WOMEN'S HEALTH

Romosozumab for the treatment of osteoporosis in women: Efficacy, safety, and cardiovascular risk

$SAGE

Sian Yik Lim[1,2] iD

Abstract

Increased understanding of the Wnt signaling pathway has led to the development of romosozumab, one of the most potent osteoanabolic agents to date for osteoporosis treatment. Romosozumab is a monoclonal antibody that inhibits sclerostin, a natural inhibitor of the Wnt signaling pathway. Romosozumab, by inhibiting sclerostin activates the Wnt signaling pathway, leading to increased bone formation and decreased bone resorption. The pivotal ARCH and FRAME studies established romosozumab's fracture reduction efficacy. Romosozumab was superior to alendronate in fracture reduction and bone mineral density gain in the ARCH study. Romosozumab treatment should be followed sequentially with a potent antiresorptive agent. The antifracture efficacy gained from romosozumab is maintained or improved after transitioning to an antiresorptive agent. As one of the most potent osteoanabolic agents, the introduction of romosozumab has significantly increased our ability to treat osteoporosis. Studies have provided important information on using romosozumab with other osteoporosis medications to optimize osteoporosis treatment. Romosozumab used before antiresorptive medications is associated with more significant bone mineral density increases than when an antiresorptive agent is used before romosozumab. Romosozumab is recommended for osteoporosis treatment in patients at very high risk for fracture with low cardiovascular risk. Romosozumab is generally well tolerated, with 4%–5% of patients having injection site reactions. The ARCH trial showed a higher risk of cardiovascular events in patients receiving romosozumab. Romosozumab carries a black box warning that romosozumab should not be initiated in patients with myocardial infarction or stroke in the preceding year. However, the information on romosozumab and increased cardiovascular risk is conflicting. The risk of cardiovascular disease with romosozumab is unclear. While romosozumab has demonstrated significant osteoanabolic effect and antifracture efficacy and will benefit high fracture risk patients, further studies are needed to investigate the cardiovascular safety of romosozumab.

Keywords

cardiovascular disease, cardiovascular risk, cardiovascular safety, fracture, osteoporosis, romosozumab, sclerostin, sclerostin inhibition, Wnt pathway

Date received: 3 July 2022; revised: 22 August 2022; accepted: 25 August 2022

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and deterioration of bone microarchitecture. Due to these changes as humans' age, osteoporosis leads to decreased bone strength, increasing the risk of fragility fractures.[1] Based on the World Health Organization's definition of osteoporosis, osteoporosis affects 6.3% of men and 21.2% of women over the age of 50 globally.[2] However, osteoporosis remains underdiagnosed and underrecognized. Unfortunately, osteoporosis-related fractures exert

significant medical and personal burdens on individuals, affecting their quality of life. Osteoporosis-related fractures

[1]Hawaii Pacific Health Medical Group, Pali Momi Medical Center, Aiea, HI, USA
[2]John A. Burns School of Medicine, University of Hawai'i at Mānoa, Honolulu, HI, USA

Corresponding author:
Sian Yik Lim, Hawaii Pacific Health Medical Group, Pali Momi Medical Center, 98-1079 Moanalua Road, Suite 300, Aiea, HI 96701, USA.
Email: limsianyik@gmail.com

are costly and pose economic burdens to the health care system and society.[3]

Postmenopausal osteoporosis is the most common type of osteoporosis, occurring in women due to estrogen deficiency.[4] Estrogen deficiency during menopause leads to increased bone turnover where bone resorption exceeds bone formation.[4] Bone loss in postmenopausal women occurs in two phases. Initially, menopause-related bone loss occurs when trabecular bone is rapidly lost within 3–5 years. Menopause-related bone loss is followed by age-related bone loss, where bone loss in the trabecular and cortical components occurs over a 5- to 10-year period.[4] The international osteoporosis foundation estimates that worldwide, 1 in 3 women over age 50 and above will experience a fragility fracture.[2]

The goal of the treatment of osteoporosis is to improve bone architecture, improve bone strength and reduce fracture risk. Treatments for osteoporosis reduce fracture risk by 50%–70%.[5] Antiresorptive agents such as bisphosphonates and denosumab primarily prevent bone resorption. Antiresorptive medications are not sufficient to restore skeletal architecture.[6] In recent years, medications that build bone have been developed, including teriparatide, abaloparatide, and romosozumab. These medications are potent osteoanabolics that stimulate bone formation, improve and restore bone architecture and reduce the risk of fracture. This article discusses romosozumab for osteoporosis treatment in women and the safety concerns, focusing on cardiovascular risk.

