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# Evenity© (romosuzumab-aqqg); A Novel Agent for Osteoporosis in Postmenopausal Women at High Risk for Fracture

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steoporosis is one of the most common bone diseases affecting as many as 10 million adults in the United States.1 It is characterized by low bone mass and deterioration of bone tissue and structure, leading to an increase risk of fractures.<sup>2</sup> In addition to those affected by osteoporosis, approximately 44 million people have decreased bone density known as osteopenia.1 Over time osteopenia can lead to osteoporosis, further escalating the risk of fractures. In the United States, over 1.5 million fractures are caused secondary to osteoporosis each year.3,4 Osteoporotic fractures are associated with significant morbidity and mortality. A majority of these fractures occur in postmenopausal women and are located at the spine, hip, or wrist due to the fragility at these sites. 4,5 Postmenopausal women are more prone to osteoporosis due to a depletion of estrogen, which consequently impairs normal bone formation and resorption. Fractures related to osteoporosis also cause a significant economic burden in the United States. Currently, osteoporosis-related fractures costs around \$19 billion annually and is projected to increase to \$25.3 billion by 2025.6 It is estimated that the prevalence of osteoporosis in the United States will also increase from 10 million to over 14 million people by 2020, based on data from the National Health and Nutrition Examination Survey (NHANES) and the estimated population count from the U.S. Census for 2020.7

Current pharmacological therapy for osteoporosis include bisphosphonates, receptor activator of nuclear factor kappa-B

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Personalized Medicine Corner: Pharmacogenetic Testing to Inform Current and Future Drug Therapy ligand (RANKL) inhibitor, parathyroid hormone (PTH), estrogen agonist/antagonist, calcitonin, calcium, and vitamin D.<sup>2,4</sup> The Endocrine's Society guideline recommends bisphosphonates as firstline initial treatment and denosumab, a RANKL inhibitor, as an alternative initial therapy for osteoporosis in postmenopausal women.<sup>8</sup> In patients with very high risk of fracture, parathyroid hormone (PTH) such as teriparatide and abaloparatide are utilized.<sup>8</sup> Estrogen agonist/antagonist like raloxifene are other options used in postmenopausal women with low risk of deep vein thrombosis or have a high risk of breast cancer. <sup>8</sup> The guideline suggests the use of calcitonin as last-line therapy in patients who cannot tolerate or have failed previous therapies.<sup>8</sup> Calcium and vitamin D are used as adjunct to osteoporosis therapies. <sup>8</sup> While current osteoporosis therapy are either antiresorptive or anabolic, none have had dual effect until romosozumab-aqqg (Evenity<sup>TM</sup>).

In April 2019, romosozumab-aqqg (Evenity<sup>M</sup>), a novel monoclonal antibody targeting sclerostin was granted FDA approval for osteoporosis in postmenopausal women with high fracture risk, defined as having a history of fracture related to osteoporosis, having multiple risk factors for fracture, or are intolerant or have failed other therapies.<sup>9</sup> According to the FDA, the four lowercase suffix "-aqqg" helps distinguish biological products with the same core name and is intended to minimize substitutions that have not been determined to be interchangeable.<sup>10</sup> The purpose of this article is to evaluate the safety and efficacy of romosozumab for the treatment of osteoporosis in postmenopausal women.

#### **CLINICAL PHARMACOLOGY**

#### Mechanism of Action

Romosozumab is the first humanized IgG2 monoclonal antibody that targets, binds, and inhibits the action of sclerostin.<sup>11</sup> Sclerostin is a glycoprotein expressed by the *SOST* gene in osteocytes, which is responsible for breaking down bones. Sclerostin works by binding to receptors on the surface of osteoblasts which inhibits the wingless-type mouse mammary virus integration site (Wnt) signaling, a pathway that regulates bone formation and regeneration.<sup>12</sup> This leads to a down-regulation of osteoblast function in bone formation.<sup>11,13</sup> By inhibiting sclerostin, romosozumab has shown to be a potent anabolic drug that increases bone formation on both trabecular and cortical bones.<sup>11,13</sup> Aside from the anabolic effect of romosozumab, bone resorption also occurs at a lesser extent.<sup>13</sup>

Romosozumab increases procollagen type 1 N-telopeptide (P1NP) and decreases type 1 collagen C-telopeptide (CTX) in postmenopausal women with osteoporosis.<sup>13</sup> P1NP and CTX are bone turnover markers (BTM) that are used as a fracture risk predictor and to monitor osteoporosis treatments.<sup>13,14</sup> While P1NP is a marker for bone formation, CTX-1 is a marker for bone resorption.<sup>14</sup>

