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Drug Class Update with New Drug Evaluation: Bone Metabolism Drugs

Date of Review: July 2019

Date of Last Review: March 2018
Dates of Literature Search: January 2018- May 23, 2019
Brand Name (Manufacturer): Evenity™
Dossier Received: yes

Generic Name: romosozumab-aqqg

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To define place in therapy for a new monoclonal antibody (romosozumab) recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women at high risk for fracture. In addition, new comparative evidence for existing bone metabolism agents (e.g.; bisphosphonates, teriparatide, abaloparatide, zoledronic acid, and denosumab) for management of osteoporosis and Paget disease will be reviewed.

Research Questions:
- Is there new comparative evidence that bone metabolism agents differ in efficacy or effectiveness for osteoporosis?
- Is there any new comparative evidence the bone metabolism agents differ in harms?
- Are there specific subpopulations (gender, fracture risk) for which one agent is better tolerated or more effective than other available agents?
- What is the evidence for efficacy and harms for the new monoclonal antibody, romosozumab, recently approved to treat postmenopausal osteoporosis**?**

Conclusions:
Class Update
- Four new systematic reviews were identified for inclusion in this drug class update.
- An updated systematic review for the US Preventive Services Task Force evaluated recent evidence on screening and treatment to prevent osteoporotic fractures.[1] One large randomized clinical trial (RCT) comparing screening with no screening reported 28% reduction in hip fractures for women with screening (2.6% vs. 3.5%; hazard ratio [HR], 0.72; 95% Confidence Interval [CI] 0.59-0.89; Absolute Risk Reduction [ARR] 0.9%) but no other statistically significant benefits or harms were observed at 5 years' follow-up.[1] Moderate quality evidence showed that for women, bisphosphonates, parathyroid hormone, raloxifene, and denosumab were associated with a lower risk of vertebral fractures (9 trials; relative risks [RRs] from 0.32-0.64].[1] Evidence was limited for men: zoledronic acid reduced the risk of radiographic vertebral fractures (1 RCT, RR 0.33; 95% CI 0.16 to 0.70); no studies demonstrated reductions in clinical or hip fractures.[1] Bisphosphonates were not consistently associated with reported harms, although rare outcomes were not generally observed in the included evidence.[1]

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- A high quality systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) summarized the effects of long-term osteoporosis drug treatment and of osteoporosis drug treatment discontinuation and holidays.[2] After 3 to 5 years of treatment, continuation of zoledronate or alendronate versus drug holiday inconsistently reduced incident vertebral fracture outcomes (based on radiographic evidence) only for zoledronate: low strength of evidence (SOE), clinical evidence only for alendronate (moderate SOE), but did not reduce nonvertebral fractures (low SOE).[2]
- A high quality systematic review and meta-analysis compared the efficacy and safety of denosumab with bisphosphonates to treat osteoporosis.[3] There was no significant difference between the risk of fracture (RR 1.13; 95% CI 0.82 to -1.55; P=0.466), adverse events [AEs], (RR 1.00; 95% CI 0.96 to 1.04; P=0.957) and withdrawal due to AEs (RR 0.68; 95% CI 0.34 to 137; P=0.280) between bisphosphonates and denosumab in the meta-analysis.[3] Evidence from this meta-analysis suggests no benefit of denosumab for reducing risk of fracture over bisphosphonates.[3]
- Six studies were included in a high quality systematic review that evaluated the safety and efficacy of romosozumab in the treatment of postmenopausal osteoporosis.[4] The meta-analysis of the trial data showed romosozumab resulted in a significantly lower risk of new vertebral fracture (RR 0.37; 95% CI, 0.18 to 0.77; P=0.008), non-vertebral fracture (RR 0.79; 95% CI, 0.68 to 0.92; P<0.003,) and hip fracture (RR 0.59; 95% CI, 0.42 to 0.83; P=0.002) compared with placebo, alendronate and teriparatide at 24 months (moderate strength of evidence).[4] There was no significant difference in the incidence of adverse events in patients with romosozumab compared to placebo (RR 1.00; 95% CI 0.98 to 1.02; p=0.93) over the 24 month study periods (moderate strength of evidence).[4] Absolute rates were not reported, refer to **Table 2** for a specific study results from the 4 Phase 3 trials with romosozumab.

Romosozumab

- The safety and efficacy of romosozumab were demonstrated in 2 clinical Phase 3 trials involving women with postmenopausal osteoporosis. One additional small Phase 3 trial evaluated the safety and efficacy of romosozumab in men with a history of fracture.
- In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial, moderate quality evidence shows that romosozumab significantly reduced the incidence of new vertebral fractures compared to placebo during the first 12 months of therapy (0.5% with romosozumab vs. 1.8% with placebo; RR 0.27; 95% CI, 0.16 to 0.47; P<0.001; ARR 1.3%; NNT 77).[5] However, the reduction in non-vertebral fractures at 12 months was not statistically significant (1.6% with romosozumab vs. 2.1% with placebo; P=0.10; 95% CI, 0.53 to 1.05).[5]
- The Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) compared the effects of romosozumab 210 mg SC once monthly with oral alendronate 70 mg once weekly for 12 months, followed by open label alendronate therapy in both treatment groups for up to an additional 2 years.[6] Moderate quality evidence shows after 24 months of therapy, new vertebral fractures occurred in 6.2% of the women who received romosozumab and in 11.9% of alendronate-treated women (RR 0.52; 95% CI, 0.40 to 0.66; P<0.001; ARR 5.7%; NNT 18).[6] In this trial, serious cardiovascular adverse events were observed more often with romosozumab than with alendronate (50 of 2040 patients [2.5%] vs. 38 of 2014 patients [1.9%]) during the first year of therapy.[6]
- The BRIDGE trial was a placebo-controlled study conducted in 245 men with a history of fracture.[7] Moderate quality evidence demonstrates that after 12 months of therapy, the mean percentage change from baseline in the lumbar spine BMD was significantly greater for the romosozumab group than for the placebo group (12.1% vs 1.2% respectively; P < 0.001; 95% CI not reported).[7] Incidence of fracture, the FDA recommended primary endpoint to assess osteoporosis therapy, was not evaluated in this small trial and romosozumab is not currently approved for use in men.
- In the FRAME and ARCH trials, the following adverse reactions that occurred in more than 2% of patients and were associated with romosozumab administration included arthralgia (13.0%), headache (5.8%) and injection site reactions (5.2%).[8]
- The romosozumab drug label has a black box warning regarding the possibility for increased the risk of myocardial infarction, stroke and cardiovascular death associated with romosozumab adminstration.[8] Patients with a history of myocardial infarction or stroke within the past year should not start on romosozumab therapy.[8]

- There is insufficient data for long-term safety and efficacy of romosozumab beyond 12 months of administration. Due to waning efficacy on bone development after 12 months, the FDA has limited duration of romosozumab therapy to 12 months.[8]

Recommendations:

- Maintain romosozumab as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Update clinical prior authorization (PA) criteria for bone metabolism agents to include romosozumab.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