Romosozumab: targeting sclerostin to activate Wnt signaling selectively in bone

Sclerosteosis and van Buchem disease are genetic conditions characterized by high bone mass with generalized osteosclerosis of the skull, mandible, ribs, clavicles, and long bones. Patients with Sclerosteosis and van Buchem disease have a very low fracture risk due to high bone mass. It was subsequently discovered that these patients had genetic abnormalities in the SOST gene that encodes sclerostin. These genetic abnormalities lead to decreased production of biologically active sclerostin, causing unregulated growth of bone in the cortical skeleton.[7–9] Insights from sclerosteosis and van Buchem led to the discovery of sclerostin and the Wnt signaling pathway.

Sclerostin is a glycoprotein mainly produced in osteocytes. Osteoblasts lay down bone matrix, are embedded in the bone matrix, then transform into osteocytes. Osteocytes have canalicular projections to other osteocytes and are mechanosensors of the mechanical response of bone. In response to weight-bearing, the osteocytes reduce sclerostin expression, leading to bone formation. With no weight-bearing, expression of sclerostin increases leading to decreased bone formation. Hormones and cytokines

such as parathyroid hormone and glucocorticoids influence sclerostin expression.[10] Sclerostin is a negative regulator of bone formation, likely through regulation of the Wnt signaling pathway.[10]

The Wnt signaling pathway activates when the Wnt proteins bind to Frizzled family receptor and low-density lipoprotein receptor-related protein (LRP) 5/6 complexes, leading to activation of downstream enzymes and increased bone formation and decreased bone resorption.[11–13] Specifically, with the activation of the Wnt signaling pathway, the intracellular destruction complex that degrades beta-catenin is inhibited. Beta-catenin enters the cell's nucleus, binding to the T-cell factor transcription factor to activate Wnt-responsive genes, stimulating bone formation. Conversely, when Wnt signaling is not activated, the destruction complex is activated and phosphorylates beta-catenin. Phosphorylated beta-catenin is ubiquitinated and degraded by a proteasome. When beta-catenin does not enter the nucleus, Wnt-responsive genes are not activated. Increased beta-catenin levels also lead to increased osteoprotegerin, which prevents the binding of RANK ligand to RANK. Binding of RANK ligand to RANK stimulates osteoclast activation.[14] Therefore, with Wnt activation, osteoclast activity is decreased, reducing bone resorption. The net effect of activation of the Wnt signaling pathway is increased bone formation and reduced bone resorption to a lesser degree. Sclerostin binds to surface osteoblasts at the LRPs. By bindings to LRPs, sclerostin acts as a competitor for Wnt proteins to attach to LRP, inhibiting the Wnt signaling pathway.[15]

Increased understanding of the Wnt signaling pathway and bone metabolism opened up opportunities to target this pathway to treat osteoporosis. However, the Wnt signaling is ubiquitous and is involved in various organ systems in normal homeostasis and repair after injury.[16] Therefore, targeting the Wnt signaling pathway raises the concern of untoward systemic side effects. Because sclerostin is predominantly restricted to cells of osteoblast lineage, especially osteocytes, it presents a unique therapeutic target for osteoporosis treatment.[10] Romosozumab is a humanized IgG2 monoclonal antibody that binds to and inhibits sclerostin. Binding to sclerostin removes inhibition of sclerostin on the Wnt-B-catenin pathway, ultimately leading to bone formation and decreased bone resorption and its utility in the treatment of osteoporosis.

