 1 in 4 men in the United States (US) over the age of 50 years will have an osteoporosis-related fracture in his remaining lifetime.<sup>17</sup> Osteoporosis is common in all racial groups but is most common in Caucasians.

There are 3 categories of osteoporosis: postmenopausal, age-related, and secondary osteoporosis. Postmenopausal osteoporosis affects mainly trabecular bone in the decade after menopause as estrogen deficiency increases bone resorption more than bone formation. Age-related osteoporosis results from increased bone resorption that begins shortly after peak bone mass is obtained. Cortical and trabecular bone are both affected. Secondary osteoporosis is caused by medications (glucocorticoids, excess thyroid replacement, some antiepileptic drugs, and long-term heparin use) or diseases (hyperthyroidism, type 1 diabetes). Both types of bone are affected.

The primary goal of osteoporosis management is to reduce fracture risk. This can be done by reducing bone loss, increasing bone mass or improving bone architecture to maintain bone strength, and minimizing or eliminating factors that may contribute to fractures (e.g., reducing the risk of falls).<sup>18</sup> Non-pharmacologic prevention and treatment methods include social habit and dietary changes, as well as exercise and fall prevention. Pharmacologic prevention and treatment focuses on limiting bone resorption. Each of the medication classes has a different mechanism of action and side effect profile. The US Preventive Services Task Force (USPSTF) advises that the choice of treatment should consider the patient's clinical situation and the tradeoff between benefits and harms.<sup>19</sup>

The North American Menopause Society (NAMS), in its 2010 position statement, recommends bisphosphonates as first-line drugs to treat postmenopausal women with osteoporosis (defined as having a T-score  $\leq -2.5$ ). Calcitonin is not a first-line drug for postmenopausal osteoporosis treatment; however, it is an option for women with osteoporosis who are more than 5 years beyond menopause.<sup>20</sup> NAMS continues to recommend that healthcare providers should consider treating patients with osteoporosis or low bone mass who have either a 10-year probability of a hip fracture of at least 3% or a 10-year probability of a major osteoporosis-related fracture of at least 20%, based on the US-adapted algorithm (e.g., the FRAX<sup>®</sup> tool) in their Clinical Care Recommendations for menopause.<sup>21</sup> Pharmacologic options approved for the treatment of postmenopausal osteoporosis include denosumab, teriparatide, and calcitonin. Pharmacologic options approved for the prevention and treatment of postmenopausal osteoporosis include bisphosphonates and the estrogen agonist/antagonist raloxifene. There are no prospective studies comparing the antifracture efficacy of these drugs. They note that there is controversy regarding the optimal duration of bisphosphonate therapy and the length of a "drug holiday" and state that these should be based on an individualized assessment of risk and benefit. Abaloparatide (Tymlos) and romosozumab-aqqg (Evenity) were not available at the time of these publications.

The 2014 National Osteoporosis Foundation (NOF) Clinician's Guide to Prevention and Treatment of Osteoporosis continues to recognize all medications approved by the US Food and Drug Administration (FDA) for the prevention and/or treatment of osteoporosis as possible options.<sup>22</sup> The guide also states that the treatment agent of choice should be based on available clinical information in addition to intervention thresholds. Further, the 2014 guide recommends that the duration of pharmacologic

therapy be specific to each individual with the need for continuation of medications reviewed on an annual basis.

The American College of Physicians (ACP) published an update in 2017 to the 2008 guidelines for the treatment of low bone density and osteoporosis to prevent fractures in men and women.<sup>23</sup> The guideline is also endorsed by the American Academy of Family Physicians (AAFP). ACP recommends physicians offer pharmacologic treatment to reduce the risk for hip and vertebral fractures in women with known osteoporosis and treatment should occur for 5 years; however, they recommend against bone density monitoring during the 5-year treatment period. ACP recommends against using menopausal estrogen or estrogen with progesterone or raloxifene for osteoporosis treatment in women. They further state that treatment decisions in older osteopenic women ( $\geq 65$  years old) who are at a high risk of fracture should be based on a discussion with the patient regarding her preference, fracture risk and treatment benefits, harms, and cost. Regarding therapy in men, ACP recommends that clinicians offer treatment with bisphosphonates to reduce the risk of vertebral fractures in those with clinical osteoporosis. These guidelines are based on a systematic review of literature and evidence for specific pharmacotherapy treatments which are detailed in the publication. Abaloparatide (Tymlos) and romosozumab-aqqg (Evenity) were not available at the time of this publication.

Regarding adherence, the International Osteoporosis Foundation (IOF)-European Calcified Tissue Society Working Group developed a position paper to screen for adherence to oral bisphosphonates.<sup>24</sup> Due to results of the key clinical studies, the group suggests assessing for improvement using bone turnover markers (CTX, PINP) at baseline and 3 months after initiation to assess for appropriate changes. They note that a lack of benefit may suggest adherence concerns. The AACE/ACE guidelines state that consistent contact with a healthcare provider following initiation of therapy for osteoporosis is one of a few interventions that improves adherence.<sup>25</sup>

Select organizations have also provided guidance on secondary osteoporosis due to select causes. In 2017, the American College of Rheumatology (ACR) updated guidance on managing glucocorticoid-induced osteoporosis in adults and children.<sup>26</sup> Fracture risk should be assessed as soon as possible, but at least within 6 months after starting long-term glucocorticoid treatment and every 12 months during treatment. Assessment should include use of the FRAX tool in patients 40 years of age and older. In those under 40 years old with a high risk of fracture, bone mineral density (BMD) testing should occur within 6 months of the initiation of glucocorticoid treatment. Treatment should include optimal calcium and vitamin D intake and lifestyle changes consistent with good bone health, such as smoking cessation, weight management, balanced diet, limited alcohol consumption, and regular weight-bearing or resistance training exercise. ACR's further recommendations on antiresorptive treatment are based on individual patient characteristics, including fracture risk, age, and special populations (e.g., childbearing age, gender, BMD, fracture risk, children, transplant recipients). Following implementation of the lifestyle recommendations listed above, no further treatment is needed in patients with a low risk of fracture, but these patients should be monitored with yearly fracture risk reassessments, including BMD testing every 2 to 3 years. In those with moderate to high risk of fracture, oral bisphosphonates are generally recommended as first-line therapy. Subsequent treatments include intravenous (IV) bisphosphonates, teriparatide, denosumab, or raloxifene. Notably, these products are not FDA-approved for use in the pediatric population.

The IOF, in conjunction with multiple other international clinical organizations, issued a joint position statement regarding the management of aromatase inhibitor-associated bone loss (AIBL) in

postmenopausal women with hormone sensitive breast cancer.<sup>27</sup> They state all patients initiating aromatase inhibitor (AI) treatment should be assessed for fracture risk and the need for exercise and supplementation with calcium and/or vitamin D should be addressed. They recommend bone-directed therapy throughout AI treatment for patients meeting the following criteria: T-score < -2 standard deviations (SD), T-score < -1.5 SD with 1 additional risk factor, or ≥ 2 risk factors. Examples of fracture risk factors include age > 65 years, low body mass index, family or personal history of select fractures, smoking, and long-term oral corticosteroid use. Patients with a T-score of > -1.5 and no risk factors should be managed based on BMD loss within the first year and local guidelines for osteoporosis. Based on review of published evidence, denosumab and IV zoledronic acid are the preferred agents for prevention and treatment of AIBL. Denosumab is preferred when fracture risk is the dominant concern while zoledronic acid is preferred when disease recurrence is priority. They further state that emerging anticancer benefits from bisphosphonates offers additional rationale to proactively use bisphosphonates during adjuvant AI therapy. Finally, the consensus group recommends routinely assessing compliance and measuring BMD following 12 to 24 months of treatment.

The Endocrine Society (ES) 2019 guidelines on osteoporosis recommend pharmacologic therapy for postmenopausal women at high risk of fracture, especially those with recent fracture. This population should be treated initially with a bisphosphonate or denosumab to reduce fracture risk.<sup>28</sup> However, ibandronate is not recommended to reduce the risk of nonvertebral or hip fracture. For postmenopausal women with a very high risk of fracture, the guidelines recommend starting with either teriparatide or abaloparatide for up to 2 years of treatment before switching to a bisphosphonate or denosumab to maintain bone density. Raloxifene, calcitonin, and hormone replacement therapy are only recommended if patients are not appropriate candidates for treatment with bisphosphonates or denosumab and do not have any other contraindications to these therapies.

Romosozumab-aqqg (Evenity) was FDA approved in April 2019. In 2020, the ES updated their 2019 guidance on the management of osteoporosis in postmenopausal women to include romosozumab.<sup>29</sup> Romosozumab was concluded to be a potential treatment option for select postmenopausal women at very high risk of osteoporotic fracture, however patients should be carefully selected due to the serious cardiovascular (CV) events observed in a clinical trial with an active comparator. To reduce the risk for vertebral, hip, and nonvertebral fractures, treatment with monthly romosozumab (210 mg) is recommended for up to 1 year in postmenopausal women with osteoporosis at very high risk for fracture, including those with low bone density T-scores (<-2.5) and fractures or with multiple vertebral fractures; however, women at high risk of stroke or CV disease (e.g., past myocardial infarction [MI] or stroke) should not receive romosozumab until further evaluation of the CV risk from this agent. After completing a course of romosozumab, it is recommended that patients receive treatment with antiresorptive therapies to maintain improvements in bone density and reductions in fracture risk.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis (2020 update) recommend alendronate, risedronate, zoledronate, and denosumab as initial therapy for most patients at high risk of fracture.<sup>30</sup> Teriparatide, abaloparatide, denosumab, romosozumab, or zoledronate should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk. Based on limited evidence, raloxifene or ibandronate may be appropriate initial therapy in some cases where patients require drugs with spine-specific efficacy. The guidelines also state use of calcitonin as a long-term treatment for osteoporosis should be limited as more effective agents are available to increase bone density and reduce fracture risk.

## PHARMACOLOGY<sup>31,32,33,34,35,36,37,38,39</sup>

Bisphosphonates adsorb to bone apatite and are permanently incorporated into bone. Osteoclasts are unable to adhere to bone surfaces containing bisphosphonates and, ultimately, are unable to resorb and turnover bone. Bisphosphonates include alendronate (Fosamax), ibandronate (Boniva), and risedronate (Actonel, Atelvia). The inclusion of vitamin D with alendronate (Fosamax Plus D) promotes calcium absorption.