#### **Pharmacokinetics**

Romosozumab possesses nonlinear pharmacokinetics with five times the concentration in AUC seen compared to dose give.13 Increased body weight decreases the exposure of romosozumab. When romosozumab is administered as a single 210 mg dose, the mean maximum serum concentration ( $C_{max}$ ) is 22.2  $\pm$ 5.8 mcg/mL and the mean area under the curve is  $389 \pm 127$ mcgday/mL.13 Romosozumab has a volume of distribution of 3.92 L, a half-life of 12.8 days, and achieves steady-state concentration (Css) within three months with monthly administrations. <sup>12,13</sup> The average time to maximum concentration  $(T_{max})$  ranges between two and seven days. While the metabolic pathway of romosozumab is not definitive, it is predicted that the metabolism works via catabolic pathways similar to endogenous IgG, in that it may be metabolized through lysosomal degradation to peptides and amino acids.15 Clearance of romosozumab is estimated to be 0.38 mL/hr/kg.15 As the dose increases, the clearance of romosozumab decreases. Based on the population studied, age (20 to 89 years), sex, race, prior alendronate use, and renal impairment had no significant difference in the pharmacokinetics of romosozumab.15 Select pharmacokinetic parameters when using recommended dosing are summarized in Table 1.

#### **CLINICAL TRIALS**

Safety and efficacy of romosozumab for osteoporosis in postmenopausal women were based on two phase III studies, the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) and the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH), which led to its FDA approval. Phase III trials such as the FRAME extension trial and trial by Langdahl et al will also be reviewed. Data from these clinical trials is summarized in **Table 2**.

#### FRAME Trial

Cosman et al. conducted an international, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy of romosozumab therapy on the risk of fracture in women with postmenopausal osteoporosis.<sup>16</sup> The FRAME trial included postmenopausal women between the ages of 55 to 90 years, with T-scores between -2.5 and -3.5 at the total hip or femoral neck. Women also had to have at least two vertebrae in the lumbar region (L1 to L4) and at least one evaluable hip based on a DXA scan. Participants were excluded if they have a history of hip fracture, severe or more than 2 moderate vertebral fractures, metabolic bone disease that affected bone metabolism, osteone-crosis of the jaw (ONJ), vitamin D levels < 20 ng/mL, current hypercalcemia or hypocalcemia defined as albumin-adjusted serum calcium outside the normal range, or recent drug use that interact with bone metabolism.

The primary endpoints observed in this study were the total incidences of new vertebral fracture at 12 months and at 24 months. Radiographs were assessed during patients scheduled visits using the Genant grading scale, a tool used to classify vertebral fractures. New vertebral fracture was defined as having an increase of at least one grade in participants with normal vertebrae prior. For those who have preexisting fractures, progression of fracture was defined as an increase of at least one grade. The secondary endpoints included total incidence of fracture, major

Table 1   Select Romosozumab Pharmacokinetics <sup>13</sup>		
Absorption		
Cmax <sup>a</sup>	22.2 ± 5.8 mcg <sup>b</sup> /mL <sup>c</sup>	
Tmax <sup>b</sup>	2 – 7 days	
Css <sup>c</sup>	3 months	
AUC <sup>d</sup>	389 ± 127 mcg <sup>g</sup> day/mL	
Distribution		
Vd <sup>e</sup>	~3.92 L <sup>i</sup>	
Metabolism		
Catabolic pathway	Degradation into peptides and amino acids	
Elimination		
Cl <sup>f</sup>	0.38 mL/hr <sup>k</sup> /kg <sup>l</sup>	
T1/2 <sup>h</sup>	12.8 days	
<sup>a</sup> Maxmium concentration; <sup>b</sup> Time to maximum concentration; <sup>c</sup> Steady-state con- centration; <sup>d</sup> Area under the curve; <sup>e</sup> Volume of distribution; <sup>d</sup> Clearance; <sup>b</sup> Half-life mcg = Micrograms; mL = milliliters; L = liters; hr = hours; kg = kilograms		