Abaloparatide was reviewed by the Pharmacy and Therapeutics Committee at the November 2017 meeting. Abaloparatide was designated as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP) and clinical prior authorization (PA) criteria for bone metabolism agents were updated to include abaloparatide. One systematic review which evaluated the use of bisphosphonates in men was presented to the committee was part of the 2017 class update. Moderate quality evidence shows that bisphosphonates reduce fracture risk for men with osteoporosis.[9] Further studies are needed to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.[9] The American College of Endocrinology (AACE/ACE) and American College of Physicians (ACP) recommend alendronate, risedronate, zoledronic acid, or denosumab as first-line treatment options for postmenopausal osteoporosis in their clinical practice guidelines.[10,11] Preferred drugs on the PMPDP for osteoporosis include alendronate, ibandronate and risedronate. Nonpreferred drugs including raloxifene, denosumab, abaloparatide and teriparatide are subject to PA review. Most of the Oregon Health Plan (OHP) Fee-For-Service (FFS) utilization for bone metabolism drugs is due to oral alendronate. The PDL status of the bone metabolism agents is presented in **Appendix 1.**

Background:

Osteoporosis is characterized by low bone mass, deterioration of bone tissue, disruption of bone architecture, compromised bone strength, and increased risk of fracture.[12] According to the World Health Organization (WHO) diagnostic classification, osteoporosis is defined by bone mineral density (BMD) at the hip or lumbar spine that is less than or equal to 2.5 standard deviations (SD) below the mean BMD of a young-adult reference population.[13] Major risk factors for osteoporosis are female gender, elderly age, low BMD, and low intake of calcium and vitamin D.[12] Medications that affect endocrine pathways may also cause secondary osteoporosis.[12] The largest risk group for osteoporosis is post-menopausal women. Although osteoporosis is more prevalent in women, it is estimated that up to one third of new osteoporotic fractures occur in men.[14] Some of the more common secondary causes of osteoporosis in men include glucocorticoid treatment, alcohol abuse, obstructive pulmonary disease, hypogonadism, post-transplantation, and androgen ablation therapy in prostate cancer.[15]

Bone fractures are the clinical consequence of osteoporosis. The most common fractures are those of the vertebrae, hip, and wrist.[12] Risk of fracture can be assessed with the Fracture Risk Assessment (FRAX) Tool, which estimates the 10-year probability of hip fracture and major osteoporotic fracture (spine or forearm) using 9 clinical risk factors including BMD.[16] Hip fractures result in disability related to difficulty with ambulation, inability to perform of activities of daily living, and are associated with increased nursing home and rehabilitation hospital admissions.[17] Approximately 20% of patients who experience hip fractures die within a year of injury.[12] Osteoporosis poses a heavy financial burden on patients, with annual direct medical costs estimated at 17 to 20 billion dollars in the United States.[18] By 2025, annual fractures and associated costs are projected to rise by almost 50%.[19] The most rapid growth in fracture risk is estimated for people 65-74 years of age.[19]

Adult bone is continuously remodeled by osteoclastic bone resorption and osteoblastic bone formation.[20] The drugs used to slow bone loss in osteoporosis are of two categories: anti-resorptive (osteoclast inhibition) and anabolic (osteoblast stimulation). Anti-resorptive agents include bisphosphonates (e.g., alendronate, ibandronate, risedronate, and zoledronic acid), selective estrogen receptor modulators (raloxifene), and a monoclonal antibody (denosumab). The parathyroid hormone analogs, teriparatide and abaloparatide are anabolic agents. The primary goal of osteoporosis management is to reduce fracture risk. Randomized clinical trials demonstrate a reduction of vertebral and hip fractures with bisphosphonates. Alendronate and risedronate also decrease vertebral fractures in men and in patients with glucocorticoid-induced osteoporosis.[21] The main concerns associated with bisphosphonate use are rare side-effects, such as atypical femur fractures and osteonecrosis of the jaw. Raloxifene has been shown to reduce the risk of vertebral, but not non-vertebral, fractures.[17] Although it reduces breast cancer risk, raloxifene increases the incidence of hot flashes and venous thromboembolism. Teriparatide decreases vertebral and nonvertebral fractures.[22] Teriparatide is approved for the treatment of postmenopausal women with severe bone loss, men with osteoporosis who have high risk of fracture, and individuals whose condition has not improved with bisphosphonate therapy.[22] Due to an increase in the risk of osteosarcoma in growing rodents treated with high doses of teriparatide, the FDA limited the treatment duration with teriparatide to 24 months.[22] Denosumab has been shown to decrease hip, vertebral, and nonvertebral fractures compared with low doses of calcium and vitamin D.[21] Since denosumab is a biologic agent, its use is associated with elevated risk for serious infection. Denosumab can also have adverse effects on bone and calcium metabolism including hypocalcemia, atypical femoral fractures, and osteonecrosis of the jaw.[23] The recently approved osteoporosis medication, romosozumab, is a monoclonal antibody that binds to sclerostin, a regulatory bone factor in bone metabolism. The safety and efficacy of romosozumab is discussed in more depth later in this report.

The discovery of sclerostin as a key inhibitor of bone formation was made by investigators studying patients with 2 rare, genetic syndromes characterized by bone overgrowth and high bone mass; sclerosteosis and van Buchem disease.[24] Of note, individuals with sclerosteosis are resistant to bone fracture.[25] These findings stimulated interest in exploring the potential of antisclerostin therapy as a strategy to increase bone formation in patients with osteoporosis.[24] Sclerostin, a protein secreted by osteocytes, inhibits wingless-related integration (Wnt) signaling within osteoblasts thus decreasing osteoblast activity. The Wnt signaling pathway plays a significant role in skeletal development, adult skeletal homeostasis, and bone remodeling.[4] In addition, Wnt signaling is increasingly recognized for its involvement in vascular pathophysiology.[26] There is a concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification.[27]

Measurement of bone density at the hip and lumbar spine with Dual X-Ray Absorptiometry (DEXA) is a surrogate marker used to diagnose osteoporosis. As well as providing diagnostic information, low BMD is recognized as a major risk factor for fractures.[28] A meta-analysis of prospective cohort studies found that every 1 SD decrease in BMD at the femoral neck in women was associated with a relative risk of 2.6 (95% CI 2.0 to 3.5) for hip fracture and 1.6 (95% CI 1.4 to 1.8) for all fractures.[29] A 1 SD decrease in lumbar spine BMD was associated with a relative risk of 2.3 (95% CI 1.9 to 2.8) for vertebral fracture and 1.5 (95% CI 1.4 to 1.7) for all fractures.[29]

Bone density monitoring via DEXA can be used to monitor the effects of pharmacologic therapy. While there are a number of approaches to monitoring therapy, there is no consensus on the optimal approach.[30] The American College of Physicians (ACP) recommends against monitoring during therapy, as many women treated with antiresorptive therapy have a reduction in fracture even when BMD does not increase.[31] In general, stability or an increase in BMD is considered to be response to osteoporosis therapy. Significant BMD loss should result in an evaluation of factors contributing to suboptimal therapeutic effect (e.g. adherence) and an assessment of alternative treatment strategies. A minimal clinically important difference has not been identified for BMD.