Romosozumab: a monoclonal antibody against sclerostin in the treatment of osteoporosis

Romosozumab was evaluated in several phase one trials at single doses or multiple doses in healthy men and postmenopausal women.[17,18] Patients in the single-dose study received romosozumab subcutaneously (0.1, 0.3, 1, 3, 5, or 10 mg/kg), intravenously (1 or 5 mg/kg) or placebo.[18]

In the study where patients received multiple doses, postmenopausal women received six doses of 1 or 2 mg/kg every 2 weeks or three doses of 2 or 3 mg/kg once every 4 weeks or placebo. Healthy men received six doses 1 mg/kg every 2 weeks or 3 mg/kg once every 4 weeks or placebo.[17] Patients tolerated romosozumab well. Adverse events were well balanced, and investigators did not note any significant safety signals.

Romosozumab exhibited nonlinear pharmacokinetics, that is, with increased romosozumab dose, clearance decreases. Therefore, exposure to romosozumab increases at a greater rate relative to a given dose at higher doses.[19,20] Although no specific studies specifically study the absorption, distribution, and excretion of romosozumab, romosozumab most likely has similar properties as most other monoclonal antibodies. Drug absorption after subcutaneous injection occurs via lymphatic drainage.[21,22] Systemic absorption occurs via convective antibody transport via the lymphatic vessels, with subsequent diffusion of antibodies across blood vessels.[21,22]

In general, hepatic and renal excretion plays a minimal role in eliminating the monoclonal antibody from the body. Monoclonal antibodies are too large to be filtered by the kidneys and are not excreted in the urine. Biliary excretion of monoclonal antibodies is minimal.[22] Monoclonal antibody elimination primarily occurs through intracellular catabolism.[22] This intracellular catabolism occurs via two processes (1) nonspecific fluid-phase endocytosis or (2) a more specific receptor-mediated endocytosis process. The receptor-mediated endocytosis process is saturated at higher concentrations, leading to nonlinear pharmacokinetics.[22]

Romosozumab: a potent osteoanabolic agent with dual mechanism of action

Romosozumab was evaluated in a phase 2 randomized, placebo-controlled, parallel-group, eight-group study.[23] The study included 419 postmenopausal women ages 55–85. Patients included had a bone mineral density *T* score of <−2.0 and >−3.5 at the lumbar spine, total hip, and femoral neck. Patients were randomized to various groups receiving (1) monthly subcutaneous romosozumab (70, 140, 210 mg), (2) every 3-month subcutaneous romosozumab (doses 140, 210 mg), (3) placebo, (4) open-label alendronate 70 mg weekly, or (5) subcutaneous teriparatide 20 µg daily. The treatment duration was 1 year. The study's primary endpoint was percentage change from baseline lumbar spine bone mineral density at 12 months. At 12 months, romosozumab significantly increased bone mineral density in the lumbar spine and the total hip and femoral neck. The highest gain in bone mineral density was in the group that received monthly romosozumab 210 mg administered subcutaneously (11.3% in the lumbar spine, 4.1% in the total hip, 3.7% in the femoral neck).
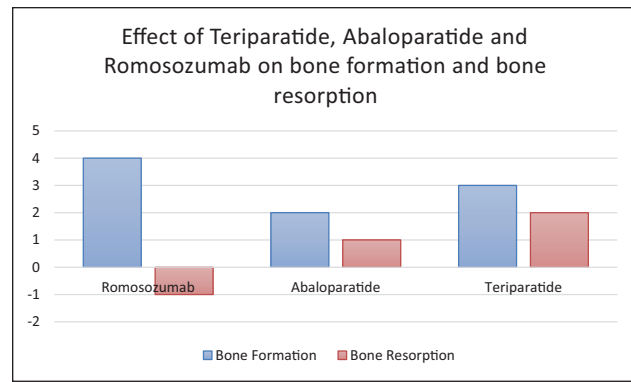
Figure 1. Directional changes of bone formation and bone resorption with subcutaneous injections of teriparatide, abaloparatide compared with romosozumab.[6]
Magnitude of bone formation and resorption are arbitrary.