and minor nonvertebral fracture, new or worsening vertebral fracture, hip fracture, and major osteoporotic fracture, during the study period. Of the 7180 women included in the study, 6390 (89%) completed the first 12 months of the trial and 6026 (83.9%) completed the total 24 months. Participants were randomized in a 1:1 ratio to receive either romosozumab 210 mg injected monthly (n=3589) or placebo (n=3591). In the first phase of the trial, participants received their intervention monthly for 12 months then proceeded to an open-label denosumab dose of 60 mg subcutaneously every six months for one year. The authors decided to assess follow-up therapy with denosumab due to evidence that bone mineral density (BMD) stabilizes or increases after adding an antiresorptive agent after a bone-forming treatment. Aside from the intervention of placebo and denosumab, participants also received calcium 500-1000 mg and vitamin D3 or D2 600-800 IU daily. In those who had a baseline serum vitamin D level of  $\leq 40$  ng/mL, a loading dose of 50,000-60,000 IU of vitamin was administered at the trial's start.

After the 12-month period, new vertebral fractures occurred in 16 (0.5%) patients in the romosozumab arm and 59 (1.8%) in the placebo arm. Thus, there was a 73% lower risk of fractures in the romosozumab arm than in those in the placebo arm (95% CI 53 to 85, p<0.001). For secondary outcomes, clinical fractures and nonvertebral fractures occurred less in the romosozumab group compared to the placebo group. In the romosozumab arm, clinical fractures occurred in 58 patients (1.6%) compared with 90 patients (2.5%) in the placebo arm. Nonvertebral fractures were seen in 56 patients (1.6%) in the romosozumab group versus 75 patients (2.1%) in the placebo group. Additionally, BMD and BTM also improved with romosozumab compared to placebo. There was a greater increase in BMD percentage change from baseline in romosozumab than placebo of 13.3% (95% CI 11.9 to 14.7, p<0.001) at the lumbar spine, 6.9% (95% CI 5.1 to 8.1, p<0.001) at the total hip, and 5.9% (95% CI 4.3 to 7.4, p<0.001) at the femoral neck.

At 24 months, romosozumab had a 75% lower risk of vertebral fractures than placebo. Vertebral fractures occurred in 21 patients (0.6%) in the romosozumab group compared to 84 patients (2.5%) in the placebo group after both groups transitioned to denosumab (p<0.001). Adverse events were balanced between

# PharmaNote

# Table 2 | Primary Endpoints from Intranasal Esketamine Phase III Trials<sup>15-18</sup>

Romosozumab 210 mg SubQ <sup>a</sup> Inj	201
monthly for 12 months (n=3589)       Cumulative incidences of new vertebral       0.5% vs 1.8%       RR <sup>b</sup> = 73% (95%       p <sup>d</sup> <0.0         fracture at 12 months       fracture at 12 months       0.5% vs 1.8%       RC <sup>b</sup> = 73% (95%       p <sup>d</sup> <0.0         FRAME <sup>16</sup> Placebo for 12 months (n=3591)       fracture at 12 months       0.5% vs 1.8%       RC <sup>b</sup> = 73% (95%       p <sup>d</sup> <0.0	100
*Both groups followed by denosumab 60 mg SubQ Inj every 6 months for an Cumulative incidences of new vertebral 0.6% vs 2.5% RR = 75% (95% CI: additional 12 months for an fracture at 24 months 60 to 84) p<0.0	001
Romosozumab 210 mg SubQ Inj monthly for 12 months (n=2851)         FRAME Extension <sup>17</sup> Placebo for 12 months (n=2892)       Cumulative incidence of new vertebral 1.0% vs 2.8%       RR = 66%       p<0.0         *Both groups followed by denosumab 60 mg SubQ Inj every 6 months for an additional 24 months       60 mg SubQ Inj every 6 months for an additional 24 months       60 mg SubQ Inj every 6 months for an       60 mg SubQ Inj every 6 months for an       60 mg SubQ Inj every 6 months for an	)01
Romosozumab 210 mg SubQ Inj monthly for 12 months followed by alendronate 70 g PO <sup>e</sup> weekly       Cumulative incidence of new vertebral at 24 months       RR = 50% (95% CI: 4.1% vs 8.0%       p<0.0         ARCH <sup>18</sup> (n=2047)       10 mg SubQ Inj cumulative incidence of new vertebral at 24 months       ARCH <sup>18</sup> RR = 50% (95% CI: 34 to 62)       p<0.0	001
Alendronate 70 mg PO weekly (n=2046) Risk of clinical fractures at the time of 9.7% vs HR <sup>f</sup> = 0.73 (95% CI: primary analysis 13.0% 0.61 to 0.88)	001
Romosozumab 210 mg SubQ Inj Mean percentage change from base- monthly for 12 months (n=218) line in BMD at total hip at 12 Months vs -0.6% (95% CI: 2.2 to 3.0) vs -0.6% (95% CI: -1.0 to 0.2)	
Teriparatide 20 mcg <sup>i</sup> SubQ Inj daily for 12 months (n=218) Total difference in baseline in total hip area 3.2% (95% CI: 2.7 to 3.8) p<0.0	001