Osteoporosis is also diagnosed when an individual experiences a fragility fracture in a location associated with osteoporosis. A fragility fracture is a low-energy fracture that would not normally be expected to result in a broken bone, such as a fall from standing height or less. The most common fractures associated with

osteoporosis are vertebral (27%), wrist (19%), hip (14%), and pelvic (7%).[19] According to the FDA, radiographic vertebral fracture is the accepted primary endpoint for fracture trials supporting an osteoporosis indication.[27]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Screening and Treatment to Prevent Osteoporotic Fractures
A high quality systematic review from the US Preventive Services Task Force evaluated recent evidence on screening and treatment to prevent osteoporotic fractures.[1] One hundred sixty-eight fair- or good-quality articles met inclusion criteria.[1] The accuracy of bone measurement tests or clinical risk assessments for identifying osteoporosis or predicting fractures varied from very poor to good.[1] Osteoporosis screening involves clinical fracture risk assessment, bone measurement testing via DEXA, or both.[1] One large, fair quality RCT comparing screening with no screening reported 28% reduction in hip fractures (2.6% vs. 3.5%; HR 0.72; 95% CI, 0.59-0.89; ARR 0.9%), but no other statistically significant benefits were observed at 5 years' follow-up (osteoporosis-related fractures, clinical fractures, or mortality).[1] This trial also assessed the effect of screening on anxiety and quality of life and found no differences between participants allocated to screening versus usual care (variance not reported , P< 0.10 for all outcomes).[1] Current evidence is insufficient to assess the balance of benefits and harms for screening for osteoporosis to prevent osteoporotic fractures in men.[1]

Moderate quality evidence showed that for women, bisphosphonates, teriparatide, raloxifene, and denosumab were associated with a lower risk of vertebral fractures compared to placebo (9 RCTs; relative risks from 0.32 to 0.64).[1] Bisphosphonates (8 RCTs, pooled RR 0.84; 95% CI 0.76-0.92) and denosumab (1 RCT, RR 0.80; 95% CI, 0.67-0.95) were associated with a lower risk of nonvertebral fractures.[1] Denosumab reduced the risk of hip fracture (1 RCT, RR 0.60; 95% CI, 0.37-0.97), but bisphosphonates did not have a statistically significant association with hip fracture reduction (3 RCTs, pooled RR 0.70; 95% CI, 0.44-1.11).[1] Absolute risk reduction was not reported. Evidence was limited for men: zoledronic acid reduced the risk of radiographic vertebral fractures (1 RCT, RR 0.33; 95% CI, 0.16-0.70); no studies demonstrated reductions in clinical or hip fractures.[1] Bisphosphonates were not consistently associated with reported harms, although rare outcomes were not generally observed in the included evidence.[1] Pooled analysis of 3 RCTs comparing raloxifene to placebo suggested a possible association of raloxifene with deep vein thrombosis, however the results were not significant (0.7% raloxifene vs. 0.3% placebo, RR 2.14; 95% CI, 0.99-4.66).[1] In summary, for women, screening to prevent osteoporotic fractures may reduce hip fractures, and treatment reduces the risk of vertebral and nonvertebral fractures. There was not consistent evidence of treatment harms.[1]

Long-Term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention

A good quality systematic review sponsored by AHRQ summarized the effects of long-term osteoporosis drug treatment and of osteoporosis drug treatment discontinuation and holidays.[2] Long-term osteoporosis drug therapy was defined as greater than 3 years and drug holidays were defined as discontinuation for 1 year or greater after 1 year or greater of medication use.[2] Sixty-one studies were included in the systematic review. No trials compared active treatments, sequential treatments, or different durations of drug holidays.[2] In addition, harms and controls were inconsistently defined.[2]

In women with osteoporosis, 4 years of alendronate reduced clinical fractures (HR 0.64; 95% CI 0.50-0.82; Absolute Risk Reduction [ARR]=7; Number Needed to Treat [NNT]=15; moderate SOE) and radiographic vertebral fractures (HR 0.50; 95% CI 0.31-0.82; ARR 3; NNT 34; moderate SOE), while 4 years of raloxifene reduced clinical vertebral fractures (relative risk 0.58; 95% CI 0.43-0.79; ARR=2; NNT=50; high SOE), but not hip (moderate SOE) or nonvertebral fractures (high SOE). In women with osteopenia or osteoporosis, 6 years of zoledronate reduced incident clinical fractures (HR 0.73; 95% CI 0.60-0.90; ARR=5; NNT=20; moderate SOE) and clinical vertebral fractures (HR 0.41; 95% CI 0.22-0.75; moderate SOE).[2] After 3 to 5 years of prior treatment, continuation of zoledronate or alendronate versus drug holiday inconsistently reduced incident vertebral fracture outcomes (radiographic only for zoledronate [low SOE], clinical only for alendronate [moderate SOE]), but did not reduce nonvertebral fractures (low SOE).[2] Hormone therapies increased cardiovascular events, mild cognitive impairment or dementia, and other harms.[2] Observational studies showed that long-term bisphosphonates may increase atypical femoral fractures (low SOE) and osteonecrosis of the jaw compared to placebo or no treatment (low SOE in 2 comparisons, insufficient in 1).[2]

Key messages include:

- Evidence on the effects of long-term osteoporosis drug treatment and drug continuation versus discontinuation is mostly limited to white, healthy, postmenopausal women.[2]
- Long-term alendronate reduces radiographic vertebral and nonvertebral fractures in women with osteoporosis; long-term zoledronate reduces vertebral and nonvertebral fractures in women with osteopenia or osteoporosis.[2]
- Long-term bisphosphonates may increase atypical femoral fractures and osteonecrosis of the jaw, although both are rare.[2]
- In women with osteoporosis, long-term raloxifene reduces vertebral fractures, but not hip or nonvertebral fractures, and increases venous thromboembolism.[2]
- Long-term oral hormone therapies reduce hip and clinical fractures but increase multiple serious harms.[2]
- Evidence is insufficient about the effects of long-term denosumab, risedronate, ibandronate, teriparatide, and abaloparatide on fractures and harms.[2]
- Continuing bisphosphonates after 3–5 years versus discontinuation reduces some measures of vertebral fractures, but not nonvertebral fractures.[2]

Denosumab Compared To Bisphosphonates to Treat Postmenopausal Osteoporosis

A good quality systematic review and meta-analysis compared the efficacy and safety of denosumab with bisphosphonates to treat osteoporosis.[3] Eleven studies with low risk of bias involving 5446 patients (denosumab = 2873, bisphosphonates = 2573) were included in the meta-analysis.[3] The publication years ranged from 2006 to 2016. Six studies were conducted in the USA, 2 in Canada, and one each in France, Spain, the United Kingdom and Australia.[3] The dose of denosumab was 60 mg via subcutaneous injection every 6 months. Four types of bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) were included. The duration of follow-up ranged from 12 to 24 months. There was no significant difference between the risk of fracture (risk ratio (RR), 1.13; 95% confidence interval (CI), 0.82 to -1.55; P = 0.466), adverse events (AEs; RR 1.00; 95% CI 0.96–1.04; P = 0.957) and withdrawal due to AEs (RR 0.68; 95% CI 0.34–137; P = 0.280).[3] Current evidence suggested no benefit of denosumab for reducing risk of fracture compared to bisphosphonates.[3] More long-term follow-up RCTs are needed to identify the potential complications of denosumab.[3]

Meta-Analysis of Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Six studies were included in a high quality systematic review that was conducted to evaluate the safety and efficacy of romosozumab in the treatment of postmenopausal osteoporosis.[4] Two trials compared romosozumab with placebo, 3 trials compared romosozumab to teriparatide and 1 trial compared romosozumab to alendronate.[4] Three trials were Phase 2 studies and the other 3 were Phase 3 studies in women. Subjects were randomly assigned to receive subcutaneous (SC) injections of romosozumab 210 mg monthly for at least 12 months. Studies were graded as having low risk of bias using the Cochrane manual.[4] The meta-analysis of the trial data showed romosozumab resulted in a significantly lower risk of new vertebral fracture (RR 0.37, 95% CI 0.18–0.77, p=0.008), non-vertebral fracture (RR 0.79, 95% CI 0.68–0.92, p<0.003) and hip fracture (RR 0.59, 95% CI 0.68–0.92 p=0.002) compared with other therapies at 24 months.[4] There was no significant difference in the incidence of adverse events in patients with romosozumab compared to placebo (RR 1.00, 95% CI 0.98–1.02; p=0.93) over the 24 month study period.[4] However, more data is needed to clarify the safety of romosozumab, particularly for cardiovascular events.