This bone mineral density gain was more significant than active comparators of subcutaneous teriparatide 20 µg daily or alendronate 70 mg weekly. Romosozumab was well tolerated, with serious adverse events balanced between all groups.[23]

In the subgroups that received romosozumab, bone formation markers (serum P1NP) showed a transitory increase which peaked at 1 month of treatment. Serum P1NP decreased back to baseline by months 2–9 depending on the romosozumab dose. Conversely, bone resorption markers (serum CTX) decreased with nadir reached in the first week. However, they remained below baseline up to 12 months of treatment. The pattern change of bone turnover markers suggests that with romosozumab treatment, there is marked initial gain in bone formation and a more prolonged decrease in bone resorption leading to a sizable osteoanabolic window where significant bone gain occurs.[23] This contrasts teriparatide, where both P1NP and serum CTX are elevated. The PTH analogs (teriparatide and abaloparatide) stimulate bone formation and absorption, leading to a smaller osteoanabolic window (Figure 1). In the alendronate group, both serum P1NP and serum CTX were decreased (serum CTX suppressed more than serum P1NP).[23]

Clinical studies establishing the efficacy of romosozumab in the treatment of osteoporosis

The efficacy of romosozumab in fracture reduction has been evaluated in large phase 3 randomized control trials. In subsequent sections, we describe pivotal studies studying the effectiveness of romosozumab in treating osteoporosis in postmenopausal women (Table 1). The two largest romosozumab trials evaluating fracture outcomes were the FRAME (**FRA**cture study in postmenopausal wo**M**en with ost**E**oporosis) study and the ARCH (**A**ctive-cont**R**olled

Table 1. Phase III trials: clinical efficacy, and safety in osteoporosis patients in postmenopausal women.

| Study	Context	Patients Enrolled	Treatment/ Comparator	Primary Outcomes	Results
Study ID: NCT01575834 **FRA**cture study in postmenopausal wo**M**en with ost**E**oporosis (FRAME)	Fracture prevention efficacy and safety study in postmenopausal women with osteoporosis	7180 postmenopausal women with osteoporosis Mean age 71 years 18% with prevalent vertebral fracture 22% with prevalent nonvertebral fracture	Romosozumab 210 mg subcutaneous qmonthly for 12 months, followed by denosumab for 12 months. **Comparator:** Placebo for 12 months followed by denosumab for 12 months.	Cumulative incidence of morphometric vertebral fracture at 12 months and 24 months	1) Vertebral fracture incidence decreased by 73% at 12 months and 75% at 24 months.
Study ID: NCT01631214 **A**ctive-cont**R**olled Fra**C**ture Study in Postmenopausal Women with Osteoporosis at **H**igh Risk of Fracture (ARCH)	Fracture prevention efficacy and safety study in a population with higher risk of fracture than FRAME	4093 postmenopausal women with osteoporosis and a fragility fracture Mean age 74 years. 96% with prevalent vertebral fracture 38% with prevalent nonvertebral fracture	Romosozumab 210mg subcutaneous qmonthly for 12 months, followed by open-label alendronate. **Comparator:** Alendronate 70mg weekly.	Cumulative incidence of new morphometric vertebral fracture at 24 months Cumulative incidence of clinical at the time of the primary analysis (when clinical fracture confirmed in ⩾330 patients)	Vertebral fracture incidence decreased by 48% at 24 months. Clinical fractures incidence decreased by 27% at the time of primary analysis (33 months)
Study ID: NCT01796301 **ST**udy evaluating effect of **R**omosoz**U**mab **C**ompared with **T**eriparatide in postmenopa**U**sal women with osteoporosis at high risk for fracture p**R**eviously treated with bisphosphonat**E** therapy (STRUCTURE)	Head-to-head study of romosozumab versus teriparatide in postmenopausal women with osteoporosis previously on bisphosphonate	436 with postmenopausal osteoporosis Mean age 71.5 years Duration of previous alendronate use 5.5 years. Duration of previous bisphosphonate use 6.2 years	Romosozumab 210mg subcutaneous qmonthly for 12 months **Comparator** Teriparatide.	Percentage change from baseline in areal BMD by dual-energy X-ray absorptiometry at the total hip through month 12	Mean percentage change from baseline in the total hip areal bone mineral density with romosozumab 2.6%, teriparatide −0.6%, difference 3.2%.