Calcium is a major substrate for mineralization and has an antiresorptive effect and decreases bone turnover. Vitamin D is required for normal bone formation, and insufficient levels are associated with negative calcium balance, increased parathyroid hormone (PTH) levels, bone loss, and increased risk of skeletal fracture.

The hormone calcitonin is secreted in response to high serum calcium levels. Calcitonin receptors have been found on osteoclasts, osteoblasts, and renal cell membranes. Stimulation of these receptors by calcitonin-salmon results in a decrease in osteoclast activity and a decrease in renal reabsorption of calcium and sodium. Bone formation may also be augmented by increased osteoblastic activity.

Abaloparatide (Tymlos) is a PTHrP(1-34) analog which acts as an agonist at the PTH1 receptor (PTH1R). This results in activation of the cAMP signaling pathway in target cells. In animal studies, abaloparatide had an anabolic effect on bone, demonstrated by increases in BMD and bone mineral content (BMC) that correlated with increases in bone strength at vertebral and/or nonvertebral sites.

RANK ligand (RANKL) is a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Denosumab (Prolia), a RANK ligand inhibitor, binds to RANKL and prevents it from activating its 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.

The biological actions of raloxifene (Evista) are largely mediated through estrogen receptor binding. Binding results in activation of certain estrogenic pathways that act to decrease resorption of bone and reduce the biological markers of bone turnover. Raloxifene antagonizes estrogenic receptors in the uterine and breast tissue and also decreases total and low density lipoprotein (LDL) cholesterol.

Romosozumab-aqqg (Evenity) inhibits the bone metabolism regulator sclerostin, leading to increased bone formation and, to a lesser extent, decreased bone resorption. Animal studies showed that romosozumab-aqqg stimulates osteoblastic activity resulting in increases in trabecular and cortical bone mass and improvements in bone structure and strength.

Parathyroid hormone increases bone resorption. Teriparatide (Teriparatide, Forteo) contains recombinant human parathyroid hormone and stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. The anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

## PHARMACOKINETICS<sup>40,41,42,43,44,45,46,47,48,49,50,51,52,53</sup>

Drug	Bioavailability (%)	Half-Life	Metabolism	Excretion (%)
<b>Bisphosphonates</b>				
alendronate (Binosto)	0.64 women, 0.59 men	> 10 yrs	No metabolism	Renal: 50
alendronate (Fosamax)	0.64 women, 0.59 men	> 10 yrs	No metabolism	Renal: 50
ibandronate (Boniva)	0.6	37-157 hrs	No metabolism	Renal and Fecal
risedronate (Actonel)	0.63	20 days	No metabolism	Renal and fecal
risedronate delayed-release (Atelvia)	Varies dependent upon food (see below)	23.4 days	No metabolism	Renal and fecal
vitamin D* (Fosamax Plus D)	0.64 women, 0.59 men		Liver hydroxylation to active form; metabolized to active form by kidneys	Renal and fecal
<b>Calcitonins</b>				
calcitonin-salmon	3	43 min	nr	nr
<b>Others</b>				
abaloparatide (Tymlos)	36	1.7 hrs	nr	nr
denosumab (Prolia)	nr	25.4 days	nr	nr
raloxifene (Evista)	2	27.7 hrs	Extensively metabolized to 3 glucuronide conjugates	Fecal
romosozumab-aqqg (Evenity)	nr	12.8 days	nr	nr
teriparatide	95	0.79 hr	nr	nr
teriparatide (Forteo)	95	1 hr	nr	nr

nr = not reported

Alendronate effervescent tablets pharmacokinetics are equivalent to similar doses of the oral tablets.

\* Alendronate pharmacokinetics are not altered by the addition of vitamin D.

Risedronate delayed-release (Atelvia) tablets contain a pH-sensitive enteric coating and a chelating agent (EDTA). The bioavailability of risedronate delayed-release (Atelvia) 35 mg tablet administered after a high-fat breakfast was approximately 2- to 4-fold greater than the risedronate immediate-release (Actonel) 35 mg tablet administered 30 minutes prior to a high-fat breakfast. Risedronate delayed-release (Atelvia) should be taken immediately following breakfast and not under fasting conditions.

## CONTRAINDICATIONS/WARNINGS<sup>54,55,56,57,58,59,60,61,62,63,64,65</sup>

### Bisphosphonates

Bisphosphonates are generally contraindicated in the following conditions: abnormalities of the esophagus which delay esophageal emptying (e.g., stricture or achalasia), an inability to stand or sit upright for 30 to 60 minutes after dosing, and hypocalcemia.

Chronic, severe musculoskeletal pain has been reported in patients taking bisphosphonates. Patients may experience pain symptoms at any time after treatment initiation with a bisphosphonate. Upon discontinuation of the bisphosphonate, relief of pain symptoms has come in the form of slow or incomplete symptom resolution to complete relief. The FDA continues to investigate this possible association.<sup>66,67</sup>

Osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection, has been reported in patients taking bisphosphonates; most cases reported in patients treated intravenously, but some reports have occurred in patients treated orally. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and comorbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection). For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ.

The FDA continues to review information regarding atypical fractures of the femur associated with the long term use of bisphosphonates to treat osteoporosis.<sup>68</sup> Currently, the FDA recommends that healthcare professionals: be aware of the possibility of atypical femur fractures in patients taking bisphosphonates; rule out an incomplete femoral fracture if a patient presents with new thigh or groin pain; discontinue potent anti-resorptive medications, including bisphosphonates, in patients who have evidence of a femoral fracture; periodically re-evaluate whether continued bisphosphonate therapy is needed, especially in patients who have been treated for more than 5 years; and instruct patients to seek medical attention if they experience new groin or thigh pain. This notice does not affect bisphosphonate drugs that only are used to treat Paget's disease or high blood calcium levels due to cancer.

### Calcitonin

In a meta-analysis of 21 randomized, controlled clinical trials with calcitonin-salmon (nasal spray or investigational oral formulations), the overall incidence of malignancies reported was higher among calcitonin-salmon-treated patients (4.1%) compared with placebo-treated patients (2.9%). This suggests a possible increased risk of malignancies in calcitonin-salmon-treated patients compared to placebo. The benefits for the individual patient should be carefully considered against possible risks.

### Others

Abaloparatide (Tymlos) carries a boxed warning regarding the risk of osteosarcoma. It is unknown whether abaloparatide will cause osteosarcoma in humans; however, a dose-dependent risk was found in animal studies in high doses. The use of abaloparatide in patients with a high risk of osteosarcoma is not recommended (e.g., unexplained elevations of alkaline phosphatase, Paget's disease of bone, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, prior external beam or implant radiation therapy involving the skeleton). Thus, it should

not be used for greater than 2 cumulative years. Bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Esophageal adverse experiences include esophagitis, esophageal ulcers, and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation. The FDA is investigating the possible risk of esophageal cancer with oral bisphosphonates but the data is conflicting.<sup>69</sup> The FDA believes that the benefits of oral bisphosphonates in reducing the risk of serious fractures in osteoporosis continue to outweigh their potential risks.

Denosumab (Prolia) is contraindicated in patients exhibiting systemic hypersensitivity reactions to any component of each medication, in pregnancy, and in patients with hypocalcemia. Pregnancy testing should be performed prior to initiating denosumab in women of reproductive potential. Hypersensitivity reactions have been known to include facial swelling and urticaria. Denosumab has also been reported to cause severe symptomatic hypocalcemia with some fatal cases noted. Pre-existing hypocalcemia must be corrected prior to initiation of therapy. Hypocalcemia may actually worsen in patients with severe renal impairment. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended within 14 days of denosumab injection in patients who are predisposed to hypocalcemia and mineral metabolism disturbances (e.g., history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment). Adequate supplementation with calcium and vitamin D is recommended. In addition, denosumab has been associated with serious skin infections that could lead to hospitalizations. Prompt medical attention is suggested upon initial signs and symptoms of skin infection, including cellulitis. Infections of the abdomen, urinary tract, and ear have also been reported and other dermatologic reactions, as well as endocarditis and osteonecrosis of the jaw (ONJ), have been reported with the use of denosumab. ONJ is typically associated with tooth extraction and/or local infection. A routine oral exam and preventive dentistry is recommended prior to starting denosumab as noted in the product label. Discontinuation of denosumab should be considered based on individual benefit-risk assessment, and **if discontinued, patients should be transitioned to an alternative antiresorptive therapy**. Fracture risk increases, including the risk of multiple vertebral fractures, following discontinuation of denosumab. New vertebral fractures occurred as early as 7 months after the last dose. There have been postmarketing cases of severe bone, joint, and/or muscle pain with time to onset from 1 day to several months after starting denosumab. Patients receiving denosumab (Prolia) should not receive denosumab (Xgeva) therapy, as Xgeva has the same active ingredient as Prolia.

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking denosumab (Prolia). The time to onset of symptoms varied from 1 day to several months after starting Prolia. Consider discontinuing use if severe symptoms develop.

Raloxifene (Evista) is contraindicated in lactating and pregnant women, as well as women who may become pregnant and women with active or a history of venous thromboembolism. There are boxed warnings for the increased risk of venous thromboembolism and death from stroke.

Romozosumab-aqqg (Evenity) is contraindicated in patients with hypocalcemia. Serum calcium levels should be corrected before starting romozosumab-aqqg and monitored closely during treatment. Patients with severe renal impairment or those on dialysis are more susceptible to hypocalcemia.

Romozosumab-aqqg is also contraindicated in patients with hypersensitivity to the active ingredient or any inactive ingredients. Reactions may include angioedema, rash, dermatitis, erythema multiforme, and urticaria. The product should be discontinued if a severe reaction occurs.

There is a boxed warning associated with romosozumab-aqgg use due to increased risk of major adverse cardiac events (MACE) including MI, stroke, and CV death. In clinical trials, the rate of MACE was higher in patients treated with romosozumab-aqgg (2%) compared to patients treated with alendronate (1.1%). Romosozumab-aqgg should not be used in patients with a history of MI or stroke in the past year and should be discontinued if an MI or stroke occurs.

Treatment with romosozumab-aqgg may result in osteonecrosis of the jaw and is usually associated with tooth extraction and/or local infection with delayed healing. Prescribers should perform a routine dental exam before starting romosozumab-aqgg treatment.

Although causality has not been established, use of romosozumab-aqgg has also been associated with atypical low trauma femoral fractures. Prescribers should ensure that patients receive calcium and vitamin D supplementation while receiving treatment. Patients should be instructed to report signs of new hip, thigh, or groin pain while on romosozumab-aqgg.