Mg = milligrams; Inj = injection; mcg = micrograms

the two groups; however, atypical femoral fracture occurred in one patient and osteonecrosis of the jaw occurred two patients from the romosozumab group. The authors concluded that romosozumab was beneficial in lowering risk of vertebral fracture compared to placebo at 12 months. Furthermore, the benefits continued after 24 months when transitioning to denosumab.

#### FRAME Extension Trial

Lewiecki and colleagues extended the FRAME Trial reviewed above for an additional 12 months.<sup>17</sup> The purpose of this trial was to report the safety and efficacy of romosozumab after following the same patients from the FRAME study for a total of 36 months. Outcomes that the authors looked at were new vertebral, clinical, and nonvertebral fractures, BMD, and safety. Of the 7180 patients previously enrolled in the FRAME study, 5743 (80%) completed the extension trial. Of the total patients who completed the trial, 2851 patients came from the romosozumabdenosumab arm and 2892 patients were from the placebodenosumab arm. Patients who remained in the extension trial received open-label denosumab 60 mg subcutaneously every 6 months for an additional 12 months.

At 36 months from baseline, risk of fracture was reduced in patient groups who received romosozumab versus placebo during the first 12-month study period. Patients who received romosozumab then denosumab had a significant reduction in risk by 66% for new vertebral fracture than those who received placebo then denosumab (1.0% versus 2.8%, p<0.001). For clinical fractures, there was a relative risk reduction (RRR) of 27% in the romosozumab group (4.0% versus 5.5%, p=0.004) and nonvertebral fracture had a RRR of 21% (3.9% versus 4.9%, p=0.039). The authors concluded that romosozumab for 12 months, followed by 24 months of denosumab showed fracture reduction benefit and continued gain in BMD.

#### ARCH Trial

The ARCH trial is a multicenter, international, randomized, double-blind trial.18 Postmenopausal women were randomly assigned in a 1:1 ratio to either receive romosozumab 210 mg subcutaneously monthly or alendronate 70 mg by mouth weekly for 12 months. Similar to the FRAME trial, also received calcium 500 -1000 mg and vitamin D<sub>3</sub> or D<sub>2</sub> 600-800 IU daily. After receiving the initial treatment for 12 months in the double-blind period, all patients then received open-label weekly oral alendronate 70 mg by mouth weekly for up to 36 months. The ARCH trial included women between the ages of 55 and 90 years and had at least one of the following criteria: (1) BMD T-score  $\leq$ -2.5, with the location being total hip or femoral neck and either  $\geq 1$  moderate or severe vertebral fracture or  $\geq 2$  mild vertebral fracture or (2) BMD Tscore of  $\leq$ -2.0 at the total hip or femoral neck and either  $\geq$ 2 moderate or severe vertebral fracture or fracture of proximal femur occurring 3 to 24 months prior to randomization. Exclusion factors for the ARCH Trial mirrored the FRAME trial with addition of patients who are unable to take alendronate oral tablets or have a contraindication to alendronate.

Primary endpoints for the ARCH trial were cumulative occurrence of new vertebral fractures and cumulative incidence of clinical fracture at 24 months. Lumbar spine, total hip, and femoral neck BMD were reviewed as a secondary outcome at 12 months and 24 months. In addition, incidence of nonvertebral fracture was another secondary outcome studied. In this study, 4093 women were included in the trial, of which 89.3% (3654) of patients completed 12 months, and 77% (3150) of patients completed the 24-month period. When looking at the risk of new vertebral fractures, the romosozumab followed by alendronate arm had 48% lower risk than the alendronate alone arm over the 24month period (6.2% versus 11.9%; 95% CI 0.40 to 0.66, p<0.001). The romosozumab group also resulted in lower risk clinical fracture and cumulative incidence of clinical fracture com-