ARCH: **A**ctive-cont**R**olled Fra**C**ture Study in Postmenopausal Women with Osteoporosis at **H**igh Risk of Fracture.

fra**C**ture Study in Postmenopausal Women with Osteoporosis at **H**igh Risk of Fracture) study. The FRAME study assessed the efficacy of romosozumab in osteoporotic postmenopausal women compared with placebo. The ARCH study evaluated the effectiveness of romosozumab in a group of patients with higher fracture risk. The ARCH study had an active comparator design comparing romosozumab to alendronate in osteoporotic postmenopausal women in the first year of treatment. The STRUCTURE (**ST**udy evaluating effect of **R**omosoz**U**mab **C**ompared with **T**eriparatide in postmenopa**U**sal women with osteoporosis at high risk for fracture p**R**eviously treated with bisphosphonat**E** therapy) study was a smaller active

comparator trial comparing romosozumab with teriparatide in patients who were previously on alendronate. The STRUCTURE study evaluated changes in bone mineral density and structural bone changes with romosozumab treatment compared with teriparatide.

Romosozumab in the treatment of osteoporosis in postmenopausal women

The FRAME study is one of the largest randomized control trials to have demonstrated the efficacy of romosozumab in treating osteoporosis. The FRAME was a
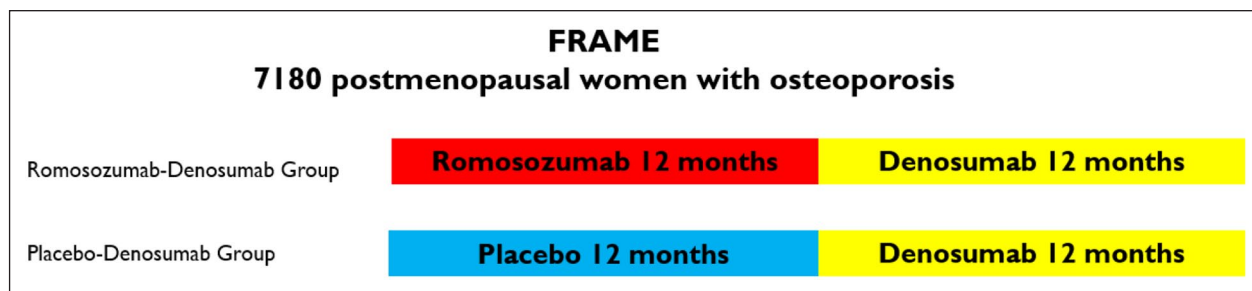
Figure 2. Study design of the FRAME study.

randomized, double-blind, placebo-controlled trial evaluating the effectiveness of romosozumab in treating osteoporosis. In this study, 7180 women with postmenopausal osteoporosis (T score of –2.5 to –3.5 at the total hip or femoral neck) were randomized to receive romosozumab 210 mg monthly or placebo in year 1.[24] Both groups received denosumab 60 mg subcutaneously q6months in year 2 (Figure 2). The study excluded patients with a history of hip fracture, severe vertebral compression fracture/2, or more vertebral compression fracture. The primary endpoint of this study was cumulative morphometric (symptomatic + asymptomatic) vertebral fracture incidence at 12 and 24 months.

At 12 months, treatment of romosozumab led to a bone mineral density gain from a baseline of 13.3% in the lumbar spine and 6.9% at the total hip. The improvements in bone mineral density were maintained/increased at 24 months after transitioning to denosumab. At 24 months, the gain in the lumbar spine was 17.6%, while the gain in the total hip was 8.8%. At 12 months, romosozumab treatment led to a 73% risk reduction of vertebral fractures compared with placebo ($p < 0.001$). Fracture reduction was noted rapidly after 6 months of treatment on romosozumab. Between 6 and 12 months, only two additional patients had vertebral compression fractures, compared with 33 patients in the placebo group. The benefit of reducing vertebral fracture risk was maintained after patients were transitioned to 1 year of denosumab, with the vertebral fracture relative risk reduction of the romosozumab–denosumab group at 75% at year two as compared with the placebo–denosumab group ($p < 0.001$). Both reductions in fracture risk were statistically significant.

