Romosozumab-aqqg (Evenity) for Osteoporosis in Postmenopausal Women at High Risk for Fracture

Cynthia R. Hall, PharmD, JD, MS

INTRODUCTION

Osteoporosis is a chronic disease characterized by porous, fragile bones that are prone to fracture as one ages. An estimated 10 million people in the United States are affected by the disease, with another 44 million having low bone density. Osteoporosis and low bone density are risk factors for fracture. Osteoporosis can affect both men and women; however, the disease is more prevalent in women. One in two women suffering from osteoporosis will have a bone fracture within her lifetime.

Osteoporosis occurs when bone resorption exceeds bone formation. In the disease, osteoclastic activity exceeds osteoblastic activity leading to decreased bone strength and bone mass, increased microdamaged bone, less healthy bone, and an imbalance of bone calcium and phosphate.

Fractures caused by osteoporosis are a burden to the aging population in the U.S. Bone fractures can lead to a loss of independence, hospitalization, disability, nursing home placement, and death. The U.S. economic cost of osteoporosis is estimated at $19 billion per year. The prevalence, and therefore the cost, of the disease are expected to continue to rise.

A majority of drugs utilized in osteoporosis treatment act by decreasing bone resorption, thereby reducing bone loss and decreasing the incidence of vertebral, nonvertebral, and hip fractures. These drugs include first-line agents such as bisphosphonates and denosumab for treatment of postmenopausal women.

While these drugs prevent bone catabolism, parathyroid hormone (PTH) and PTH-related peptide analogs teriparatide (Forteo, Lilly) and abaloparatide (Tymlos, Radius Health) treat osteoporosis via an anabolic effect on bone. Studies of novel drug therapies to increase bone formation have been reported. One such class of drug acts by inhibiting sclerostin, a negative regulator of the Wnt/beta-catenin pathway expressed by osteocytes that inhibit osteoblast activity. Inhibition of sclerostin increases bone formation.

This review will focus on the safety and effectiveness of romosozumab-aqqg (Evenity, Amgen/UCB), referred to as romosozumab hereafter. Romosozumab is a sclerostin inhibitor approved in April 2019 by the Food and Drug Administration for the treatment of osteoporosis in postmenopausal women at high risk for fracture (i.e., women with a history of osteoporotic fracture or multiple risk factors for fracture) or patients who have failed or cannot tolerate other osteoporosis agents.

PHARMACOLOGY AND PHARMACODYNAMICS

Romosozumab is a monoclonal antibody that acts by binding with and inhibiting the protein sclerostin, thereby stimulating osteoblastic activity and formation of new bone on trabecular and cortical bone surfaces. Romosozumab also decreases bone resorption to a lesser extent. By inhibiting sclerostin, romosozumab increases bone mass and bone density and improves the structure of bone and bone strength.

A phase 3 study of postmenopausal women with osteoporosis found that the bone formation marker procollagen type 1 N-telopeptide (P1NP) peaked at 145% from baseline in comparison to placebo 14 days after initial romosozumab treatment. P1NP then declined to levels similar to placebo at nine months and further declined from baseline approximately 15% below the placebo's concentration change at 12 months. The bone resorption marker type 1 collagen C-telopeptide (CTX) was reduced approximately 55% from baseline in comparison to placebo 14 days after initial treatment and continued to remain below concentrations of placebo. Additionally, at month 12, CTX was 25% below placebo concentration change. Upon romosozumab discontinuation, P1NP levels were observed to return to baseline at 12 months while CTX increased to above baseline within three months, returning to baseline at 12 months. Therefore, romosozumab is approved for the treatment of osteoporosis for 12 months followed by antiresorptive therapy if needed.

PHARMACOKINETICS

Pharmacokinetic parameters are summarized in Table 1. After the administration of a single dose of romosozumab via two separate subcutaneous injections of 105 mg/1.17 mL given consecutively to healthy subjects, a mean maximum serum concentration of 22.2 (standard deviation [SD], 5.8) mcg/mL along with a mean area under the curve of 389 (SD, 127) mcg*day/mL was achieved. After three months of administering romosozumab 210 mg monthly to postmenopausal women, a steady-state concentration resulted with mean trough serum levels between 8 to 13 mcg/mL at months 3, 6, 9, and 12.