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[33-38]

New Guidelines: No new high quality guidelines were identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Denosumab	Prolia®	4/19	Warnings and Precautions	Hypocalcemia may be exacerbated by the use of Prolia®. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis, treatment with other calcium-lowering drugs), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended within 14 days of Prolia® injection. In some post marketing cases, hypocalcemia persisted for weeks or months and required frequent monitoring and intravenous and/or oral calcium replacement, with or without vitamin D.

Randomized Controlled Trials:

A total of 109 citations were manually reviewed from the initial literature search. After further review, 109 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

The humanized monoclonal antibody romosozumab was FDA-approved April 2019 for treatment of osteoporosis in postmenopausal women with a high risk of fracture.[8] Romosozumab inhibits sclerostin, a protein secreted by osteocytes that blocks bone formation. As a result of romosozumab administration, bone formation is increased and bone resorption decreased. One 210 mg dose of romosozumab consists of two (105 mg) injections, one immediately following the other, given once a month by a health care professional.[8] Duration of romosozumab therapy is limited to 1 year because the bone-forming effect of the drug wanes after 12 doses.[8]

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The safety and efficacy of romosozumab were evaluated in 3 clinical trials involving women with postmenopausal osteoporosis and 1 trial in older men with previous fracture. FDA approval for romosozumab was based on 2 large Phase 3 trials, FRAME and ARCH.[27] The good quality FRAME trial was an international, randomized, double blind study in 7180 women with an average age of 71 years and mean T score at femoral neck of -2.7.[5] A small percentage (18%) of subjects had previous vertebral fracture at baseline.[5] Subjects received either romosozumab 210 mg subcutaneously (SC) once a month or placebo for 12 months followed by an additional 12 months of open label therapy with denosumab 60 mg SC every 6 months (to preserve the BMD gains with romosozumab) in both treatment groups.[5] All participants received daily calcium 500-1,000 mg and vitamin D 600-800 International Unit (IU) supplementation. The co-primary endpoints were the proportion of subjects with new vertebral fractures at 12 and 24 months.[5] Secondary end points included clinical (a composite of nonvertebral and symptomatic vertebral) fractures and nonvertebral fractures.[5] During the first 12 months of therapy, romosozumab significantly reduced the incidence of new vertebral fractures compared to placebo (0.5% with romosozumab vs. 1.8% with placebo; RR 0.27; 95% CI, 0.16 to 0.47; P<0.001; ARR 1.3%; NNT 77).[5] At 24 months, the rates of vertebral fractures remained lower in the romosozumab group than in the placebo group after each group made the transition to denosumab (0.6% in the romosozumab group vs. 2.5% in the placebo group, RR 0.75; 95% CI, 0.16 to 0.40; P<0.001; ARR 1.9%; NNT 53).[5] However, the reduction in non-vertebral fractures at 12 months was not statistically significant (1.6% with romosozumab vs. 2.1% with placebo; P=0.10; 95% CI, 0.53 to 1.05).[5]

The good quality ARCH study compared the effects of romosozumab 210 mg SC once monthly with oral alendronate 70 mg once weekly for 12 months, followed by open label alendronate therapy in both treatment groups for up to an additional 2 years.[6] A total of 4093 women were enrolled in this study. The women enrolled in this trial were at much higher risk of fracture than the women in the placebo-controlled FRAME study. The average age of the study participants was 74 years, and more than half of the women were age 75 or older. Ninety-nine percent of the women had a history of a fragility fracture.[6] The co-primary endpoints of the study were the reduction in new vertebral fracture incidence at 24 months and the cumulative incidence of clinical fracture through the primary analysis period.[6] The primary analysis period ended when at least 330 subjects had a clinical fracture and all subjects had completed the 24-month visit; median time on study at time of primary analysis was 33 months.[6] Secondary endpoints included nonvertebral and hip fracture risk reduction at 24 months. After 24 months of therapy, new vertebral fractures occurred in 6.2% of the women who received romosozumab and in 11.9% of alendronate-treated women (RR 0.52; 95% CI, 0.40 to 0.66; P<0.001; ARR 5.7%; NNT 18).[6] Clinical (nonvertebral and symptomatic vertebral) fractures occurred in 9.7% of subjects in the romosozumab-to-alendronate group versus 13.0% in the alendronate-to-alendronate group, representing lower risk clinical fracture with romosozumab (RR 0.73; 95 CI 0.61 to 0.88; <0.001; ARR 3.3%; NNT 31).[6]

The fair quality STRUCTURE trial compared the effects of 12 months of romosozumab with teriparatide in women who were transitioning from bisphosphonate therapy.[39] Previous data suggest that the clinical benefit of teriparatide might be reduced in patients transitioning from bisphosphonates compared with bisphosphonate-naive patients.[39] This trial was a randomized, open-label assessment conducted in 436 postmenopausal women with osteoporosis at high risk for fracture.[39] The average age of subjects was 72 years and all the participants had experienced a previous fracture. The open-label study design was necessary due to the inability to mask the teriparatide pen. The primary endpoint was percentage change from baseline in total hip BMD after 12 months of therapy. The mean percentage change from baseline in total hip BMD was 2.6% in the romosozumab group and - 0.6% in the women who received teriparatide (mean difference (MD) 3.2%; 95% CI, 2.7 to 3.8; p<0.0001).[39] Fracture incidence, the primary endpoint recommended by the FDA for osteoporosis trials, was not evaluated in this trial. The findings from this trial suggest that romosozumab might be an effective treatment option for patients at increased risk for fracture who are transitioning from oral bisphosphonate therapy.[39]

The fair quality BRIDGE trial was a placebo-controlled study conducted in 245 men with a history of fracture.[7] Subjects were randomized 2:1 to receive romosozumab 210 mg SC monthly or placebo for 12 months. The primary efficacy endpoint was percentage change from baseline in lumbar spine BMD at month 12. After 12 months of therapy, the mean percentage change from baseline in the lumbar spine BMD was significantly greater for the romosozumab group than for the placebo group (12.1% vs 1.2% respectively; P < 0.001; 95% CI not reported).[7] Fracture incidence was not evaluated in this trial. Currently, romosozumab does not have FDA approval for use in men. More details about the study design of all 4 trials is summarized in **Table 5.**

Study Limitations:

The study population in the FRAME trial was not representative of the US population (only about 3% North American while about 40% were Latin American).[5] A total of 132 patients (1.8%) were from the United States. In addition, this study noted lower rates of non-vertebral fracture and lower FRAX scores in Latin American regions, which may have underestimated the non-vertebral rate in the placebo group.[27] The investigator attributes the lack of significance of the nonvertebral fracture reduction to a regional subgroup interaction in Central/Latin America where a lower than expected nonvertebral fracture rate in the placebo group was observed (assumed 3.5%, observed 1.2%).[27] The observed nonvertebral fracture rate was also lower than expected in the small enrolled population in North America (assumed 3.5%, observed 1.1%).[27] Thirdly, although romosozumab treatment decreased drastically the risk of vertebral fractures at 12 months, reductions of similar magnitude (61–65%) in such fractures have already been described after 1 year of treatment with anti-resorptive agents.[40] Finally, the 25% reduction in the incidence of nonvertebral fractures observed after 1 year of treatment with romosozumab, although clinically relevant, was not statistically significant.[40]