After 1 year of romosozumab treatment, clinical fractures were reduced by 36% ($p = 0.008$), while nonvertebral fractures decreased by 25% ($p = 0.096$). A fixed sequence testing procedure was used for coprimary endpoints and selected secondary endpoints to adjust for multiple comparisons. Due to the lack of statistical significance for nonvertebral endpoint and prespecified testing sequence, all other endpoint analyses were considered exploratory (Table 2).[24,25] Although there was a trend of reduction in clinical (24 months) and nonvertebral fracture risk (12 and 24 months), these reductions were not

statistically significant. In post hoc analysis, it was noted a low placebo fracture rate in patients enrolled from Latin America. The FRAME has a more substantial proportion of patients enrolled from Latin America than ARCH. When the analysis was performed, romosozumab reduced vertebral fracture risk in Latin America by 70% ($p = 0.014$) and the rest of the world by 74% ($p < 0.001$). Although a statistically significant 42% risk reduction in nonvertebral fracture was noted in the rest of the world, no treatment effect was noted in Latin America.[26]

In the FRAME study, adverse and serious adverse events were well balanced between patients who received romosozumab–denosumab and those who received placebo–denosumab.[24] Notably, there was no difference in the incidence of adjudicated serious cardiovascular events in both groups. Patients who received romosozumab had higher rates of injection site reactions. 5.3% of patients who received romosozumab had injection site reactions. In comparison, only 2.9% of patients who received placebo had injection site reactions. Two cases of osteonecrosis of the jaw were noted in the romosozumab–denosumab group, one case after 12 months of romosozumab, and 1 case after 12 months of romosozumab and one dose of denosumab. One atypical femoral fracture was noted 3.5 months after the first dose of romosozumab. There were no cases of atypical femoral fracture or osteonecrosis of the jaw in the placebo–denosumab group.

Romosozumab in the treatment of osteoporosis of postmenopausal women: patients at high risk for fracture

The ARCH study evaluated the utility of romosozumab in the treatment of osteoporosis in a group of postmenopausal osteoporotic women who were at a higher risk of fracture than the FRAME study. Specifically, the ARCH study enrolled 4093 postmenopausal women with osteoporosis with a history of fragility fracture. The inclusion criteria of the ARCH study were a total hip or femoral neck bone mineral density T score $\leqslant$ –2.5, with either one or more moderate/severe vertebral fractures or two or more mild

Table 2. Major Adverse Cardiac Event (MACE) in the ARCH and FRAME studies.[27].

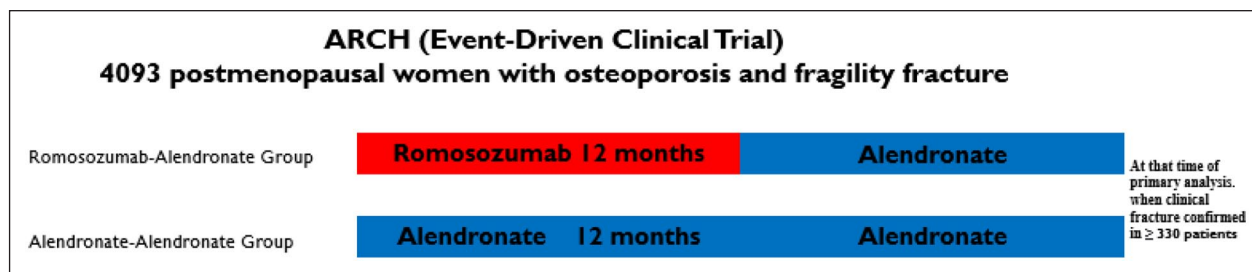|	Frame Study				ARCH Study			
	Placebo (N=3576)	Romosozumab (N=3581)	Placebo–Denosumab (N=3576)	Romosozumab–Denosumab (N=3581)	Alendronate (N=2014)	Romosozumab (N=2040)	Alendronate–Alendronate (N=2014)	Romosozumab–Alendronate (N=2040)
MACE, n (%)	29 (0.8)	30 (0.8)	86 (2.4)	95 (2.7)	22 (1.1)	41 (2.0)	102 (5.1)	117 (5.7)
Cardiovascular Death, n (%)	15 (0.4)	17 (0.5)	50 (1.4)	43 (1.2)	12 (0.6)	17 (0.8)	68 (3.4)	67 (3.3)
Nonfatal myocardial infarction, n (%)	8 (0.2)	9 (0.3)	19 (0.5)	23 (0.6)	5 (0.2)	16 (0.8)	21 (1.0)	23 (1.1)
Nonfatal stroke, n (%)	10 (0.3)	8 (0.2)	31 (0.9)	37 (1.0)	7 (0.3)	13 (0.6)	24 (1.2)	42 (2.1)