Romosozumab’s pharmacokinetics are nonlinear. Immunoegenicity was observed with use and was associated with decreased serum concentrations; however, antibodies to romosozumab were not associated generally with differences in drug safety or effectiveness.

Race, sex, age, disease state, prior alendronate exposure, or renal impairment of any stage did not produce clinically significant differences in pharmacokinetic parameters. The effect of end-stage renal disease not requiring dialysis is not known.
Table 1 Pharmacokinetic Characteristics of Romosozumab

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Description</th>
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<tr>
<td>Absorption</td>
<td>Median time to maximum concentration range between 2 to 7 days, resulting in $T_{max}$ of 5 days.</td>
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<tr>
<td>Distribution</td>
<td>At steady state, the estimated volume of distribution is 3.92 L.</td>
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<tr>
<td>Metabolism</td>
<td>Not characterized, but it is expected to be catabolized via a pathway similar to endogenous Immunoglobulin G.</td>
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<tr>
<td>Elimination and excretion</td>
<td>Nonlinear pharmacokinetics. Clearance decreases as dose increases, with mean estimated systemic clearance at 0.38 mL/hr/kg after recommended dose. Mean effective $t_{1/2}$ was 12.8 days after three doses of 3 mg/kg (the approved recommended dose) every 28 days.</td>
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**CLINICAL TRIALS**

**Cosman et al.**

The “FRActure study in postmenopausal woMen with OstEoporosis” (FRAME) was a phase 3, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and effectiveness of romosozumab in postmenopausal women with osteoporosis. The women were randomized 1:1 to receive 210 mcg of romosozumab or placebo subcutaneously each month for 12 months. The participants also received 500 mg to 1000 mg of calcium and 600 IU to 800 IU of vitamin D daily. After 12 months, both groups received open-label denosumab 60 mg, an anti-resorptive agent, subcutaneously every six months for 12 more months. The study enrolled 7,180 ambulatory postmenopausal women 55 to 90 years of age who had a bone mineral density (BMD) T-score of −2.5 to −3.5 at the total hip or femoral neck.

The coprimary efficacy endpoints were the number of new vertebral fractures at month 12 and month 24 in the romosozumab group compared to the placebo group. Results of the 12-month efficacy endpoint revealed a 73% lower risk of new vertebral fracture compared with placebo (an incidence of 0.5% in romosozumab-treated patients versus 1.8% in placebo-treated patients; risk ratio, 0.27; 95% confidence interval [CI], 0.16–0.47; $P < 0.001$). The nonvertebral fracture endpoint lacked statistical significance and was considered exploratory, even though these fractures represented 88% of the fractures that occurred.

The 24-month efficacy endpoint, which included the transition of all patients to denosumab after 12 months, showed a 75% lower risk of new vertebral fracture in romosozumab-treated patients compared with placebo-treated patients (an incidence of 0.6% in the romosozumab group versus 2.5% in the placebo group; risk ratio, 0.25; 95% CI, 0.16–0.40; $P < 0.001$). The risk of nonvertebral fracture at 24 months was again found to be non-significant and therefore exploratory.

An increase in BMD from baseline was observed by six months and was greater in the romosozumab group than the placebo group, and BMD continued to increase in this group after transition to denosumab. P1NP markers indicating bone formation increased quickly and peaked on the 14th day of treatment, then declined to baseline at nine months. CTX, a bone-resorption marker, declined rapidly in the romosozumab group and remained lower than placebo levels at 12 months.

The secondary endpoints included clinical fractures (which were a composite of nonvertebral and symptomatic vertebral) and nonvertebral fractures. Adverse events observed in this study included hypersensitivity reactions and injection-site reactions. Also, two adjudicated events of osteonecrosis of the jaw and one atypical femoral fracture occurred at 24 months in the romosozumab group. Binding antiromosozumab antibodies and neutralizing antibodies developed but were not found to have a detectable effect on drug safety or efficacy.