The FDA noted that reduction of clinical fractures is not an appropriate endpoint in the FRAME and ARCH trials because the term, clinical fracture, does not have clinical meaningfulness among healthcare professionals and can be subject to different interpretation in the labeling.[27] In addition, clinical fracture rates in the FRAME study are combined from nonvertebral fractures (85%) and clinical vertebral fractures (15%).[27] As nonvertebral fracture endpoints were not statistically significant, the incidence rate differences for clinical fractures in the romosozumab group compared to placebo are from clinical vertebral fractures which were already counted in the primary endpoint.[27]

A limitation of the STRUCTURE trial was the open-label study design, which was necessary because of the inability to mask the teriparatide pen. Although the treatment assignments were open label, the efficacy endpoints were objective measurements and assessed by investigators who were masked to treatment allocation.[39] Also, this study was not powered to assess the difference in fracture incidence between treatment groups, and fracture events were not adjudicated or confirmed.[39] Efficacy endpoints in the BRIDGE trial were intermediate (BMD changes) and did not include study fracture incidence after therapy in men.[27]

Clinical Safety:
In the FRAME trial, the incidence of nonfatal serious adverse events was 8.7% in the placebo group and 9.6% in the romosozumab group.[5] The most common adverse reactions reported with romosozumab (greater than or equal to 5% and at a higher incidence than placebo) were arthralgia and headache in both the FRAME and ARCH trials.[5] The most common adverse reaction leading to discontinuation of romosozumab was arthralgia (6 subjects [0.2%] in the placebo group and 5 subjects [0.1%] in the romosozumab group).[5] In the ARCH trial, the incidence of nonfatal serious adverse events was 13.3% in the alendronate group and 11.9% in the romosozumab group.[6] The percentage of patients who withdrew from the study due to adverse events was 1.2% in the alendronate group and 1.2% in the romosozumab group.[6] Adverse reactions occurring in greater than 2% of women treated with romosozumab compared to placebo are presented in **Table 3.**

Table 3. Adverse reactions occurring in ≥ 2% of romosozumab-treated women compared to placebo[8]

Adverse Reaction	Placebo	Romosozumab
Arthralgia	434 (12.1%)	468 (13.1%)
Headache	208 (5.8%)	235 (6.6%)
Muscle Spasms	140 (3.9%)	163 (4.6%)
Edema	67 (1.9%)	86 (2.4%)
Asthenia	79 (2.2%)	84 (2.3%)
Neck Pain	54 (1.5%)	80 (2.2%)
Insomnia	68 (1.9%)	72 (2.0%)
Paresthesia	62 (1.7%)	72 (2.0%)

The immunogenicity of romosozumab was evaluated using an immunoassay for the detection of anti-romosozumab antibodies.[8] Antibody formation against romosozumab occurred in 20% of patients on romosozumab and neutralizing capability occurred in 5% of patients with binding antibodies.[27] The presence of antibodies can reduce romosozumab exposure but do not appear to affect the effectiveness of romosozumab.[27]

Severe adverse events observed during clinical trials included osteonecrosis of the jaw (< 1%) and atypical fracture (<1%).[8] In the ARCH trial, serious cardiovascular events were observed more often with romosozumab than with alendronate (50 of 2,040 patients (2.5%) compared with 38 of 2,014 patients (1.9%); OR 1.31; 95% CI 0.85–2.00).[6] Sixteen patients (0.8%) treated with romosozumab had cardiac ischemic events compared with six (0.3%) treated with alendronate (OR 2.65; 95% CI 1.03–6.77).[6] Based on this data, the romosozumab drug label has a black box warning regarding the possibility for increased risk of myocardial infarction, stroke and cardiovascular death associated with romosozumab adminstration.[8] Romosozumab should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year.[8] If a patient experiences a myocardial infarction or stroke during therapy, romosozumab should be discontinued.[8]

Notably, the FRAME trial did not identify any imbalance in cardiovascular events in the romosozumab compared with the placebo groups.[5] The differences in adverse effects may be due to differences in the patient populations studied in the FRAME and ARCH trial. Women in the ARCH study were, on average, 4 years older than those enrolled in the FRAME trial. In addition, 96% of women in the ARCH trial had a prevalent vertebral fracture compared with only 18% of women in the FRAME trial. As osteoporotic fractures are associated with other ageing co‑morbidities, including cardiovascular disease, women in the ARCH trial may have been less healthy than the women in the FRAME trial.[27]

Look-alike / Sound-alike Error Risk Potential: No issues identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Percentage of patients with new vertebral fractures
2) Percentage of patients with new non-vertebral fractures
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percentage of patients with new vertebral fractures at 12 and 24 months

Table 4. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	Sclerostin inhibitor which increases bone formation
Bioavailability	81%
Distribution	Volume of distribution: 3.92 Liters
Elimination	Monoclonal antibody unlikely to be filtered by the kidney or excreted in urine
Half-Life	12.8 days after 3 doses every 4 weeks
Metabolism	Metabolic pathway has not been characterized

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Cosman F, et al.[5] FRAME Phase 3 RCT, DB, PC, MC, PG N=7180	1. Romosozumab 210 mg SC monthly for 12 months followed by OL denosumab 60 mg SC every 6 months for 12 months 2. Placebo SC monthly for 12 months followed by OL denosumab 60mg SC every 6 months for 12 months	Demographics: 1. Mean age: 71 yo 2. Mean T-score at lumbar spine and femoral neck: -2.7 3. Previous vertebral fracture at baseline: 18% 4. Previous nonvertebral fracture: 22% 5. Ethnic group: -Hispanic 40% -Non-Hispanic 60% Key Inclusion Criteria: 1. Ambulatory, postmenopausal women aged 55 to 90 yo 2. Total hip or femoral neck BMD T-score between -2.5 and -3.5 Key Exclusion Criteria: 1. Total hip or femoral neck T-score ≤ 3.5 2. Previous hip fracture or more than 2 vertebral fractures 3. History of metabolic bone disease 4. Osteonecrosis of the jaw 5. Vitamin D level < 20 ng/ml 6. Current use of medications that affect bone metabolism	ITT: 1. 3589 2. 3591 PP: (completed 12-mo DB period) 1. 3185 2. 3205 Attrition: 12 mos- 1. 404 (11%) 2. 386 (11%) 24 mos- 1. 595 (17%) 2. 559 (16%)	Co-Primary Endpoints: 1. Percentage of patients with new vertebral fractures at 12 mos 1. 16 (0.5%) 2. 59 (1.8%) RR 0.27 (95% CI 0.16 to 0.47) P<0.001 2. Percentage of patients with new vertebral fractures at 24 mos 1. 21 (0.6%) 2. 84 (2.5%) RR 0.25 (95% CI 0.16 to 0.40) P<0.001 Secondary Endpoints: 1. Percentage of patients with new nonvertebral fractures at 12 mos 1. 56 (1.6%) 2. 75 (2.1%) HR 0.75 (95% CI 0.53 to 1.05) p=0.10 2. Percentage of patients with new nonvertebral fractures at 24 mos 1. 96 (2.7%) 2. 129 (3.6%) HR 0.75 (95% CI 0.57 to 0.97) p=0.06	1.3%/77 1.9%/53 NS NS	TEAEs at 12 mos 1. 2806 (78.4%) 2. 2850 (79.7%) SAEs at 12 mos 1. 344 (9.6%) 2. 312 (8.7%) Drug discontinuation due to AE at 12 mos 1. 103 (2.9%) 2. 94 (2.6%) Injection Site Reactions 1. 187 (5.1%) 2. 104 (2.9%) CV events 1. 46 (1.3%) 2. 46 (1.3%) Death 1. 29 (0.8%) 2. 23 (0.6%) 95% CI and p value NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Stratified by age (<75, ≥75yo) and prevalent vertebral fracture. Baseline characteristics similar in both arms. Performance Bias: Low. Placebo presented in identical containers and stored/packaged the same as romosozumab. Detection Bias: Low. Patients, investigators, and sponsors blinded to initial treatment assignment. Central radiologic facility used for fracture assessment, DEXA and CT readings. Radiologists unaware of treatment assignments. Attrition Bias: Low. Similar attrition rates in both arms noted at 12 and 24 months. Reasons for discontinuation were similar in both arms. ITT analysis used to assess treatment effect. Multiple-imputation approach used to handle missing data. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Amgen and UCB Pharm designed the trial and Amgen was responsible for trial oversight. Several authors received grant support from Amgen. **Applicability**: Patient: The study population was not representative of the US population in postmenopausal women with osteoporosis. Small percentage of subjects had previous vertebral fracture at baseline. Intervention: Romosozumab dose was proven to be efficacious in Phase 2 trial. Comparator: Would be more informative to compare romosozumab with bisphosphonate. Outcomes: Cumulative incidence of new vertebral fractures is a reasonable endpoint to assess treatment effect. Setting: 222 centers in 25 countries: Central/Latin America: 43% Central/Eastern Europe: 29% Western Europe, Australia, New Zealand: 14% Asia/Pacific: 12% North America: 3%