ARCH: **A**ctive-cont**R**olled Fra**C**ture Study in Postmenopausal Women with Osteoporosis at **H**igh Risk of Fracture; MACE: major adverse cardiac event.
Information in table assessed from I. United States Food and Drug Administration (FDA)[28]; FDA presentation: Cardiovascular Safety Assessment.

vertebral fractures; bone mineral density T score ≤ –2.0, with either two or more moderate/severe vertebral fractures, or a fracture of the proximal femur sustained 3–24 months before randomization. The ARCH study is one of the few head-to-head trials showing the fracture benefit of one osteoporosis drug versus another. In the ARCH study, 1 year of romosozumab treatment followed by alendronate treatment was superior to alendronate treatment alone.[29]

In the ARCH study, patients were randomized to receive either subcutaneous romosozumab 210 mg monthly or alendronate 70 mg weekly in the first year. After 1 year, both groups transitioned to open-label oral alendronate until the time of primary analysis (Figure 3). The primary analysis was performed when at least 330 events of clinical fracture (nonvertebral and symptomatic vertebral fracture) had been confirmed, and all patients completed the month 24 visit.[30] The study's primary endpoints were cumulative incidence of new morphometric vertebral fractures at 24 months and cumulative incidence of clinical fractures (symptomatic vertebral fractures + nonvertebral fractures) at the time of primary analysis.[30]

At 24 months, the study met the primary endpoints, where the cumulative incidence of vertebral fractures in the romosozumab–alendronate group was 48% lower than in the alendronate–alendronate group ($p < 0.001$). At the time of primary analysis (33 months), the romosozumab–alendronate group had a 27% lower risk of clinical fractures ($p < 0.001$), while nonvertebral fractures were reduced by 19% ($p = 0.04$). Patients who received romosozumab had more significant bone mineral density gains from baseline than those who received alendronate alone at all time points. At 12 months, patients who received romosozumab had bone mineral density gains of 13.7% (lumbar spine), 6.2% (total hip), as compared with 5.0% (lumbar spine), 2.8% (total hip) in patients who received alendronate. Bone density continued to gain when patients were transitioned from romosozumab to alendronate in year 2, with gains at 24 months being 14.9% in the lumbar spine and 7.0% in the total hip.

Similar to the FRAME study, incidences of adverse events and serious adverse events were similar in the romosozumab–alendronate group versus the alendronate–alendronate group, except for serious cardiovascular events. Injection site reactions were more common in the romosozumab–alendronate group (4.4%) than in the alendronate–alendronate group (2.6%). In the ARCH study, adjudicated serious cardiovascular events were imbalanced. In the ARCH study's first year, a higher frequency of serious cardiovascular adverse events (50 patients in the romosozumab group versus 38 patients in the alendronate group: difference not statistically significant) (Figure 4).[30] This led to further analysis contributing to a boxed warning for romosozumab that it may increase the risk of heart attack, stroke, and cardiovascular death. We discuss romosozumab and cardiovascular risk in the subsequent section.