**Saag et al.**

The phase 3, multicenter, international, randomized, double-blind “Active-Controlled FraCture Study in Postmenopausal Women with Osteoporosis at High Risk” (ARCH) was designed to evaluate the superiority of romosozumab over alendronate. The trial enrolled 4,093 ambulatory postmenopausal women; 3,654 completed 12 months, while 3,150 completed the primary analysis period. They were randomized in a 1:1 ratio to romosozumab or alendronate. Participants had a BMD T-score of −2.5 or less at the total hip or femoral neck with one or more moderate or severe vertebral fractures or two or more mild vertebral fractures; or a T-score of −2.0 or less at the total hip or femoral neck and two or more moderate or severe vertebral fractures or a fracture of the proximal femur occurring between three and 24 months prior to randomization. Women were excluded if they were unable to take oral tablets of alendronate, if alendronate was contraindicated, or if their glomerular filtration rate was less than 35 mL/min/1.73 m².

The trial had two phases. During the first 12 months, patients were randomized to receive romosozumab 210 mg subcutaneously once a month or oral tablets of alendronate 70 mg weekly. After this phase, patients received open-label oral alendronate 70 mg weekly for 12 months. All patients received daily supplementation of calcium and vitamin D.

The primary endpoints of the trial consisted of the number of new vertebral fractures at 24 months and number of clinical fractures at the time of primary analysis, which ended when at least 330 subjects had a clinical fracture and all subjects completed a month 24 visit. Secondary endpoints were BMD at the lumbar spine, total hip, and femoral neck at month 12 and month 24 and the number of nonvertebral fractures at primary analysis.

Treatment with romosozumab followed by alendronate resulted in a 48% lower risk for vertebral fractures compared with alendronate alone (6.2% versus 11.9%; risk ratio, 0.52; 95% CI, 0.40–0.66; $P < 0.001$) and a 27% lower risk of clinical fracture than alendronate (hazard ratio, 0.73; 95% CI, 0.61–0.88; $P < 0.001$). BMD was greater from baseline in the romosozumab treatment group at all sites throughout the study compared to alendronate alone. Romosozumab increased P1NP and decreased CTX within 12 months. At 36 months, P1NP and CTX decreased and remained below baseline.

Adverse events and serious adverse events included injection-site reactions (4.4% for romosozumab versus 2.6% for alendronate). Adjudicated serious cardiovascular events were more prevalent.
with romosozumab than alendronate (2.5% versus 1.9%; odds ratio, 1.31; 95% CI, 0.85–2.00). Two events of osteonecrosis of the jaw occurred in each treatment group during the open-label period and 10 total events of atypical femoral fracture occurred (six in the romosozumab-to-alendronate group and four in the alendronate-only group). Antibodies occurred with no detectable effect on safety or efficacy.15

The results of this study showed romosozumab rapidly increased BMD from bone formation and reduced fracture risk when followed by antiresorptive therapy in patients at high risk for fracture. This study showed a preventive benefit for patients with nonvertebral fractures, unlike the FRAME study. In the ARCH study, romosozumab delivered better results than alendronate alone. However, the romosozumab-treated group had more serious adjudicated cardiovascular events, such as cardiac ischemic events and cerebrovascular events.11,14,15

SAFETY
Boxed Warning for Cardiac Events

Major adverse cardiac events (MACE), a composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, were reported in Study 1, Cosman et al.14 Myocardial infarction occurred in nine women taking romosozumab during the 12-month phase and eight women in the placebo group (0.3% versus 0.2%), stroke occurred in eight women in romosozumab group and 10 in placebo group (0.2% versus 0.3%), and cardiovascular death occurred in 17 women treated with romosozumab and 15 with placebo (0.5% versus 0.4%).11,14

In study 2, Saag et al.,15 MACE occurred in the 12-month phase as follows: myocardial infarction, 16 women taking romosozumab and 5 taking alendronate (0.8% versus 0.2%); stroke, 13 in the romosozumab group and seven in the alendronate group (0.6% versus 0.3%); and cardiovascular death, 17 in the romosozumab group and 12 in the alendronate group (0.8% versus 0.6%).11,15

Due to the number of positively adjudicated major adverse cardiac events occurring in romosozumab-treated patients in both trials, the FDA required a boxed warning for the potential risk of myocardial infarction, stroke, and cardiovascular death.10,11,14,15

Common Adverse Events

The main adverse effects reported in both studies were arthralgia and headache.11 Injection-site reactions, most commonly pain and erythema (4.9% for the romosozumab group versus 2.8% for the control group), resulted in discontinuation of treatment in 0.1% of the romosozumab group and less than 0.1% of the control group.11