Teriparatide (**Teriparatide**, Forteo) has a boxed warning indicating that osteosarcoma has been seen in both male and female rats. The osteosarcoma was dependent on dose and treatment duration. Teriparatide should not be used in patients who are at increased risk of osteosarcoma, including those with Paget's disease, open epiphyses, previous recipients of radiation of the bone, or those with unexplained elevations of alkaline phosphatase. In addition, patients with a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or underlying hypercalcemic disorder, should not be treated with teriparatide. Teriparatide also carries warnings for orthostatic hypotension (typically within 4 hours of injection) and hypercalciuria and urolithiasis. Due limited long-term safety and efficacy data, use of teriparatide beyond 2 years is not recommended. Its use is contraindicated in patients with known hypersensitivity to teriparatide or any of its excipients, as adverse reactions have included angioedema and anaphylaxis.

## **Risk Evaluation and Mitigation Strategies (REMS)<sup>70</sup>**

Denosumab (Prolia) has an active REMS programs to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, multiple vertebral fractures following discontinuation or disruption, serious infections, and dermatologic reactions. The program consists of a medication guide and a communication plan.

The REMS program for teriparatide (Forteo) has been removed.

## **DRUG INTERACTIONS<sup>71,72,73,74,75,76,77,78,79,80,81,82,83,84</sup>**

### **Bisphosphonates**

Concomitant use of bisphosphonates with hormone replacement therapy (HRT) in women shows a greater degree of bone turnover suppression than with either HRT or a bisphosphonate alone. Concomitant use of risedronate delayed-release (Atelvia) with estrogens and estrogen agonist/antagonists has not been studied. The safety of concomitant use of raloxifene with systemic estrogens has not been established, and its use is not recommended.

Calcium supplements and antacids, as well as other oral medications, may interfere with the absorption of bisphosphonates. Patients should not take other medications until the 30 to 60 minute period following administration is completed.

The incidence of upper gastrointestinal adverse events is higher in patients taking aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) concomitantly with bisphosphonates. Administration with a proton pump inhibitor (PPI) or H2-blocker may decrease the incidence. However, drugs such as H2-blockers, PPIs, and antacids that raise stomach pH may affect the enteric coating on risedronate delayed-release (Atelvia) tablets and thereby reduce its bioavailability. The effects of concomitant administration of these agents on bioavailability of risedronate delayed-release tablets have not been evaluated.

## Calcitonin

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. Currently, no drug interactions with calcitonin-salmon have been observed.

## Others

No drug interaction studies have been conducted with denosumab (Prolia) or with abaloparatide (Tymlos).

As this agent is highly protein bound, raloxifene (Evista) should be used with caution with other highly protein-bound medications, such as diazepam.

Cholestyramine, and possibly other bile acid resins, can cause a decrease in the absorption of raloxifene (Evista), thus concomitant use of these agents is not recommended.

Hypercalcemia may predispose patients to digitalis toxicity. Because teriparatide (Teriparatide, Forteo) transiently increases serum calcium, patients receiving digoxin should use teriparatide with caution.

There are no known drug interactions with romosozumab-aqqg (Evenity).

## ADVERSE EFFECTS<sup>85,86,87,88,89,90,91,92,93,94,95,96,97</sup>

Drug	Abd. pain	Nausea	Dyspepsia	Constipation	Diarrhea	Flatulence	Musculoskeletal pain	Headache
<b>Bisphosphonates</b>								
alendronate (Binosto) 70 mg once-weekly	3.7	1.9	2.7	0.8	2.8	0.4	2.9	nr
alendronate (Fosamax) 5-10 mg daily	1.5-6.6	1.1-3.6	1.1-3.6	0-3.1	0.6-3.1	0.2-4.1	0.4-4.1	0.2-2.6
alendronate (Fosamax) 35 mg once-weekly	2.2	1.4	1.7	0.3	0.6	nr	2.2	nr
alendronate (Fosamax) 70 mg once-weekly	3.7	1.9	2.7	0.8	< 1	0.4	2.9	< 1
ibandronate (Boniva) 150 mg once-monthly	7.8-8.0	5.1	5.6	4.0	5.1	nr	nr	3.3
risedronate (Actonel) 5 mg daily	7.3-12.2	10.5-13.2	6.9-10.8	12.9	4.7-10.8	nr	11.5-24.7	7.3-9.9
risedronate (Actonel) 35 mg once-weekly	7.6	7.3	7.6	nr	4.9	nr	13.9-14.2	nr
risedronate (Actonel) 75 mg 2 days/month	nr	nr	nr	nr	reported	nr	nr	nr
risedronate (Actonel) 150 mg once/month	nr	nr	nr	nr	8.2	nr	nr	nr
risedronate delayed-release (Atelvia) 35 mg weekly	2.9	3.6	3.9	4.9	8.8	nr	2	2.6

**Adverse Effects (continued)**

Drug	Abd. pain	Nausea	Dyspepsia	Constipation	Diarrhea	Flatulence	Musculoskeletal pain	Headache
<b>Calcitonins</b>								
calcitonin-salmon	1-3	1-3	1-3	1-3	1-3	< 1	3.8 (5.3)	3.2 (4.6)
<b>Others</b>								
abaloparatide (Tymlos)	3	8	nr	nr	nr	nr	nr	8
denosumab (Prolia)	3.3 (2.9)	nr	nr	reported	nr	2.2 (1.4)	7.6 (7.5)	nr
raloxifene (Evista) 60 mg daily	6.6	8.3-8.8	5.9	nr	7.2	1.6-3.1	10.7-15.5	9.2
romosozumab-aqqg (Evenity)	nr	5.2-6.6 (5.5-5.8)						
teriparatide (Teriparatide, Forteo)	nr	8.5 (6.7)	5.2 (4.1)	5.4 (4.5)	5.1 (4.6)	nr	10.1 (8.4)	7.5 (7.4)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all-inclusive. nr = not reported. Numbers in parentheses are reported placebo adverse effect rates.

## Bisphosphonates

Although there has been no study of adverse events with alendronate/ vitamin D (Fosamax Plus D), in 1 study with 682 women and 35 men, a combination of alendronate and vitamin D over 15 weeks had a safety profile similar to alendronate 70 mg once weekly.

Bisphosphonates have had reports of bone, joint, and muscle pain, rash, Stevens-Johnsons syndrome as well as osteonecrosis of the jaw.

## Calcitonin

Calcitonin-salmon causes rhinitis (12%), epistaxis (3.5%), and other bothersome effects of the nose. Periodic nasal examinations are recommended during nasal calcitonin-salmon therapy.

## Others

The most common adverse reactions occurring more often with abaloparatide (Tymlos) than with placebo and in at least 5% of treated patients were hypercalciuria (11% versus 9%, respectively), dizziness (10% versus 6%, respectively), nausea (8% versus 3%, respectively), headache (8% versus 6%, respectively), and palpitations (5% versus 0.4%, respectively). Orthostatic hypotension (4%) and tachycardia (2%) may also occur. Abaloparatide also had a higher rate of injection site reactions compared to placebo including injection site redness (58% versus 28%, respectively), edema (10% versus 3%, respectively), and pain (9% versus 7%, respectively).

The most common treatment-emergent adverse effects associated with denosumab (Prolia) for patients on active therapy include back pain (34.7% versus 34.6% for placebo), extremity pain (11.7% versus 11.1% for placebo), musculoskeletal pain (7.6% versus 7.5% for placebo), hypercholesterolemia (7.2% versus 6.1% for placebo), and cystitis (5.9% versus 5.8% for placebo). **Alopecia has also been reported as a post-marketing experience adverse reaction.**

There have been reports of atypical femoral fractures occurring in patients receiving denosumab (Prolia). While a causality has not been established, as these type of fractures are also seen in patients who have not been administered anti-resorptive agents, many reports indicate these patients also received glucocorticoid therapy at the time of the fracture. Atypical femoral fractures commonly occur with minimal or no trauma to the area. They may be bilateral and are often accompanied by prodromal pain in the area for some time prior to the resultant fracture.

As with all therapeutic proteins, there is potential for immunogenicity with denosumab. Binding antibodies were detected in < 1% of patients treated with denosumab for up to 5 years and none of the patients tested positive for neutralizing antibodies.

Other common adverse events reported with raloxifene (Evista) include leg cramps, hot flashes, varicose veins, peripheral edema, and vaginal hemorrhage.

The most common adverse reactions (incidence of  $\geq 5\%$  and versus placebo) reported in clinical trials of romosozumab-aqqg (Evenity) were arthralgia (8.1% to 13.1% versus 9.6% to 12.1%) and headache (5.2% to 6.6% versus 5.5% to 5.8%).

As with all therapeutic proteins, romosozumab-aqqg is associated with a risk of immunogenicity. In romosozumab-aqqg studies, the incidence of antibody formation was 18.1%, with 4.7% being classified as neutralizing. Formation of antibodies to romosozumab-aqqg did not alter its safety or efficacy.

Adverse effects reported with teriparatide (Teriparatide, Forteo) included hypertension (7.1%), angina pectoris (2.5%), syncope (2.6%), rhinitis (9.6%), dizziness (8%), depression (4.1%), insomnia (4.3%), and sweating (2.2%). Transition elevation of serum calcium has been seen in both women and men. As a therapeutic protein, there is a potential for immunogenicity with teriparatide. Based on limited data, immunogenicity of both formulations of teriparatide appeared similar (incidence of 2.2% each).

## SPECIAL POPULATIONS<sup>98,99,100,101,102,103,104,105,106,107,108,109,110,111</sup>

### Pediatrics

These products are not FDA-approved for use in the pediatric population. There are limited data available studying the use of alendronate or risedronate in pediatric disorders such as osteogenesis imperfecta, but large, properly-designed studies have not been conducted. The safety and effectiveness of denosumab (Prolia) and romosozumab-aqqg (Evenity) for pediatric patients have not been established. Furthermore, denosumab is not recommended in patients less than 4 years of age due to high rates of skeletal growth and the risk of negative effect on long-bone growth and dentition. Due to the increased baseline risk of osteosarcoma, pediatric patients with open epiphyses or hereditary disorders predisposing them to osteosarcoma should not use abaloparatide (Tymlos).