## PharmaNote

Adverse Event	Romosozumab (n=2040) vs Alendronate Arm (n=2014)	Odds Ratio (95% Cl <sup>a</sup> )
Serious Cardiovascular adverse event	50 (2.5%) vs 38 (1.9%)	1.31 (0.85-2.00)
Ischemic event	16 (0.8%) vs 6 (0.3%)	2.65 (1.03-6.77)
Cerebrovascular event	16 (0.8%) vs 7 (0.3%)	2.27 (0.93-5.22)
<sup>a</sup> Confidence Interval		

pared to the alendronate alone group; however, no significant difference was shown with risk of nonvertebral fracture. Furthermore, increase in P1NP and decrease in CTX was shown in the romosozumab group.

When reviewing the safety of romosozumab, a greater number of patients had serious cardiovascular adverse events in the romosozumab group (2.5%, 50 patients) compared to the alendronate group (1.9%, 38 patients). **Table 3** summarizes select cardiovascular adverse events found in this trial. ONJ and atypical femoral fracture was also observed in this trial. In the romosozumab followed by alendronate group, one patient reported ONJ and six patients reported atypical femoral fracture. Similarly, the alendronate alone group had one patient report ONJ; however, only four patient reported atypical femoral fracture.

#### Langdahl et al

In a randomized, phase III, open-label, active controlled study by Langdahl et al, postmenopausal women were randomized 1:1 to received either romosozumab 210 mg subcutaneously once monthly or teriparatide 20 mcg subcutaneously once daily over 12 months for osteoporosis therapy after transitioning from an oral bisphosphonate therapy at an approved dose for postmenopausal osteoporosis for at least three years before screening and alendronate the year immediately before screening.19 In addition to romosozumab or teriparatide, all patients were given calcium 500-1000mg/day and vitamin D 600-800 IU/day. Patients in the romosozumab with serum vitamin D concentration of 50-100 nmol/L received 50,000-60,000 IU vitamin D after randomization. Patients were included if they had a T-score ≤-2.5 at the total hip, femoral neck, or lumbar spine and if they had taken an oral bisphosphonate for at least three years prior to screening or alendronate within one year prior to screening. The primary endpoint measured was the percentage change from baseline in BMD at the total hip.

A total of 436 patients were enrolled, in which 218 patients were assigned to the romosozumab group and 218 patients were assigned to the teriparatide group; however, 206 patients and 209 patients were included in the analysis respectively. After 12 months, the authors reported a 2.6% (95% CI 2.2 to 3.0) mean change from baseline in total hip BMD in the romosozumab arm and -0.6% (95% CI -1.0 to 0.2) in the teriparatide group. The total difference in baseline in total hip area was reported as 3.2% (95% CI 2.7 to 3.8, p<0.0001). Both groups had balanced adverse events reported with nasopharyngitis, hypercalcemia, and arthralgia being the most commonly reported. Additionally, 17 (8%) patients in the romosozumab arm reported serious adverse events compared to 23 (11%) in the teriparatide group; however, none were deemed treatment-related. In regard to withdrawal due to adverse events, six (3%) patients on romosozumab withdrew from the study compared to 12 (6%) on teriparatide. The authors concluded that romosozumab showed benefit in hip BMD compared to teriparatide.

#### **Adverse Events and Precautions**

Romosozumab contains a boxed warning for potential risk of myocardial infarction, stroke, and cardiovascular death and should be avoided in patients with a history of myocardial infarction or stroke within a year after the event.13 Due to the potential of a major adverse cardiac event (MACE), it is important to monitor for symptoms of myocardial infarction and stroke while on romosozumab.13 Furthermore, romosozumab is contraindicated in patients with hypocalcemia. In patients with pre-existing hypocalcemia, it is recommended to correct calcium levels prior to starting romosozumab.13 Hypersensitivity reactions such as angioedema, erythema multiforme, dermatitis, rash, and urticaria have also been reported with the use of romosozumab.12 Other precautions of romosozumab to note are osteonecrosis of the jaw and atypical subtrochanteric and diaphyseal femoral fractures.<sup>13</sup> Common adverse reactions reported (>5%) in romosozumab include arthralgia and headaches.13 A summary of common adverse reactions of romosozumab from clinical trials can be found in Table 4