2. Saag KG, et al.[41] ARCH trial Phase 3 RCT, DB, MC N=4093	1. Romosozumab 210 mg SC once monthly for 12 months followed by OL alendronate 70 mg orally once weekly 2. Alendronate 70 mg orally once weekly followed by OL alendronate 70 mg orally once weekly	Demographics: 1. Mean age: 74 yo 2. Mean T-scores: -Lumbar spine: -2.96 -Total hip: -2.80 -Femoral neck: -2.90 3. Ethnic group: -Non-Hispanic: 68 % -Hispanic: > 32% 4. Previous fracture: 99% Key Inclusion Criteria: 1. Postmenopausal women aged 55 to 90 yo with total hip or femoral neck BMD T-score ≤ -2.5 and at least one moderate or severe vertebral fracture OR T-score ≤ -2.0 with either ≥ 2 moderate to severe vertebral fractures or a fracture of the proximal femur 3-24 mos before randomization Key Exclusion Criteria: 1. Severe metabolic or bone disease 2. Current use of bone metabolism agents 3. Cr Cl < 35 ml/min	ITT: 1. 2046 2. 2047 PP: (completed study through primary analysis) 1. 1574 2. 1576 Attrition at 12 mos: 1. 215 (11%) 2. 224 (11%)	Co-primary Endpoints: 1. Cumulative incidence of new vertebral fracture at 24 months 1. 127 (6.2%) 2. 243 (11.9%) RR 0.50 (95% CI, 0.40 to 0.66), P<0.001 2.Cumulative incidence of new clinical (nonvertebral fracture and clinical vertebral fracture) fracture through primary analysis period (> 24 mos) 1. 198 (9.7%) 2. 266 (13%) HR 0.73 (95% CI 0.61 to 0.88), P<0.001 Secondary Endpoints: 1. Cumulative incidence of new vertebral fracture at 12 months 1. 82 (4.0%) 2. 128 (6.3%) RR 0.63 (95% CI, 0.47 to 0.85), P=0.003 2. Incidence of nonvertebral fracture at 12 months 1. 70 (3.4%) 2. 95 (4.6%) RR 0.74 (95% CI 0.54 to 1.01) P=0.057 3. Incidence of hip fracture at 12 months 1. 14 (0.7%) 2. 22 (1.1%) RR 0.64 (95% CI 0.3 to 1.26 P=0.19	5.7%/18 3.3%/31 2.3%/44 NS NS	TEAEs at 12 mos 1. 1544 (76%) 2. 1584 (79%) SAEs at 12 mos 1. 262 (13%) 2. 278 (14%) SAEs leading to drug discontinuation at 12 mos 1. 70 (3.4%) 2. 64 (3.2%) Injection Site Reaction at 12 mos 1. 90 (4.4%) 2. 53 (2.6%) Death 1.30 (1.5%) 2. 21 (1.0%) CV Events at 12 mos 1. 50 (2.5%) 2. 38 (1.9%) OR 1.31 (95% CI 0.85 to 2.00) P value and 95% CI NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Stratified according age (<75 yo vs. ≥75 yo). Baseline demographics balanced between groups. Performance Bias: Low. Subjects received a matched oral placebo or matched subcutaneous placebo depending on treatment assignment to maintain blinding. Detection Bias: Low. Patients, outcome assessors, health care providers, data collectors, and data analysts blinded to treatment assignment. All DEXA scan data submitted electronically to the central imaging vendor for analysis. Attrition Bias: Low. 11% of subjects withdrew from the trial, reasons for discontinuation were similar in both arms. ITT analysis used to assess treatment effect. Multiple imputation used for missing fracture status. Reporting Bias: Low. Protocol available online Other Bias: Unclear. Funded by Amgen. Amgen and UCB Pharma designed the trial, and Amgen was responsible for trial oversight and data analyses per a prespecified statistical analysis plan. An external independent data monitoring committee monitored unblinded safety data. **Applicability**: Patient: Women at high risk for fracture were included in the trial – 99% of subjects had a previous fracture. Intervention: Romosozumab dose evaluated in Phase 2 trials. Comparator: Bisphosphonate therapy is standard of care to manage osteoporosis. Outcomes: Incidence of vertebral fracture is an established endpoint for evaluating osteoporosis therapy. Setting: 125 centers: Central or Eastern Europe: 40% Latin America: 34% Western Europe, Australia, New Zealand: 13% Asia-Pacific or South Africa: 11% North America: 2%