### Pregnancy

The majority of products in this class are or were previously categorized as Pregnancy Category C, with the exception of denosumab (Prolia) and raloxifene (Evista), which are Pregnancy Category X. Calcitonin-salmon nasal spray, alendronate (Fosamax, Fosamax Plus D), risedronate (Actonel), and teriparatide (Forteo) have had the labeling updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). For calcitonin-salmon nasal spray, labeling now states that it is not indicated for use in females of reproductive potential as there are no data for use its use in pregnant women. Alendronate and risedronate labeling state data are inadequate to determine a drug-associated risk of adverse maternal or fetal outcomes when used in pregnant women, but alendronate should be discontinued when pregnancy is recognized. Teriparatide (no trade name) was not assigned a Pregnancy Category upon approval based on the PLLR. Although there are no data on teriparatide (Teriparatide, Forteo) in pregnant women to inform of a drug-associated risk to the mother or fetus, consider discontinuation of therapy when pregnancy is confirmed. Abaloparatide (Tymlos) is not indicated in pregnant women or in women of reproductive potential. Romosozumab-aqqg (Evenity) is not indicated for use in women of reproductive potential. Based on data from animal studies, romosozumab-aqqg may cause fetal harm when administered during pregnancy.

### Hepatic Impairment

Raloxifene (Evista) should be used with caution in patients with hepatic impairment.

### Renal Impairment

The use of bisphosphonates is not recommended in patients with severe renal dysfunction. Patients with renal impairment should be closely monitored.

Raloxifene (Evista) should be used with caution in patients with moderate or severe renal impairment.

No dosage adjustment of denosumab (Prolia) is required for patients with renal impairment; however, patients with severe renal impairment or receiving dialysis may be at greater risk of developing hypocalcemia and marked elevations of serum parathyroid hormone.

No dosage adjustment is required for patients with mild, moderate, or severe renal impairment for abaloparatide (Tymlos) or romosozumab-aqqg (Evenity).

## DOSAGES<sup>112,113,114,115,116,117,118,119,120,121,122,123,124,125</sup>

Drug	Treatment of osteoporosis in postmenopausal women	Prevention of osteoporosis in postmenopausal women	Treatment to increase bone mass in men with osteoporosis	Treatment of glucocorticoid-induced osteoporosis	Paget's disease	Availability
<b>Bisphosphonates</b>						
alendronate (Binosto)	70 mg once per week	--	70 mg once per week	--	--	70 mg effervescent tablets
alendronate (Fosamax)	10 mg per day or 70 mg once per week	5 mg per day or 35 mg once per week	10 mg per day or 70 mg once per week	5 mg per day, For post-menopausal women not receiving estrogen: 10 mg once daily	40 mg per day for 6 months May retreat if relapse occurs following a 6-month post-treatment evaluation	70 mg tablets 5 mg, 10 mg, 35 mg, 40 mg, tablets (generics only) 70 mg/75 mL oral solution (generic only)
alendronate/vitamin D (Fosamax Plus D)	70 mg/2,800 IU or 70 mg/5,600 IU weekly	--	70 mg/2,800 IU or 70 mg/5,600 IU weekly	--	--	70 mg/ 2,800 IU, 70 mg/ 5,600 IU tablets
ibandronate (Boniva)	150 mg per month	150 mg per month	--	--	--	150 mg tablets
risedronate (Actonel)	5 mg per day or 35 mg once per week or 75 mg for 2 consecutive days every month or 150 mg once a month	5 mg per day or 35 mg once per week or 75 mg for 2 consecutive days every month or 150 mg once a month	35 mg once per week	5 mg per day	30 mg per day for 2 months May retreat if relapse occurs, after a 2-month post-treatment observation.	5 mg, 30 mg (generic only), 35 mg, and 150 mg tablets
risedronate delayed-release (Atelvia)	35 mg once weekly	--	--	--	--	35 mg delayed-release tablets
<b>Calcitonins</b>						
calcitonin-salmon	200 IU intranasally per day, alternating nostrils daily	--	--	--	--	3.7 mL (30 dose) bottle

**Dosages (continued)**

Drug	Treatment of osteoporosis in postmenopausal women	Prevention of osteoporosis in postmenopausal women	Treatment to increase bone mass in men with osteoporosis	Treatment of glucocorticoid-induced osteoporosis	Paget's disease	Availability
<b>Others</b>						
abaloparatide (Tymlos)	80 mcg SC per day	--	--	--	--	3,120 mcg/1.56 mL prefilled pen
denosumab (Prolia)	60 mg SC every 6 months, administered by a healthcare professional	--	60 mg SC every 6 months; administered by a healthcare professional	60 mg SC every 6 months; administered by a healthcare professional	--	60 mg/1 mL single use pre-filled syringe
raloxifene (Evista)	60 mg per day	60 mg per day	--	--	--	60 mg tablets
teriparatide	20 mcg SC per day	--	20 mcg SC per day	20 mcg SC per day	--	620 mcg/2.48 mL prefilled pen (contains 28 doses)
teriparatide (Forteo)	20 mcg SC per day	--	20 mcg SC per day	20 mcg SC per day	--	600 mcg/2.4 mL prefilled pen
romosozumab-aqqg (Evenity)	210 mg (as 2 consecutive 105 mg injections) SC per month, administered by a healthcare professional; duration is 12 monthly doses	--	--	--	--	105 mg/1.17 ml pre-filled syringe

## ***Dosages (continued)***

Optimal duration of use for bisphosphonates has not been determined. For patients at low-risk for fracture, consider discontinuation after 3 to 5 years of use.

Alendronate and risedronate (Actonel) must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only. Patients should not lie down for at least 30 minutes after taking the medication. Ibandronate must be taken at least 1 hour before the first food, beverage, or medication of the day with plain water, and patients should not lie down for at least 60 minutes after taking the medication. Raloxifene may be administered any time of day without regard to meals. All regimens should include an adequate intake of calcium and vitamin D.

Alendronate is available generically in 5 mg, 10 mg, 35 mg, and 40 mg tablet strengths and a 70 mg/75 mL solution; however, Fosamax is currently only available as a 70 mg strength tablet.

When compared with risedronate immediate-release (Actonel), treatment with risedronate delayed-release (Atelvia) resulted in a significantly higher incidence of abdominal pain when administered before breakfast under fasting conditions. Risedronate delayed-release (Atelvia) should be taken immediately following breakfast and not under fasting conditions.

Patients taking abaloparatide (Tymlos) or romosozumab-aqqg (Evenity) should be supplemented with calcium and vitamin D if dietary intake is not sufficient.

Patients receiving denosumab (Prolia) should also maintain a regimen of calcium 1,000 mg daily and at least 400 IU of vitamin D daily. Denosumab should be refrigerated until use. Prior to administration, the container may be brought to room temperature by removing it from the refrigerator to stand for 15 to 30 minutes.

Raloxifene (Evista) dosing is 60 mg daily for the reduction in risk of invasive breast cancer in postmenopausal women.

The safety, efficacy and benefit of abaloparatide (Tymlos) and teriparatide (Teriparatide, Forteo) have not been evaluated beyond 2 years of treatment. Therefore, use for more than 2 years during a patient's lifetime is not recommended.

Romosozumab-aqqg carries a limitation for use in that it should only be used for a maximum of 12 monthly doses because of decreased efficacy after that time. If further treatment for osteoporosis is necessary, it is recommended to switch to another antiresorptive agent.

Two separate syringes (and 2 separate SC injections) are needed to administer the total dose of 210 mg of romosozumab-aqqg. Injections should be administered one after the other into the abdomen, thigh, or upper arm.

## **CLINICAL TRIALS**

### **Search Strategies**

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human

participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Binosto: alendronate effervescent tablets 70 mg (Binosto) was approved based on the evidence demonstrated in clinical data of alendronate sodium 10 mg daily and alendronate sodium 70 mg weekly for fracture reduction efficacy and bone mineral density changes.<sup>126</sup> The same clinical trial results have been attributed to Binosto and are based on the demonstrated bioequivalence of alendronate effervescent tablets 70 mg to oral alendronate sodium tablet 70 mg.

The submission for approval of teriparatide (no trade name) utilized clinical data for teriparatide (Forteo).<sup>127</sup>

## Bisphosphonates

### *alendronate (Fosamax) versus placebo*

Two double-blind, multicenter studies were conducted enrolling postmenopausal women who were 45 to 80 years of age with osteoporosis (BMD at least 2.5 standard deviations below the mean value in premenopausal white women).<sup>128</sup> The women were randomized to receive placebo or 5, 10, or 20 mg of alendronate per day for 2 years. During the third year, women continued with open-label therapy with the 20 mg per day group changing to 5 mg per day. All women also received 500 mg of calcium daily. A total of 909 women completed at least 1 year of the study. There were significant increases in the BMD of the spine, femoral neck, trochanter, and total body at 36 months in all 3 alendronate groups. The 10 mg dose was significantly more effective than the 5 mg dose and, at 2 years, was as effective as the 20 mg dose. During the study, 6.2% of the placebo group had at least 1 new vertebral fracture compared with 3.2% of the alendronate-treated females (p=0.03).

In the Fracture Intervention Trial (FIT), 4,432 women with a femoral neck BMD  $\leq 0.68$  g/cm<sup>2</sup> were randomized in a double-blind manner to receive alendronate 5 mg per day for 2 years followed by 10 mg per day for 2 years or placebo.<sup>129</sup> Alendronate increased BMD at all sites studied and reduced clinical fractures from 312 in the placebo group to 272 in the intervention group. However, the clinical fracture reduction was not significant.

A randomized, double-blind trial enrolled 1,099 postmenopausal women who had received alendronate treatment in the FIT trial for a mean of 5 years. These patients were again randomized to alendronate 5 or 10 mg daily or placebo for an additional 5 years. The primary outcome measure was total hip BMD; secondary measures were BMD at other sites and biochemical markers of bone remodeling. Patients who switched to placebo for 5 years had a decline in BMD at the total hip (-2.4%; p<0.001) and spine (-3.7%; p<0.001), but mean levels remained at or above pretreatment levels 10 years earlier. After 5 years, the cumulative risk of nonvertebral fractures was not significantly different between those continuing and discontinuing alendronate (relative risk [RR], 1; 95% confidence interval

[CI], 0.76 to 1.32). Among those who continued, there was a significantly lower risk of clinically recognized vertebral fractures (RR, 0.45; 95% CI, 0.24 to 0.85) but no significant reduction in morphometric vertebral fractures.