Hypersensitivity Reactions

Reactions indicative of hypersensitivity such as angioedema, erythema multiforme, dermatitis, urticaria, and rash occurred. Romosozumab should be discontinued if a clinically significant allergic reaction develops.11

Immunogenicity

Although antibodies to romosozumab developed in some patients, this did not affect drug safety and efficacy.11,14,15

CONTRAINDICATIONS AND PRECAUTIONS

Hypocalcemia

Romosozumab is contraindicated in patients with hypocalcemia and in people with a known hypersensitivity to romosozumab or its components.11 Hypocalcemia must be corrected before treatment, and calcium and vitamin D supplementation is recommended during therapy. Providers should monitor serum calcium, especially in patients with severe renal impairment or receiving dialysis.11

MACE

Due to a higher rate of adjudicated MACE in Study 2—41 women in the romosozumab group and 22 in the alendronate group (2.0% versus 1.1%; hazard ratio, 1.87; 95% CI, 1.11–3.14)—romosozumab should not be started in patients who suffered a stroke or myocardial infarction within the previous year. The benefits and risks must be assessed in patients with major cardiovascular risk factors, and romosozumab should be discontinued in patients who have a myocardial infarction while taking the drug. Monitoring for signs and symptoms of myocardial infarction and stroke is essential.11,15

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) may occur and is usually associated with a dental issue or procedure. Patient oral care must be maintained, and an oral exam is recommended prior to initiation of romosozumab. Drugs associated with ONJ may increase the risk of developing ONJ.11,14,15

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical subtrochanteric and diaphyseal femoral fractures can occur, but romosozumab has not been established as causative agent.11 Patients should report abnormal hip, thigh, or groin pain.11

Drug Interactions

Patients should be monitored when utilizing drugs causing hypocalcemia. Calcium and vitamin D supplementation are advised with romosozumab use. Drugs associated with ONJ may increase the risk for ONJ in patients treated with romosozumab.11

DOSAGE, STORAGE, AND ADMINISTRATION

Romosozumab is available as a clear-to-opalescent, colorless-to-light-yellow solution in single-use prefilled syringes containing 105 mg of active ingredient in 1.17 mL. A full dose of romosozumab is 210 mg, to be given once monthly by a health care provider using two 105-mg prefilled syringes subcutaneously back-to-back. The product should be stored under refrigeration at 36° to 46° Fahrenheit (2° to 8° Celsius) in its original container; it can be kept at room temperature at up to 77° Fahrenheit (25° Celsius) in the original container but must be used within 30 days or discarded.11

The 210-mg dose should be delivered subcutaneously in the abdomen, thigh, or upper arm monthly for 12 months. If a dose is missed, it should be administered as soon as possible and then given monthly after the last dose. Adequate supplementation with calcium and vitamin D is advised.11

Before administration, the two syringes of romosozumab should be removed from the carton and visually inspected for particulates or discoloration. Do not use a syringe if it contains particles, is cloudy or discolored, the grey needle cap is missing, the syringe is cracked, or the medication is expired. Remove the syringe carefully from the tray as indicated in
the packaging. Allow syringes to remain at room temperature for 30 minutes; do not warm them. Use alcohol wipes to clean two injection sites on the abdomen (avoiding a two-inch area surrounding the navel), outer upper arm, or thigh; let the injection sites dry. Injections should be administered in a different site each time and should not be given in bruised, red, hard, or tender skin; scars; or stretch marks. Pull the gray needle cap up and off the first syringe and do not recap it. Inject all liquid subcutaneously into the chosen site, avoiding muscle and blood vessels. After administration, gently lift the syringe off the skin and dispose of the syringe and cap in a sharps container. Repeat all steps with the second syringe in the other chosen site.11

**CONCLUSION**

For postmenopausal woman with osteoporosis at severe risk for vertebral fracture, romosozumab is a clinical option in those desiring an effective, rapid-acting anabolic agent with a more-convenient, once-monthly dosing regimen. The boxed warning for risk of myocardial infarction, stroke, and cardiovascular death with romosozumab use must be considered in patients with a history of a prior stroke or myocardial infarction within one year prior to treatment. Romosozumab should be utilized for one year followed by an antiresorptive agent, if needed, for maintenance of bone improvements.13,18

**REFERENCES**