3. Langdahl BL, et al.[39] STRUCTURE trial Phase 3 trial, OL, MC, PG N=436	1. Romosozumab 210 mg SC once monthly 2. Teriparatide 20 mcg SC once daily	Demographics: 1. Mean age: 72 yo 2. Mean baseline BMD T-score: -Total hip: -2.2 -Lumbar spine -2.9 -Femoral neck -2.4 3. Average duration of bisphosphonate therapy: 6.2 years 4. Ethnic group: -White: 89% -Other: 11% 5. Previous fracture: 100% Key Inclusion Criteria: 1. Ambulatory, postmenopausal women aged 55 to 90 yo with osteoporosis (T-score ≤ -2.5 at total hip, lumbar spine, femoral neck) and history of fracture after age 50 previously treated with bisphosphonate therapy for minimum of 3 years Key Exclusion Criteria: 1. Use of osteoporosis agents other than bisphosphonates 2. Vitamin D level < 50 nmol/L 3. History of metabolic or bone disease 4. Hyper- or hypocalcemia 5. Uncontrolled hyper- or hypothyroidism	ITT: 1. 218 2. 218 PP: 1. 198 2. 200 Attrition: 1. 20 (9%) 2. 18 (8%)	Primary Endpoint: Mean percentage change from baseline in total hip BMD at 12 months 1. 2.6% 2. -0.6% MD 3.2% (95% CI 2.7 to 3.8) p<0.0001 Secondary Endpoints: 1. Percent change from baseline in femoral neck BMD at 12 months 1. 3.2% 2. -0.2% MD 3.4% (95% CI NR) p<0.0001 2. Percent change from baseline in lumbar spine BMD at 12 months 1. 9.8% 2. 5.4% MD 4.4% (95% CI NR) p<0.0001	NA NA NA	SAEs 1. 17 (8%) 2. 23 (11%) SAEs leading to drug discontinuation 1. 6 (3%) 2. 12 (6%) Hypercalcemia 1. 2 (<1%) 2. 22 (10%) Arthralgia 1. 22 (10%) 2. 13 (6%) Injection Site Reaction 1. 17 (8%) 2. 6 (3%) Death 1. 1 (< 1%) 2. 1 (< 1%) P value and 95% CI NR		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Baseline demographics similar in both treatment groups. Performance Bias: High. Open label study due to inability to conceal teriparatide pen formulation. Patients assigned to teriparatide self-injected the study medication while patients assigned to romosozumab were administered the medication by HCPs. Detection Bias: Unclear. Investigators assessing efficacy endpoints were masked to treatment assignment. Attrition Bias: Low. Similar rates of study withdrawal in both arms with similar reasons for discontinuation. Reporting Bias: Low. Protocol is available at European Clinical Trial Register. Other Bias: Unclear. Funded by Amgen, Astellas, and UCB Pharma. Amgen and UCB Pharma designed the study in collaboration with external investigators. Amgen was responsible for study monitoring, oversight, and statistical analysis. A significant percentage of contributing authors received financial support from Amgen or were employed by Amgen. **Applicability**: Patient: Patients at high risk for fracture; primarily European, exposed to bisphosphonate therapy for 3 years with history of fracture. Intervention: Dose of romosozumab evaluated in Phase 2 trials Comparator: Teriparatide is a bone forming agent with a different MOA from romosozumab. Clinical benefit of teriparatide may be reduced by prior bisphosphonate therapy. Outcomes: Efficacy endpoints were intermediate (BMD changes) and did not include study fracture incidence after therapy due to inadequate power to assess differences in fracture rate. Setting: 46 sites in North America (7%), Latin America (18%), and Europe (75%)

4. Lewiecki EM, et al.[7] BRIDGE trial Phase 3 RCT, MC, DB, PC N=245	1. Romosozumab 210 mg SC once monthly for 12 months 2. Placebo SC once monthly for 12 months	Demographics: 1. Mean age: 72 yo 2. Baseline lumbar spine T-score: -2.3 3. Previous fracture: 54% 4. Ethnic group: White: 74% Asian: 11% Other: 15% Key Inclusion Criteria: 1.Men aged 55 to 90 yo with T-score ≤ -2.5 at the spine or hip or ≤ 1.5 at the spine or hip with a history of nonvertebral or vertebral fractures after age 45 Key Exclusion Criteria: 1. T-score ≤ -3.50 at the hip 2. History of hip fracture 3. History of metabolic or bone disease 4. Current use of medications that affect bone metabolism	ITT: 1. 163 2. 82 PP: 1. 152 2. 79 Attrition: 1. 11 (7%) 2. 3 (4%)	Primary Endpoint: Percent changes from baseline in lumbar spine BMD at 12 months 1. 12.1% 2. 1.2% P<0.001 95% CI NR Secondary Endpoints: 1. Percent change from baseline in DXA BMD at total hip at 12 months 1. 2.5% 2. -0.5% P<0.001 95% CI NR 2. Percent change from baseline in DXA BMD at femoral neck at 12 months 1. 2.2% 2. -0.2% P<0.001 95% CI NR	NA NA NA	TEAEs at 12 mos 1. 123 (76%) 2. 65 (80%) SAEs 1. 21 (12.9%) 2. 10 (12.3%) SAE leading to drug discontinuation 1. 5 (3.1%) 2. 1 (1.2%) Injection Site Reactions 1. 9 (5.5%) 2. 3 (3.7%) CV events 1. 8 (4.9%) 2. 2 (2.5%) p-value and 95% CI NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to receive romosozumab or placebo via IVRS. Stratified by geographic region. Baseline demographics balanced between groups. Performance Bias: Low. Matched placebo given to subjects in the placebo arm. Detection Bias: Low. BMD measurements analyzed by a central imaging vendor. Attrition Bias: Low. Similar attrition rates in both arms. Reporting Bias: Low. Protocol available at ClinicalTrials.gov Other Bias: Unclear. Amgen Inc., UCB Pharma and Astellas Pharma provided financial support for this trial. The authors all report grant support from Amgen and UCB Pharma. **Applicability**: Patient: Primarily studied in Europe (66%) with relatively few participants in North America (9%). Applies to older men with 54% having a previous fracture. Intervention: Modeled after FRAME trial, as Phase 2 trials did not include men. Comparator: Would be more informative to compare romosozumab to standard of care (bisphosphonate) approved to treat osteoporosis in men. Outcomes: Efficacy endpoints were intermediate (BMD changes) and did not include study fracture incidence. Setting: 31 centers in Europe (66%), Latin America (14%), Japan (11%) and North America (9%)

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BMD = bone mineral density; CI = confidence interval; CV = cardiovascular; DB = double blind; DEXA = dual-energy x-ray absorptiometry; HCP = health care professional; HR = hazard ratio; ITT = intention to treat; IVRS = interactive voice-response system; MC = multi-center; MD = mean difference; mITT = modified intention to treat; MOA = mechanism of action; Mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NR = not reported; NNT = number needed to treat; OL = open label; OR = odds ratio; PC = placebo controlled; PG = parallel group; PP = per protocol; RCT = randomized clinical trial; RR = risk ratio; SAE = serious adverse event; SC = subcutaneous; SEAs = serious adverse effects; TEAE = treatment emergent adverse effects; YO = years old

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40. Papapoulos SE. Bone: Romosozumab - getting there but not quite yet. *Nature Reviews Endocrinology.*12(12):691-692.
41. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *N Engl J Med.* 2017;377(15):1417-1427.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
alendronate sodium	ALENDRONATE SODIUM	TABLET	PO	Y
alendronate sodium	FOSAMAX	TABLET	PO	Y
ibandronate sodium	BONIVA	TABLET	PO	Y
ibandronate sodium	IBANDRONATE SODIUM	TABLET	PO	Y
risedronate sodium	ACTONEL	TABLET	PO	Y
risedronate sodium	RISEDRONATE SODIUM	TABLET	PO	Y
abaloparatide	TYMLOS	PEN INJCTR	SQ	N
alendronate sodium	ALENDRONATE SODIUM	SOLUTION	PO	N
alendronate sodium	BINOSTO	TABLET EFF	PO	N
alendronate sodium/vitamin D3	FOSAMAX PLUS D	TABLET	PO	N
calcitonin,salmon,synthetic	CALCITONIN-SALMON	SPRAY/PUMP	NS	N
calcitonin,salmon,synthetic	MIACALCIN	VIAL	IJ	N
denosumab	PROLIA	SYRINGE	SQ	N
etidronate disodium	ETIDRONATE DISODIUM	TABLET	PO	N
ibandronate sodium	BONIVA	SYRINGE	IV	N
ibandronate sodium	IBANDRONATE SODIUM	SYRINGE	IV	N
raloxifene HCl	EVISTA	TABLET	PO	N
raloxifene HCl	RALOXIFENE HCL	TABLET	PO	N
risedronate sodium	ATELVIA	TABLET DR	PO	N
risedronate sodium	RISEDRONATE SODIUM DR	TABLET DR	PO	N
teriparatide	FORTEO	PEN INJCTR	SQ	N
denosumab	XGEVA	VIAL	SQ	
ibandronate sodium	IBANDRONATE SODIUM	VIAL	IV	
pamidronate disodium	PAMIDRONATE DISODIUM	VIAL	IV	
zoledronic ac/mannitol/0.9NaCl	ZOLEDRONIC ACID	PIGGYBACK	IV	
zoledronic acid	ZOLEDRONIC ACID	VIAL	IV	
zoledronic acid	ZOMETA	VIAL	IV	
zoledronic acid/mannitol-water	RECLAST	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOLEDRONIC ACID	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOMETA	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOLEDRONIC ACID	PIGGYBACK	IV	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to May 23, 2019