In a 1-year, double-blind study, 1,258 osteoporotic women were randomized to receive alendronate 10 mg daily, 35 mg twice weekly, or 70 mg once weekly.<sup>130</sup> The percent increases for BMD of the lumbar spine at month 12 were 5.4%, 5.2%, and 5.1% for the 3 dosing regimens, respectively. Upper gastrointestinal adverse experiences occurred in 23.5%, 23.8%, and 22.4% of patients in the daily, twice-weekly, and once-weekly treatment groups, respectively.

In a 1-year, double-blind, multicenter study of postmenopausal women aged 40 to 70 years, 362 patients were randomized to alendronate 35 mg once weekly, and 361 patients received alendronate 5 mg once daily.<sup>131</sup> Lumbar spine BMD at 12 months increased to the same degree in both groups. Both treatments were well tolerated.

A multicenter, international, randomized, blinded, 12-month study was conducted to assess the effect of alendronate on BMD in women who had recently discontinued HRT.<sup>132</sup> One hundred forty-four postmenopausal women were randomized to receive either a daily dose of 10 mg alendronate or matching placebo. A high rate of bone loss was observed in the first 12 to 15 months after discontinuation of HRT. Alendronate increased or maintained both spine and hip BMD and prevented the increase in bone resorption seen with withdrawal of HRT in this population. Bone turnover decreased significantly with alendronate but increased in the placebo group. Alendronate was well tolerated, with no increase in adverse events compared with placebo.

#### ***alendronate (Fosamax) versus raloxifene (Evista)***

A randomized, double-masked, double-dummy multicenter international study was done to compare the efficacy and tolerability of alendronate to raloxifene in postmenopausal women with low-bone density.<sup>133</sup> A total of 487 postmenopausal women with low bone density, based on BMD of the lumbar spine or hip (T-score < -2.0), received either alendronate 70 mg once weekly and daily placebo identical to raloxifene or raloxifene 60 mg daily and weekly placebo identical to alendronate for 12 months. Alendronate demonstrated substantially greater increases in BMD than raloxifene at both lumbar spine and hip sites at 12 months. Lumbar spine BMD increased 4.8% with alendronate compared to 2.2% with raloxifene ( $p < 0.001$ ). The increase in total hip BMD was 2.3% with alendronate and 0.8% with raloxifene ( $p < 0.001$ ). The proportion of patients reporting vasomotor events was significantly higher with raloxifene (9.5%) than with alendronate (3.7%,  $p = 0.01$ ). Reductions in bone turnover were significantly larger with alendronate than raloxifene. The proportion of patients reporting gastrointestinal events was similar between groups.

To compare the efficacy and tolerability of once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis, a 12-month, randomized, double-blind study enrolled 456 patients.<sup>134</sup> Over 12 months, alendronate produced a significantly greater increase in lumbar spine BMD than raloxifene (4.4% versus 1.9%;  $p < 0.001$ ). The percentage of women with an increase in lumbar spine BMD (94% versus 75%;  $p < 0.001$ ) and at least a 3% increase (66% versus 38%;  $p < 0.001$ ) was significantly greater with alendronate than raloxifene. Total hip and trochanter BMD increases were also significantly greater ( $p < 0.001$ ) with alendronate. No significant differences in the incidence of upper gastrointestinal or vasomotor adverse experiences were seen.

### ***alendronate (Fosamax) versus risedronate immediate-release (Actonel)***

A total of 515 postmenopausal women received risedronate 5 mg or alendronate 10 mg daily for 2 weeks.<sup>135</sup> At baseline and days 8 and 15, subjects underwent endoscopy and evaluator-blinded assessment of the esophageal, gastric, and duodenal mucosa. Gastric ulcers were seen in 4.1% of risedronate-treated patients and in 13.2% of the alendronate group ( $p < 0.001$ ). Esophageal ulcers were noted in 3 subjects in the alendronate group compared to none in the risedronate group. Duodenal ulcers were found in 1 patient in the alendronate-treated group and in 2 patients in the risedronate group.

In a similarly conducted study, 318 subjects received risedronate 5 mg and 317 received alendronate 10 mg daily for 14 days.<sup>136</sup> Overall, gastric ulcers greater than 3 mm were observed in 18 (6%) of 300 evaluated subjects in the risedronate group and 36 (12.1%) of 297 in the alendronate group during treatment ( $p = 0.013$ ). Mean gastric endoscopy scores at days 8 and 15 were significantly lower in the risedronate group than in the alendronate group ( $p < 0.001$ ). Mean esophageal and duodenal endoscopy scores were similar in the 2 groups at days 8 and 15. Upper GI adverse events were reported by 18 (5.7%) subjects in the risedronate group (19 events) and 28 (8.8%) subjects in the alendronate group (32 events).

In a multicenter, double-blind trial, 235 men and postmenopausal women were randomized to receive 28 days of alendronate 40 mg per day, risedronate 30 mg per day, placebo, or placebo with aspirin 650 mg 4 times a day for the last 7 days.<sup>137</sup> Endoscopy showed alendronate- and risedronate-treated patients with comparable mean gastric and duodenal erosion scores that were significantly lower than those of the aspirin group. Gastric ulcers and/or large numbers of gastric erosions occurred in approximately 3% of alendronate and risedronate patients versus 60% with aspirin.

In FACT, a total of 1,053 patients were randomized in a double-blind study to alendronate 70 mg once weekly ( $n = 520$ ) or risedronate 35 mg once weekly ( $n = 533$ ) taken in the morning after fasting.<sup>138</sup> Greater increases in hip trochanter BMD were seen with alendronate (3.4%) than risedronate (2.1%) at 12 months ( $p < 0.001$ ), as well as 6 months ( $p < 0.001$ ). Significant gains in BMD were greater with alendronate at all BMD sites measured (12-month difference: total hip, 1%; femoral neck, 0.7%; lumbar spine, 1.2%). No significant differences were seen between treatment groups in the incidence of upper gastrointestinal adverse events or those causing discontinuation.

A randomized, double-blind, 1-year extension of FACT compared changes in BMD, bone turnover, and upper gastrointestinal tolerability over 2 years of treatment.<sup>139</sup> Of the 1,053 women who completed 1 year of treatment, 833 postmenopausal women with low BMD entered the extension, continuing their same treatment allocation. Alendronate produced greater increases from baseline in BMD at 24 months than did risedronate at the trochanter (alendronate 4.6%; risedronate 2.5%,  $p < 0.001$ ), as well as at all other BMD sites. Fewer alendronate patients had measured decreases of 3% or more at all BMD sites. Significantly greater reductions in all biochemical markers of bone turnover occurred with alendronate, compared with risedronate. No differences were seen in occurrence or discontinuations due to upper gastrointestinal adverse effects. The manufacturer of alendronate supported the study.

A 3-month, randomized, double-blind, placebo-controlled study with a double-blind extension to 12 months enrolled 549 postmenopausal women who were 60 years of age or older.<sup>140</sup> Patients received alendronate 70 mg once weekly or risedronate 5 mg daily. Over 3 months, alendronate produced a significantly greater mean reduction in biochemical markers of bone turnover than did risedronate,

which was maintained at 12 months. Alendronate produced a significantly greater mean BMD increase than did risedronate at 6 months, and it was maintained at 12 months at the lumbar spine (4.8 versus 2.8%,  $p < 0.001$ ) and total hip (2.7% versus 0.9%,  $p < 0.001$ ), as well as at the trochanter and femoral neck. Tolerability was generally similar among alendronate, risedronate, and placebo, and the incidence of adverse events was similar in both active treatment groups.

### ***alendronate with vitamin D (Fosamax Plus D) versus alendronate (Fosamax)***

In a 15-week study, 717 men and postmenopausal women with osteoporosis were randomized to receive weekly alendronate/vitamin D 70 mg/2,800 IU tablets or weekly alendronate 70 mg.<sup>141</sup> Patients who were vitamin D deficient at baseline were excluded. Treatment with alendronate/vitamin D resulted in a smaller reduction in serum calcium levels (-0.9% versus -1.4%, respectively) as well as a significantly smaller increase in parathyroid hormone levels when compared to alendronate alone (14% versus 24%, respectively).

### ***ibandronate (Boniva) versus placebo***

In total, 653 women (mean BMD T-score  $> -2.5$  at the lumbar spine) who had been postmenopausal for at least 1 year were enrolled in a multicenter, double-blind, randomized, placebo-controlled, phase 2/3 study to receive calcium (500 mg daily) plus either placebo ( $n=162$ ) or ibandronate 0.5 mg ( $n=162$ ), 1 mg ( $n=166$ ), or 2.5 mg ( $n=163$ ) as daily treatment for 2 years.<sup>142</sup> After 2 years, daily ibandronate produced a dose-related and sustained maintenance or increase in BMD at the lumbar spine and hip (total hip, femoral neck, trochanter), together with a dose-related reduction in the rate of bone turnover. The greatest increases in spinal and hip BMD were observed with the 2.5 mg dose, which produced statistically significant BMD gains compared with placebo at 6 months and all subsequent time-points (3.1% and 1.8% increase in lumbar spine and total hip BMD, respectively, versus placebo;  $p < 0.0001$  after 24 months). Ibandronate was well tolerated with an incidence of upper gastrointestinal adverse events similar to placebo.

A randomized, double-blind, placebo-controlled, parallel-group, phase 3 study enrolled 2,946 postmenopausal women with a BMD T score  $\leq -2.0$  at the lumbar spine in at least 1 vertebra and 1 to 4 prevalent vertebral fractures.<sup>143</sup> Patients received placebo or ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every 3 months. After 3 years, ibandronate significantly reduced the risk of new vertebral fractures by 62% ( $p=0.0001$ ) for the daily group and 50% ( $p=0.0006$ ) for the intermittent group, versus placebo. Significant and progressive increases in lumbar spine and hip BMD, normalization of bone turnover, and significantly less height loss than in the placebo group were also observed for both ibandronate regimens. Ibandronate did not reduce the incidence of nonvertebral fractures, which was a secondary efficacy measure. The percentages of nonvertebral fractures over 3 years were similar for ibandronate 2.5 mg (9.1%; 95% CI, 7.1 to 11.1), 20 mg group (8.9%), and placebo groups (8.2%; 95% CI, 6.3 to 10.2). Ibandronate was well tolerated.

MOBILE study: A total of 1,609 women with postmenopausal osteoporosis were assigned to 1 of 4 oral ibandronate regimens, 2.5 mg daily, 50 mg/50 mg monthly (single doses, consecutive days), 100 mg monthly, or 150 mg monthly, in a 2-year, randomized, double-blind, phase 3, non-inferiority trial.<sup>144</sup> After 1 year, lumbar spine BMD increased by 3.9, 4.3, 4.1, and 4.9% in the 2.5, 50/50, 100, and 150 mg arms, respectively. All monthly regimens were proven non-inferior to the daily regimen in increasing lumbar BMD, while the 150 mg regimen was superior. All arms of the study produced similar hip BMD gains, and all arms were similarly well tolerated.