#### **DOSING AND ADMINISTRATION**

Romosozumab is available as a 105 mg/1.17 mL solution in a single-use prefilled syringe.13 The recommended dose for romosozumab is 210 mg administered subcutaneously by a health care provider.13 Therefore, romosozumab is given as two 105 mg injections consecutively in the abdomen, thigh, or upper arm.<sup>13</sup> Romosozumab should be administered once per month for 12 months.13 After 12 months, the anabolic effect of romosozumab decreases shown in a phase II trial by McClung and colleagues.<sup>20</sup> Patients on romosozumab should have adequate supplementation of calcium and vitamin D.13 While no dose adjustment is required for patients with renal impairment, it is imperative to monitor serum calcium in patients with severe renal impairment, defined as having an estimated glomerular filtration rate (eGFR) of 15 to 29 mL/min/1.73m<sup>2</sup> or receiving dialysis due to the increased risk of hypocalcemia.13 If patients miss a dose, it is recommended to reschedule romosozumab administration as soon as possible.13

The cost of romosozumab is \$1,825 per dose of two 105 mg/1.17 mL syringes, which totals to \$21,900 for the complete 12 -month course treatment.<sup>21</sup> According to Amgen biopharmaceutical company, 80% of romosozumab is covered under Medicare Part B after a deductible is met.<sup>22</sup> Patients with commercial insurance and meet eligibility for the copay card for romosozumab may pay \$25 or less; however, there is a coverage limit.<sup>22</sup>

#### **CLINICAL IMPLICATIONS**

Romosozumab appears to be effective and relatively safe in the treatment of osteoporosis in postmenopausal women at high risk for fracture. Although there are currently no guideline recommendations, romosozumab may be beneficial in patients who cannot tolerate or have failed previous osteoporosis therapies . Additionally, it has shown to have positive effects when used before alendronate rather than alendronate alone. Therefore, romosozumab could potentially be used prior to bisphosphonates for added benefit. As a novel monoclonal antibody targeting sclerostin, it has shown to have anabolic effects as well as reducing bone resorption activity. After two weeks of initiating romosozumab, P1NP increased from baseline to a maximum of around 145% in comparison to placebo and CTX decreased by a maximum of 55% compared to placebo in the FRAME Trial.<sup>11,16</sup>

In the trials reviewed, a decrease in cumulative incidence of new vertebral fracture compared to placebo and alendronate was reported. Additionally, total BMD in total hip was increased in romosozumab versus teriparatide. Furthermore, Romosozumab has the most potent effect on bone in one year, compared to similar effects of 2 years in teriparatide, 5 years in denosumab, or 10 years in alendronate.<sup>23</sup> Although romosozumab is only FDA approved in women at this time, a study by Lewiecki and colleagues have showed benefit in the use of romosozumab in men with osteoporosis.<sup>24</sup> Another area of interest is potential carcinogenic risk with monoclonal antibodies, however, romosozumab was not carcinogenic in animal studies.<sup>25</sup> Romosozumab may continue to show more promising results in the future.

It is important to note that there are many limitations with romosozumab. One being that the efficacy of romosozumab diminishes after one year of administration. After completion of the therapy in 12 months, both P1NP levels and CTX level returned towards baseline levels.<sup>13</sup> Therefore, romosozumab is only intended for a 12-month course treatment due its waning effect.

Additional therapy such as denosumab may be needed after romosozumab is completed which further drives the cost for patients. While transition to a bone-forming agent is seen in patients treated with bisphosphonates, more studies are warranted to guide the order of therapy with romosozumab.

Some limitations noted from the studies review include patients stratified by ages by < 75 and  $\geq 75$  years in the FRAME and ARCH trials, while the average menopausal age is around 51 years old. In addition to this, the FRAME trial excluded patients with a history of hip fracture and having severe or moderate vertebral fracture which are factors in patients of high risk of fracture. This is a major weakness to the study since romosozumab is indicated for postmenopausal women with high risk of fracture. In the trial by Langdahl et al, only patients in the romosozumab arm received additional calcium and vitamin D. This could potentially affect the outcome seen in this study. Furthermore, medications aside from romosozumab were self-administered. Thus, adherence with comparator medications were not accounted for. All trials reviewed were funded by the drug manufacturer and disclosed.

When thinking about patient standpoint, a major limitation to romosozumab is its high cost of \$21,900 per year. In addition to cost, the full dose of romosozumab requires two subcutaneous injection in the same visit. Romosozumab must be administered by a healthcare provider which may deter patients from coming to multiple office visits; however, it would allow patients to be followed-up by a healthcare provider more often.