1.	Paget Disease, Extramammary/ or Pagets disease.mp.	6843
2.	Osteoporosis, Postmenopausal/ or Osteoporosis/ or osteoporosis.mp.	73213
3.	Risedronate Sodium/	1146
4.	Alendronate/	3547
5.	ibandronate.mp.	869
6.	Etidronic Acid/	2714
7.	calcitonin/	15604
8.	Raloxifene Hydrochloride/	2560
9.	Teriparatide/	1813
10.	Denosumab/	1364
11.	Zoledronic acid.mp.	3905
12.	Pamidronate.mp.	2816
13.	Abaloparatide.mp	53
14.	Romosozumab	90
15.	1 or 2	79425
16.	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	32101
17.	limit 16 to (english language and humans and yr="2018 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	109

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EVENITY safely and effectively. See full prescribing information for EVENITY.

EVENITY™ (romosozumab-aqqg) injection, for subcutaneous use
Initial U.S. Approval: 2019

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH
See full prescribing information for complete boxed warning.

- **EVENITY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)**
- **EVENITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. (5.1)**
- **If a patient experiences a myocardial infarction or stroke during therapy, EVENITY should be discontinued. (5.1)**

----------INDICATIONS AND USAGE----------
EVENITY is a sclerostin inhibitor indicated for the 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. (1)

Limitations of Use: Limit duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Two separate subcutaneous injections are needed to administer the total dose of 210 mg. Inject two syringes, one after the other. (2.1)
- Should be administered by a healthcare provider. (2.1)
- Administer 210 mg subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm. (2.2)
- Adequately supplement calcium and vitamin D during treatment. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 105 mg/1.17 mL solution in a single-use prefilled syringe. A full dose of EVENITY requires two single-use prefilled syringes. (3)

----------CONTRAINDICATIONS----------
- Hypocalcemia (4)
- Known hypersensitivity to EVENITY (4)

----------WARNINGS AND PRECAUTIONS----------
- Major Adverse Cardiac Events (MACE): Monitor for symptoms of MI and stroke and seek prompt medical attention if symptoms occur. (5.1)
- Hypersensitivity: Hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria. Discontinue EVENITY if a clinically significant allergic reaction occurs. (5.2)
- Hypocalcemia: Adequately supplement calcium and vitamin D during treatment with EVENITY. (5.3)
- Osteonecrosis of the Jaw: Monitor for symptoms. Consider discontinuation of therapy based on benefit-risk assessment. (5.4)
- Atypical Femoral Fracture: Evaluate new or unusual thigh, hip, or groin pain to rule out an incomplete femur fracture. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) reported with EVENITY in clinical trials were arthralgia and headache. (6.1)

----------USE IN SPECIFIC POPULATIONS----------
Renal Impairment: Patients with severe renal impairment or receiving dialysis are at greater risk of developing hypocalcemia. Monitor serum calcium and supplement with calcium and vitamin D. (5.3, 8.7)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2019

Appendix 4: Key Inclusion Criteria

Population	Post-menopausal women at risk for fracture (Total hip or femoral neck T-score between -2.5 and -3.5)
Intervention	Romosozumab 210 mg SC once a month for 12 months
Comparator	Placebo, teriparatide, alendronate
Outcomes	Percentage of women experiencing new vertebral fracture
Timing	1-2 years
Setting	Primarily Europe and Latin America

Bone Metabolism Agents

Goal(s):

To ensure appropriate drug use and safety of bone metabolism ~~resorption suppression~~ agents by authorizing utilization in specified patient populations.

Length of Authorization:

- 12 to 24 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Note: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed an oral bisphosphonate (alendronate, risedronate, or ibandronate) or do they have contraindications to these treatments? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh; deny and recommend trial of oral bisphosphonate
5. Is the request for raloxifene?	**Yes:** Go to #6	**No:** Go to #7
6. Is the patient pregnant and/or at increased risk for thromboembolism or stroke?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: inform prescriber of pregnancy category X and boxed warning for venous thromboembolism and stroke.	**No:** Approve for up to 12 months
7. Is the request for teriparatide and is the patient at high risk for fracture? Examples include: • Postmenopausal women with osteoporosis and T-score ≤ - 2.5 or history of fracture • Men with primary or hypogonadal osteoporosis* • Men or women with osteoporosis associated with sustained systemic glucocorticoid therapy	**Yes:** Go to #10	**No:** Go to #8

Approval Criteria		
8. Is the request for abaloparatide and is the patient a postmenopausal woman aged 49 to 86 years with osteoporosis at high risk for fracture? Inclusion criteria from the ACTIVE[1] trial: • Women with T score between - 2.5 and -5.0 AND radiologic evidence of vertebral fracture or history of nonvertebral fracture within the past 5 years OR • Women aged 65 years or older with T score between -3.0 and -5.0 without history of fracture OR T score between -2.0 and 5.0 with history of fracture.	**Yes:** Go to #9	**No:** Go to #11
9. Has the patient received treatment with anticonvulsants that affect Vitamin D metabolism (phenobarbital, phenytoin, carbamazepine or primidone) or with chronic heparin within the past 6 months OR has the patient received daily treatment with oral, intranasal, or inhaled corticosteroids in the past 12 months?	**Yes:** Pass to RPh. Deny; medical appropriateness. (These patients were excluded from the ACTIVE[1] trial)	**No:** Go to #10.
10. Does the patient meet one of the following conditions: • Concomitant bisphosphonate; or • Pediatric or young adult with open epiphyses; or • History of osteosarcoma or skeletal malignancies; or • Metabolic bone disease; or • Underlying hypercalcemic disorders; or • Unexplained elevated alkaline phosphatase levels?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 24 months (depending on when therapy was initiated. Teriparatide and abaloparatide are only FDA approved for a total duration of therapy of 2 years.)
11. Is the request for romosozumab and is the patient a postmenopausal women with osteoporosis and T-score ≤ -2.5 or history of fracture?	**Yes:** Go to # 12	**No:** Go to # 13

Approval Criteria		
12. Has the patient had a myocardial infarction or stroke within the past year?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months maximum.* *Note: FDA has only approved use of romosozumab for a total of 12 months. If continued osteoporosis therapy is warranted, continue therapy with an anti-resorptive agent (e.g. bisphosphonates, denosumab, or raloxifene).
13. RPh only: All other indications need to be evaluated as to whether they are funded by the OHP or not.	If funded and clinic provides supporting literature, approve for up to 12 months	If non-funded, deny; not funded by the OHP

P&T Review: *7/19 (DM); 3/18; 7/16; 9/10*
Implementation: *TBD; 4/16/18; 8/16, 1/1/11*

** FDA approved osteoporosis treatments for men include alendronate, risedronate, zoledronic acid, teriparatide, and denosumab.*

1. Miller PD, Hattersley G, Riis BJ, et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. JAMA.316 (7):722-733.