### ***ibandronate (Boniva) versus alendronate (Fosamax)***

MOTION study: A 12-month, randomized, multinational, multicenter, double-blind, double-dummy, parallel-group, non-inferiority trial enrolled postmenopausal women with mean lumbar spine (L2-L4) BMD T-score < -2.5 and > -5.<sup>145</sup> Patients received either ibandronate 150 mg once monthly or alendronate 70 mg once weekly. The primary efficacy endpoints were 12-month percent change from baseline in mean lumbar spine and total hip BMD, while percent changes from baseline in trochanter and femoral neck BMD were also evaluated. Once-monthly ibandronate was considered non-inferior to weekly alendronate if the lower boundary of the one-sided 97.5% confidence interval (CI) (or 2-sided 95% CI) was > -1.41% for lumbar spine and > -0.87% for total hip. The mean relative 12-month changes were 5.1% and 5.8% (95% CI, -1.13 to -0.23) in lumbar spine and 2.9% and 3.0% (95% CI, -0.38 to 0.18) in total hip BMD with once-monthly ibandronate and weekly alendronate, respectively. Therefore, once-monthly ibandronate was shown to be clinically comparable to weekly alendronate at increasing BMD after 12 months in both the lumbar spine and total hip.

### ***risedronate immediate-release (Actonel) versus placebo***

A randomized, double-blind, placebo-controlled trial of 2,458 postmenopausal women younger than 85 years with at least 1 vertebral fracture at baseline were randomly assigned to receive oral treatment for 3 years with risedronate 2.5 or 5 mg daily or placebo.<sup>146</sup> The risedronate 2.5 mg daily arm was discontinued after 1 year; the placebo (450 subjects) and risedronate 5 mg daily (489 subjects) arms completed all 3 years of the trial. Treatment with 5 mg daily of risedronate significantly reduced the cumulative incidence of new vertebral fractures over 3 years versus placebo (11.3% versus 16.3%, respectively;  $p=0.03$ ). The cumulative incidence of nonvertebral fractures over 3 years was significantly reduced versus placebo (5.2% versus 8.4%, respectively). BMD increased significantly compared with placebo at the lumbar spine (5.4% versus 1.1%, respectively), femoral neck (1.6% versus -1.2%, respectively), femoral trochanter (3.3% versus -0.7%, respectively), and midshaft of the radius (0.2% versus -1.4%, respectively).

In a 2-protocol study, 9,331 women were randomized to evaluate the effects of risedronate 2.5 mg, 5 mg, or matching placebo given daily for 3 years to prevent hip fractures.<sup>147</sup> All women also received supplemental calcium carbonate. The women were divided into 2 groups: (1) 70 to 79 years of age with osteoporosis and (2) 80 years of age or older with 1 or more clinical risk factors for hip fracture. The mean duration of therapy was 2 years, and 64% of patients had complete follow-up data. There was a significant decrease in the risk of hip fracture in all patients who were on risedronate versus placebo treatment (2.8% compared to 3.9%, respectively;  $p=0.02$ ). Patients in the 80 years of age and older group did not show a significant decrease in risk of hip fracture when treated with risedronate.

In order to determine the effects of 5 years of risedronate treatment, the authors extended a 3-year, placebo-controlled vertebral fracture study in osteoporotic women for an additional 2 years.<sup>148</sup> Women who entered the extension study continued to receive 5 mg risedronate or placebo according to the original randomization, with maintenance of blinding. The risk of new vertebral fractures was significantly reduced with risedronate treatment in years 4 and 5 by 59% ( $p=0.01$ ) compared with a 49% reduction in the first 3 years. Significant decreases in markers of bone turnover observed in the first 3 years were similarly maintained in the next 2 years of treatment. Increases in spine and hip BMD that occurred in the risedronate group during the first 3 years were maintained or increased with a further 2 years of treatment.

In an 18-month, randomized, double-blind trial, 280 male patients 65 years or older who were post-stroke received a risedronate 2.5 mg daily (n=140) or placebo (n=140).<sup>149</sup> Ten patients sustained hip fractures in the placebo group, and 2 hip fractures occurred in the risedronate group. The relative risk (RR) of a hip fracture was 0.19 (95% CI, 0.04 to 0.89). BMD increased by 2.5% in the risedronate group and decreased by 3.5% in the placebo group (p<0.001).

In a multinational, 2-year, double-blind study, male patients (n=284) with osteoporosis were randomized to receive risedronate 35 mg once a week or placebo. All patients also took 1,000 mg elemental calcium and 400 to 500 IU vitamin D daily.<sup>150</sup> Treatment with risedronate resulted in a significant increase from baseline to endpoint in lumbar spine BMD compared with placebo (p<0.001). Few new vertebral and nonvertebral fractures were reported, with no differences in fracture rates between the 2 groups. There was a significant (p<0.01) reduction from baseline in bone turnover markers for the risedronate group compared with placebo at all time points. No differences in adverse effects were observed.

### ***risedronate delayed-release (Atelvia) versus risedronate immediate-release (Actonel)***

A randomized, double-blind, active-control trial of approximately 900 subjects with postmenopausal osteoporosis compared the efficacy of risedronate delayed-release (DR) 35 mg once-a-week and risedronate immediate-release (IR) 5 mg daily.<sup>151</sup> All patients in the study received supplemental calcium (1,000 mg/day) and vitamin D (800 to 1,000 IU/day). The primary efficacy endpoint was percent change in lumbar spine bone mineral density at 1 year. Risedronate delayed-release 35 mg once-a-week administered after breakfast was shown to be non-inferior to risedronate sodium immediate-release 5 mg daily (3.1% versus 3.3%, respectively).

## **Calcitonin**

### ***calcitonin salmon versus placebo***

For 5 years, 1,255 randomized, postmenopausal women with osteoporosis received salmon calcitonin nasal (100, 200, or 400 IU) or placebo daily in a double-blind manner.<sup>152</sup> The 200 IU dose of salmon calcitonin nasal spray significantly reduced the risk of new vertebral fractures by 33% compared with placebo (p=0.03). The reductions in vertebral fractures in the 100 and 400 IU groups were not significantly different from placebo. Lumbar spine BMD increased significantly from baseline (1% to 1.5%, p<0.01) in all active treatment groups.

## **Others**

### ***abaloparatide (Tymlos) versus placebo***

An 18-month, randomized, multicenter, double-blind, placebo-controlled trial (ACTIVE) was conducted in women with postmenopausal osteoporosis to assess the efficacy and safety of abaloparatide for the prevention of new vertebral fractures.<sup>153</sup> Women were randomized to receive abaloparatide 80 mcg (n=824), placebo (n=821), or open-label teriparatide 20 mcg (n=818) SC once daily for 18 months. Patients also took daily calcium (500 to 1,000 mg) and vitamin D (400 to 800 IU). The primary endpoint was to compare the percent of patients with a new vertebral fracture in the abaloparatide versus placebo groups. Secondary endpoints included change in BMD in the hip, femoral neck, and lumbar spine and the time to first nonvertebral fracture. Of the 2,463 patients entering the study, 1,901 (77.2%) completed it, and evidence showed that new vertebral fractures occurred less frequently in

the abaloparatide treatment groups (0.58%) compared to placebo (4.22%) (risk difference [RD] versus placebo, -3.64% [95% CI, -5.42 to -2.1]; RR, 0.14 [95% CI, 0.05 to 0.39];  $p < 0.001$ ); new vertebral fractures occurred in 0.84% of teriparatide-treated patients. Estimated event rate for nonvertebral fractures was lower in the abaloparatide treatment group (2.7%) compared to placebo (4.7%) (RD, -2.01% [95% CI, -4.02 to 0]; HR, 0.57 [95% CI, 0.32 to 1]  $p = 0.049$ ); the estimated event rate for nonvertebral fractures for the teriparatide group was 3.3%. BMD increases were greater with abaloparatide compared to placebo at the total hip, femoral neck, and lumbar spine,  $p < 0.001$ . The study concluded treatment with abaloparatide reduced the risk of new vertebral and nonvertebral fractures over 18 months compared to placebo in postmenopausal women with osteoporosis.

The ACTIVEExtend trial, an extension of the ACTIVE trial, enrolled 1,139 patients who completed the ACTIVE trial to assess the efficacy and safety of 18 months of abaloparatide (ABL) or placebo (PBO) followed by 24 months of alendronate (ALN) (there was 1 month between studies for re-consent).<sup>154,155</sup> Over the full 43-month treatment period, new radiographic vertebral fractures were reported in 0.9% of evaluable women in the ABL/ALN group versus 5.6% in the PBO/ALN group (RR reduction, 84%;  $p < 0.001$ ). For ACTIVEExtend only, vertebral fractures RRR was 87% with ABL/ALN versus PBO/ALN ( $p = 0.001$ ). The reported incidence of other fracture types was also significantly lower for ABL/ALN versus PBO/ALN (all  $p < 0.05$ ). BMD continued to increase during ACTIVEExtend.

At the time of the publication the trial was still ongoing but interim analysis showed the percent of patients with new vertebral fractures was 4.4% in the placebo/alendronate group and 0.55% in the abaloparatide/alendronate group (RR reduction, 87%; RR, 0.13 [95% CI, 0.04 to 0.41;  $p < 0.001$ ]). The estimated rates for nonvertebral fractures were 5.6% for placebo/alendronate treated patients and 2.7% for abaloparatide/alendronate patients (risk reduction, 52%; HR, 0.48 [95% CI, 0.26 to 0.89;  $p = 0.02$ ]). At 25 months, the BMD percent change, using ACTIVE levels as baseline, for lumbar spine, total hip, and femoral neck was 12.8%, 5.5%, and 4.5% for abaloparatide/alendronate, respectively, versus 3.5%, 1.4%, and 0.5% for placebo/alendronate, respectively ( $p < 0.001$  for all abaloparatide versus placebo). The extension study concluded abaloparatide for 18 months followed by alendronate for 6 months reduced the risk of fracture throughout the body and improved BMD; abaloparatide/alendronate may be an effective treatment option for osteoporosis in post-menopausal women.