In regard to safety, romosozumab holds a boxed warning for serious cardiovascular events. While the cause of cardiovascular events is unknown at this time upon further literature review, it is thought that lipid accumulation occurs due to activating the Wnt

# Table 4 | Common Adverse Reactions of Romosozumab from Clinical Trials<sup>13</sup>

Adverse Reactions ≥ 2%	FRAME Trial <sup>15</sup> (n=3581)	ARCH Trial <sup>28</sup> (n=2040)
Arthralgia	13.1%	8.1%
Headache	6.6%	5.2%
Muscle Spasms	4.6%	3.4%
Peripheral edema	2.4%	1.7%
Asthenia	2.3%	2.5%
Neck pain	2.2%	1.7%
Insomnia	2.0%	1.7%
Paresthesia	2.0%	1.4%

signaling pathway.<sup>26</sup> Therefore it may be best to avoid romosozumab in patients with past medical history of cardiovascular events until more data is published.

#### CONCLUSIONS

Romosozumab-aqqg (Evenity<sup>TM</sup>) is a novel humanized monoclonal antibody approved for osteoporosis in postmenopausal women at high risk for fracture. It targets sclerostin and has increased bone formation and decreased bone resorption effect. Overall romosozumab adds to the therapeutic options for preventing osteoporotic fractures especially considering its effect in as little as one year compared to other therapeutic options on the market. There have been no changes in treatment guidelines since the approval of romosozumab so its true place in treatment has yet to be determined.

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# **PERSONALIZED MEDICINE CORNER**

# Using Pharmacogenetic Testing to Inform Current and Future Drug Therapy Amanda Elchynski. PharmD

Pharmacogenetic testing for *CYP2C19* and *CYP2D6* can help guide the use and dosing of selected antidepressants, including sertraline, citalopram, escitalopram, and paroxetine.<sup>1</sup> These agents, though, are just a handful of those currently available to treat depressive disorders. In the majority of cases, integrating genetic data into drug therapy decisions for antidepressants requires balancing pharmacogenetic test results, history of antidepressant response and adverse effects, cost considerations, and other clinical factors (e.g., renal function, age, comorbidities). In this article, we describe a patient who was referred to the UF Health Pharmacogenetic testing into antidepressant treatment selection.

# Patient Case

A 29-year-old female with a past medical history of major depressive disorder and generalized anxiety disorder presented to the clinical pharmacogenetics pharmacist. She reports experiencing symptoms of social anxiety, panic, agoraphobia, and recurring obsessive thoughts that are affecting her quality of life and activities of daily living. She has previously taken alprazolam, sertraline, fluoxetine, bupropion, trazodone, and propranolol for her symptoms with inadequate response or adverse effects. Her current drug therapy regimen includes venlafaxine, mirtazapine, buspirone, and clonidine. She reports that she is experiencing sexual dysfunction with current medications.

The patient undergoes pharmacogenetic testing and she has normal CYP2D6 enzyme activity (CYP2D6 \*1/\*1; normal metabolizer) and decreased CYP2C19 enzyme activity (CYP2C19 \*1/\*2; intermediate metabolizer). These results indicate she has an increased risk of experiencing adverse effects from citalopram, escitalopram, and sertraline, all of which are inactivated by the CYP2C19 enzyme.

The pharmacist recommended avoiding these SSRIs in the future and optimizing her current non-SSRI therapy to address her symptoms. Potential drug therapy options include increasing the dose of one or more of her current medications if sexual dysfunction is tolerable. In particular, patient may benefit from increase in venlafaxine dose. Alternatively, this patient may benefit from switching venlafaxine to a medication with serotonin agonist as well as reuptake inhibition effects, such as vilazodone, which may be associated with less sexual dysfunction.

#### Discussion

Pharmacogenetic testing can help narrow drug therapy options for treatment of depression as well as predict or explain an increased risk of adverse effects or inadequate treatment response for selected antidepressants.1 In this case, although the patient had genetic variability leading to decreased CYP2C19 activity, the immediate treatment plan was not directly informed by her pharmacogenetic test results. Rather, pharmacogenetic test results identified antidepressant options that should be avoided in the future. These test results also inform the use of other drugs that are affected by decreased CYP2C19 activity (e.g., PPIs, clopidogrel). As such, it is important to maintain lifetime documentation of pharmacogenetic test results in the patient's electronic health record as their health conditions and drug therapies continue to change.

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