### ***denosumab (Prolia) versus placebo***

FREEDOM: Women between the ages of 60 and 90 years ( $n = 7,868$ ) who had a bone mineral density T score of less than -2.5 but not less than -4 at the lumbar spine or total hip were randomly assigned to receive either denosumab 60 mg or placebo subcutaneously every 6 months for 36 months.<sup>156</sup> The primary endpoint was new vertebral fracture. Secondary endpoints included nonvertebral and hip fractures. Denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group versus 7.2% in the placebo group (hazard ratio [HR], 0.32; 95% CI, 0.26 to 0.41;  $p < 0.001$ ). Denosumab reduced the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group versus 1.2% in the placebo group (HR, 0.6; 95% CI, 0.37 to 0.97;  $p = 0.04$ ). Denosumab also reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab group versus 8% in the placebo group (HR, 0.8; 95% CI, 0.67 to 0.95;  $p = 0.01$ ). There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to injection for denosumab.

A total of 4,550 enrolled in the 7-year FREEDOM extension trial in which all women received denosumab and 2,626 women completed the extension study.<sup>157</sup> Of the subjects, 1,283 switched from placebo to denosumab. The primary outcome was safety and secondary outcomes included fracture incidence. The rate of adverse event was stable over time (range, 11.5 to 14.4 per 100 participant-years). During the extension, 1 atypical femoral fracture occurred in each group (denosumab original long-term and crossover groups). Osteonecrosis of the jaw were reported in 7 women in the long-term group and 6 cases in the crossover group. The annual rate of new vertebral fractures was similar to rates observed in the original 3-year FREEDOM study.

ADAMO: A phase 3 randomized, double-blind, placebo-controlled, multicenter trial was performed in 242 men with low BMD.<sup>158</sup> At 1 year, compared with placebo, SC denosumab 60 mg every 6 months resulted in BMD increases at the primary endpoint of lumbar spine (5.7% versus 0.9%), and for the secondary endpoints of total hip (2.4% versus 0.3%) and femoral neck (2.1% versus 0%), (adjusted  $p \leq 0.0144$  for BMD percent differences at all sites compared with placebo). Effects of Prolia on BMD at the lumbar spine were independent of baseline testosterone levels, age, BMD status, and estimated fracture risk. Treatment with denosumab significantly reduced the bone resorption marker serum type 1 C-telopeptide (CTX) levels at day 15 (adjusted  $p < 0.0001$ ). The incidence of adverse events was similar between groups.

### ***raloxifene (Evista) versus placebo***

To evaluate the 3-year effects of raloxifene treatment on BMD, 1,145 postmenopausal women were enrolled in a randomized, double-blind trial.<sup>159</sup> They received raloxifene 30, 60, or 150 mg or placebo daily. Lumbar spine BMD changed from baseline to 36 months as follows: placebo, -1.32%; raloxifene 30 mg, +0.71%; raloxifene 60 mg, +1.28%; and raloxifene 150 mg, +1.2%. Comparable BMD changes were observed in the hip and total body. The significant adverse effect of active treatment was hot flashes (25% in the raloxifene 60 mg group versus 18% in the placebo group).

In a randomized double-blind trial, 7,705 women who had osteoporosis received raloxifene 60 or 120 mg per day or placebo.<sup>160</sup> Women receiving raloxifene had fewer new vertebral fractures. One hundred seventeen women had 2 or more new vertebral fractures. Compared to placebo, BMD increased after 36 months by 2.1 and 2.6% at the femoral neck and spine, respectively, in the 60 mg raloxifene group and by 2.4 and 2.7% at the femoral neck and spine, respectively, in the 120 mg raloxifene group (all  $p < 0.001$ ). Thromboembolic events were reported more frequently in the raloxifene groups (1% for each active treatment group compared to 0.3% for the placebo group). In an extension of the study, placebo-treated women continued with placebo ( $n=1,286$ ), but those previously given raloxifene 60 or 120 mg daily received raloxifene 60 mg daily ( $n=2,725$ ).<sup>161</sup> As a secondary endpoint, new non-vertebral fractures were analyzed in 4,011 postmenopausal women after 8 years. The risk of at least 1 new non-vertebral fracture was similar in the placebo (22.9%) and raloxifene (22.8%) groups, and the incidence of at least 1 new non-vertebral fracture at 6 major sites (clavicle, humerus, wrist, pelvis, hip, lower leg) was 17.5% in both groups. The differences in mean lumbar spine and femoral neck BMD with raloxifene were 1.7% ( $p=0.3$ ) and 2.4% ( $p=0.045$ ), respectively, from placebo. Compared with baseline, raloxifene treatment significantly increased lumbar spine (4.3% from baseline, 2.2% from placebo) and femoral neck BMD (1.9% from baseline, 3% from placebo).

### ***romosozumab-aqgg (Evenity) versus placebo***

FRAME: In this double-blind study, a total of 7,180 post-menopausal women with T-scores at the total hip or femoral neck of -2.5 to -3.5 were randomized (1:1) to receive either romosozumab-aqgg 210 mcg or placebo administered SC once monthly for 12 months.<sup>162</sup> After the initial 12 months, treatment with romosozumab-aqgg was stopped and both groups received 1 additional year of treatment with denosumab 60 mg administered every 6 months. Supplemental calcium and vitamin D were also prescribed throughout the study. The primary endpoints were the total number of new vertebral fractures at 12 and 24 months. At month 12, 0.5% of patients in the romosozumab-aqgg group experienced new vertebral fractures compared to 1.8% in the placebo group (relative risk reduction [RRR] of 73%;  $p < 0.001$ ). After switching to denosumab, patients in the romosozumab-aqgg group experienced new vertebral fractures at a rate of 0.6% by month 24 compared to a rate of 2.5% in the placebo group, representing a RRR of 75% ( $p < 0.001$ ). The difference in patients experiencing non-vertebral fractures was not statistically significant between the treatment groups at months 12 and 24. There was a statistically significant increase in BMD at the lumbar spine, total hip, and femoral neck in patients treated with romosozumab-aqgg, however; after discontinuation of romosozumab-aqgg, BMD returned to baseline levels within a year if the patient did not continue on any osteoporosis treatment.

### ***romosozumab-aqgg (Evenity) versus alendronate (Fosamax)***

ARCH: In this double-blind study, a total of 4,093 post-menopausal women with a T score  $\leq -2.5$  at the total hip or femoral neck and either 1 moderate or severe vertebral fracture or 2 mild vertebral fractures, or with a T score  $\leq -2.0$  at the total hip or femoral neck and either 2 moderate or severe vertebral fractures or a history of proximal femur fracture were randomized (1:1) to receive either romosozumab-aqgg 210 mg SC once monthly or oral alendronate 70 mg once weekly.<sup>163</sup> After the initial 12 months, treatment with romosozumab-aqgg was stopped and both groups continued to take alendronate 70 mg once weekly for an additional 12 months. The primary endpoints were the total number of new vertebral fractures and clinical fractures at 24 months. In the romosozumab-aqgg group, 6.2% of patients experienced a new vertebral fracture compared to 11.9% in the alendronate group, demonstrating a RRR of 48% with romosozumab-aqgg compared to alendronate. In addition, 9.7% of patients in the romosozumab-aqgg group experienced a clinical fracture compared with 13% of patients in the alendronate group (hazard ratio 0.73). At month 12, there was a statistically significant difference in patients experiencing nonvertebral fractures and increases in BMD at the lumbar spine, total hip, and femoral neck in the romosozumab-aqgg group compared to the alendronate group. During the open-label alendronate period, adjudicated events of osteonecrosis of the jaw were similar in both groups (1 even each in the romosozumab-to-alendronate and alendronate-to-alendronate groups) and atypical femoral fracture (2 events and 4 events, respectively) were observed.

### ***teriparatide (Forteo) versus placebo***

A total of 1,637 postmenopausal women with prior vertebral fractures were randomized to receive recombinant human parathyroid hormone 20 or 40 mcg subcutaneously (SC) or placebo daily for a median duration of 21 months.<sup>164</sup> In the blinded trial, new vertebral fractures occurred in 5%, 4%, and 14% of the 20 mcg and 40 mcg parathyroid hormone compared to placebo patients, respectively. New nonvertebral fragility fractures occurred in 6% of the women in the placebo group and in 3% of those in each parathyroid hormone group. BMD was increased by 9 and 13 more percentage points in the lumbar spine and by 3 and 6 more percentage points in the femoral neck for the 20 mcg and 40 mcg

parathyroid hormone groups compared to the placebo groups. Occasional nausea and headache occurred in the parathyroid hormone patients. The 40 mcg dose increased BMD more than the 20 mcg dose but had similar effects on the risk of fracture and was more likely to have side effects. Teriparatide is recombinant human parathyroid hormone.

### ***teriparatide (Forteo) versus alendronate (Fosamax)***

In a double-blind study of 146 postmenopausal women with osteoporosis, 73 women were randomized to once daily SC injections of teriparatide 40 mcg, and 73 women were randomized to once daily alendronate 10 mg for 14 months.<sup>165</sup> At 3 months, teriparatide increased lumbar spine BMD by 12.2%, and alendronate increased BMD by 5.6% ( $p<0.001$ ). Teriparatide also increased femoral neck BMD and total body bone mineral significantly more than did alendronate ( $p<0.05$ ). Additionally, nonvertebral fracture incidence was significantly lower in the teriparatide group ( $p<0.05$ ). Both treatments were well tolerated despite transient mild asymptomatic hypercalcemia with teriparatide treatment.

A randomized and blinded clinical trial involving 238 postmenopausal women with low hip or spine BMD was carried out at 4 centers.<sup>166</sup> In the study, the women were given a daily regimen of PTH, alendronate, or a combination of the 2. After 12 months, results showed no significant benefit to combining treatments.

In an 18-month, randomized, parallel, double-blind study, 203 postmenopausal women with osteoporosis received teriparatide 20 mcg or alendronate 10 mg.<sup>167</sup> Teriparatide significantly increased markers of bone turnover that peaked at 6 months (serum procollagen type I N-terminal propeptide, 218% and urinary N-telopeptide corrected for creatinine, 58%;  $p<0.001$ ); alendronate significantly decreased the markers at 6 months (-67% and -72%, respectively;  $p<0.001$ ). At 18 months, areal and volumetric spine BMDs were significantly higher with teriparatide than with alendronate (10.3% versus 5.5% [ $p<0.001$ ] and 19% versus 3.8% [ $p<0.01$ ], respectively). Areal femoral neck BMD was significantly higher than baseline in the teriparatide and alendronate groups (3.9% and 3.5%, respectively). There were no significant differences in trabecular femoral neck BMD between the teriparatide and alendronate groups (4.9% and 2.2%, respectively). Cortical volumetric femoral neck BMD was significantly different between the teriparatide and alendronate groups (-1.2% and 7.7%, respectively;  $p=0.05$ ).

A 36-month randomized, double-blind, controlled trial in 428 subjects compared teriparatide (20 micrograms/day) with alendronate (10 mg/day) for treating glucocorticoid-induced osteoporosis.<sup>168</sup> Patients had received  $\geq 5$  mg/day of prednisone equivalent for at least 3 months preceding screening. Increases in BMD from baseline were significantly greater in the teriparatide group than in the alendronate group, and at 36 months were 11% versus 5.3% for lumbar spine, 5.2% versus 2.7% for total hip, and 6.3% versus 3.4% for femoral neck ( $p<0.001$  for all). Fewer subjects had vertebral fractures in the teriparatide group than in the alendronate group (1.7% versus 7.7%;  $p=0.007$ ), with most occurring during the first 18 months. There was no significant difference between groups in the incidence of nonvertebral fractures (7.5% for teriparatide versus 7% for alendronate;  $p=0.843$ ). More subjects in the teriparatide group (21%) versus the alendronate group (7%) had elevated pre-dose serum calcium concentrations ( $p<0.001$ ).

### ***teriparatide (Forteo) versus raloxifene (Evista)***

A 6-month randomized, double-blind trial comparing teriparatide plus raloxifene (n=69) versus teriparatide plus placebo (n=68) was conducted in postmenopausal women with osteoporosis.<sup>169</sup> Bone formation increased similarly in both treatment groups. However, the increase in bone resorption in the combination group was significantly smaller than in the teriparatide-alone group (p=0.015). Lumbar spine BMD significantly increased 5.19% from baseline in the teriparatide-alone group, and 6.19% in the combination group. Also, femoral neck and total hip BMD significantly increased in the combination group, and the increase in total hip BMD was significantly greater than in the teriparatide-alone group (p=0.04). The safety profile of combination therapy was similar to teriparatide alone.

## **META-ANALYSIS**

A 2019 meta-analysis of 41 randomized controlled trials (RCT) evaluated the impact of drug therapy on prevention of secondary osteoporotic vertebral compression fracture (OVCF), non-vertebral fracture, and discontinuation due to adverse effects.<sup>170</sup> Moderate to high quality evidence was found for efficacy of the bisphosphonates (zoledronate, alendronate, risedronate, etidronate, ibandronate), parathyroid hormone, denosumab, and selective estrogen receptor modulators (raloxifene, bazedoxifene [not available in the US]) on prevention of secondary OVCF. In addition, moderate quality evidence demonstrated romosozumab had greater efficacy than alendronate (relative risk [RR] 0.64; 95% CI, 0.49 to 0.84; p=0.001). High quality evidence was found for teriparatide exhibiting greater efficacy than risedronate (risedronate versus teriparatide, RR 1.98; 95% CI, 1.44 to 2.7; p<0.0001); however, teriparatide also exhibited a higher likelihood for adverse effects.

### ***teriparatide versus risedronate***

A 2020 systematic review and meta-analysis of 7 studies evaluated the efficacy and safety of teriparatide compared to risedronate in patients with osteoporosis.<sup>171</sup> Outcomes assessed were the percentage change in bone mineral density (BMD) of lumbar spine, femoral neck, and hip, clinical fracture incidence, serum bone markers, and safety. Overall, teriparatide was associated with a significant increase in BMD in the lumbar spine (weight mean difference [WMD], 4.24; 95% CI, 3.11 to 5.36; p<0.001) as well as in femoral neck (WMD, 2.28; 95% CI, 1.39 to 3.18; p<0.001) and total hip (WMD, 1.19; 95% CI, 0.47 to 1.91; p=0.001) compared to BMD in patients who received risedronate. Furthermore, patients who received teriparatide exhibited a statistically significant lower rate of fractures (risk ratio [RR] 0.48; 95% CI, 0.32 to 0.72; p<0.001), new vertebral fracture (RR 0.45; 95% CI, 0.32 to 0.63; p<0.001), and non-vertebral fracture (RR 0.63; 95% CI, 0.40 to 0.98; p=0.042) compared with patients in the risedronate arm. Pooled data demonstrated the proportion of adverse events was comparable between teriparatide and risedronate (RR 0.93; 95% CI, 0.69 to 1.25; p=0.61).

## **Adherence to Treatment Regimen**

### ***Daily dosing versus weekly dosing***

Claims data for 30 health plans between 1997 and 2002 were used to identify postmenopausal women with osteoporosis who had been newly prescribed a once weekly bisphosphonate (alendronate 35 mg or 70 mg; n=731) or a once daily bisphosphonate (alendronate 5 mg or 10 mg or risedronate 5 mg; n=2,010).<sup>172</sup> Data were examined for 12 months from the date of the initial prescription in an attempt to compare weekly and daily bisphosphonate treatment regimens relative to compliance and persistence. Medication possession ratios (MRPs) were used to measure refill compliance during follow

up. Patients treated with a weekly bisphosphonate were found to have significantly higher medication compliance as compared to patients taking daily treatment (69.2% versus 57.6% MRP,  $p \leq 0.0001$ ). Those patients on weekly treatment were also found to persist with treatment significantly longer than patients on daily treatment ( $p < 0.0001$ ) and had higher rates of retention on treatment at 12 months (44.2% versus 37.1%, respectively). Dosing frequency was the strongest predictor of time to discontinuation ( $p < 0.0001$ ).

### ***Weekly dosing versus monthly dosing***

A study compared the relative rates of treatment persistence and medication adherence in patients taking either weekly risedronate or monthly ibandronate.<sup>173</sup> Prescription claims data from the IMS longitudinal prescription database were used to identify patients taking either risedronate 35 mg weekly ( $n=234,862$ ) or ibandronate 150 mg monthly ( $n=5,139$ ). Two study periods were examined: May through November 2005 and 6 months after initial market availability of each agent. Prescription refill history was tracked for 180 days from the date the original prescription was filled to evaluate adherence and persistence. Patients being treated with weekly risedronate were found to have significantly higher mean persistence and compliance rates than those patients receiving monthly ibandronate.

## **SUMMARY**

Clinical trials have shown a decreased risk of fractures with alendronate (Fosamax), calcitonin-salmon, ibandronate (Boniva), raloxifene (Evista), risedronate (Actonel, Atelvia), denosumab (Prolia) and teriparatide (Forteo) in women with osteoporosis. The data are less clear in women who are postmenopausal but have not been diagnosed with osteoporosis. Additionally, data in men show an increase in BMD but a less clear picture on fracture reduction.

Teriparatide (Teriparatide, Forteo) showed the greatest increase in BMD in clinical trials, ranging from 5% to more than 10%. In general, bisphosphonates increased BMD about 2% to 5% in patients in randomized controlled trials. Gains in BMD vary by the bone measured; however, BMD gains are greater in vertebral sites compared to those found in hips. Calcitonin and raloxifene (Evista) trials showed BMD increases of approximately of 1% to 2%.

Ibandronate (Boniva) and risedronate immediate-release (Actonel) are both available in a once monthly dosage form. Risedronate immediate-release (Actonel) is also available in a dosing regimen that is taken 2 consecutive days each month. Alendronate (Fosamax) and risedronate (Actonel, Atelvia) are available for once weekly dosing. Based on currently available studies, it appears that bisphosphonates dosed weekly foster greater medication adherence, as well as longer treatment persistence compared to daily dosing regimens. However, when compared to once-weekly regimens, once monthly dosing regimens do not appear to give rise to greater treatment adherence and persistence. Binosto is a once weekly effervescent alendronate formulation. It is considered equivalent in efficacy to oral once weekly alendronate dosage forms and offers an alternative delivery form.

Risedronate delayed-release (Atelvia) is indicated for the treatment of osteoporosis in postmenopausal women. A significantly higher incidence of abdominal pain has been reported for risedronate delayed-release (Atelvia) when administered under fasting conditions compared to risedronate immediate-release (Actonel) tablets. Risedronate delayed-release (Atelvia) should be taken immediately following breakfast and not under fasting conditions, unlike other bisphosphonates which should be given prior

to breakfast. Risedronate immediate-release (Actonel) is approved for treatment and prevention of osteoporosis in postmenopausal women, treatment to increase bone mass in men with osteoporosis, prevention and treatment of glucocorticoid-induced osteoporosis in men and women, and treatment of Paget's disease of bone in men and women. Patients should not lie down for at least 30 minutes after taking any oral bisphosphonate.

Subcutaneous injectable formulations used in the treatment of osteoporosis include the RANK ligand inhibitor denosumab (Prolia), parathyroid analogs, abaloparatide (Tymlos) and teriparatide (Forteo), and the sclerostin inhibitor romosozumab-aqqg (Evenity). Use of teriparatide (Forteo) and abaloparatide (Tymlos) should be reserved for patients who are at very high risk for fractures. Teriparatide (Forteo) has a boxed warning regarding use in patients at increased risk for osteosarcoma (e.g., patients with Paget's disease, pediatric patients, patients with prior radiation therapy) and also can increase calcium levels. While denosumab does not require administration by a healthcare professional, it has a dosing frequency of only twice a year. Abaloparatide (Tymlos) and teriparatide (Forteo) should not be used for more than 2 years in a patient's lifetime. Romosozumab-aqqg (Evenity) labeling carries a boxed warning for an increased risk of major adverse cardiac events (MACE) including myocardial infarction (MI), stroke, and cardiovascular death. Romosozumab-aqqg should not be used in patients with a history of MI or stroke in the past year and should be discontinued if an MI or stroke occurs. In addition, it should only be used for a maximum of 12 monthly doses due to decreased efficacy associated with longer use.

Clinical practice guidelines are available from multiple organizations and focus heavily on individualized therapy; recommendations are dependent on the population needing treatment and the risk of fracture. Romosozumab-aqqg was not available at the time of development of treatment recommendations, however the Endocrine Society published an update to their 2019 guidelines in 2020 to address the role of romosozumab as a potential treatment option for select postmenopausal women with osteoporosis at a very high risk for fracture; however, women at high risk of stroke or cardiovascular (CV) disease (e.g., past myocardial infarction or stroke) should not receive romosozumab until further evaluation of the CV risk from this medication has been determined.

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