Figure 3. Study design of the ARCH study.
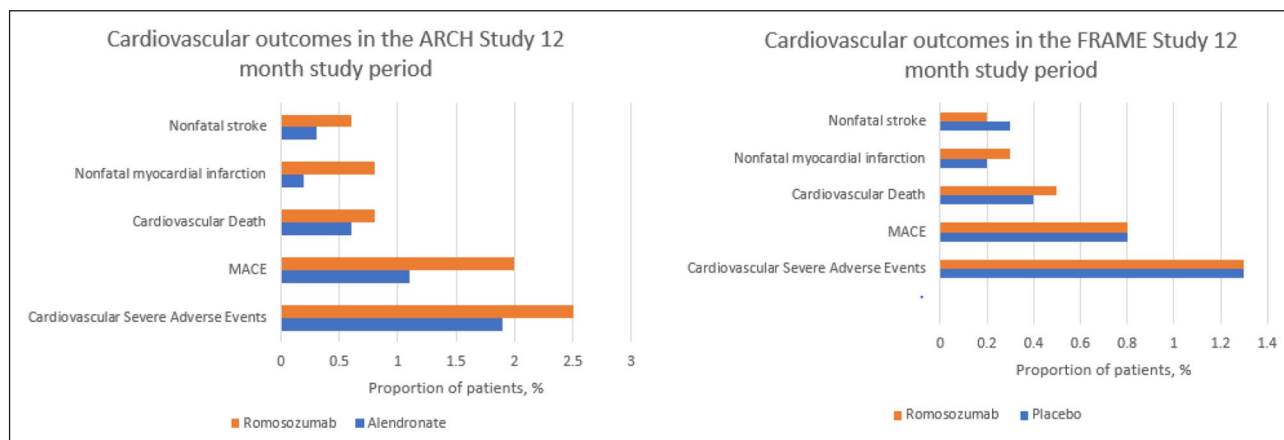
Figure 4. Cardiovascular outcomes in the ARCH and FRAME studies 12-month study period.
Information in table assessed from 1. United States Food and Drug Administration (FDA)[28]; FDA presentation: Cardiovascular Safety Assessment.

Switching high-risk patients previously on bisphosphonates to romosozumab

In clinical practice, there may be a need to transition to osteo-anabolic agents in patients at higher risk for fractures previously treated with bisphosphonates. This could be due to poor response to bisphosphonates, fracture while on treatment, or patient remains at increased risk for fracture after treatment. This clinical situation was evaluated in the STRUCTURE study.[31] The STRUCTURE study enrolled 436 postmenopausal women with osteoporosis with prior oral bisphosphonates for at least 3 years and alendronate the year before enrollment. Patients had a *T* score of –2.5 or lower at the total hip, femoral neck, or lumbar spine and a history of fracture. Patients were randomized to receive 1 year of romosozumab 210 mg monthly or subcutaneous teriparatide 20 µg daily. The primary endpoint was the percentage from baseline BMD by DEXA at the total hip through month 12 (mean of months 6 and 12). Bone strength was further evaluated by Quantitative Computed Tomography (QCT).

After 1 year of treatment, romosozumab led to a mean percentage gain from baseline in the total hip areal bone mineral density of 2.6%, while teriparatide led to a loss of 0.6%. The difference between groups was 3.2% (statistically significant). Other sites, including the spine, noted more significant gains in bone mineral density with romosozumab treatment than with teriparatide treatment. Furthermore, romosozumab is associated with increased estimated hip strength compared with teriparatide. When transitioning from alendronate to romosozumab, romosozumab was associated with a gain in cortical bone volumetric bone mineral density in 1 year. At the same time, there was a loss in cortical volumetric bone mineral density with teriparatide. Because recent studies show that more significant BMD increases are associated with reduced fracture risk, these data suggest that romosozumab may benefit high-risk osteoporosis patients transitioning from bisphosphonates to osteoanabolic agents.

Compared with the ARCH and FRAME trials (no prior antiresorptive treatment), the gain of BMD in the hip and spine in the STRUCTURE study after 1-year of romosozumab treatment was lower when preceded by alendronate treatment. Lower BMD gains were also noted when romosozumab treatment was preceded by denosumab.[32] Taken together, romosozumab used before rather than after alendronate leads to more significant bone mineral density increases and BMD responder rates. Therefore, with BMD gain with treatment being an essential indicator for bone strength and reduction in fracture risk, using romosozumab before an antiresorptive agent might be the ideal sequence for treatment.[32]

Clinical considerations when using romosozumab

Romosozumab is given as two subcutaneous injections (210 mg) once monthly for 12 months. Each injection is in a single-use, prefilled syringe containing 105 mg of the medication. A healthcare provider administers the medication subcutaneously into the abdomen, thigh, or upper arm.[6] Due to its superior antifracture efficacy, potent anabolic properties, and rapid onset of action, romosozumab has been recommended for patients at very high risk for fracture in various guidelines.[9,33] Treatment with romosozumab should be followed sequentially with a potent antiresorptive agent. The bone mineral density gains are maintained or improved after transitioning to an antiresorptive agent. The transition to an antiresorptive agent also maintains fracture reduction efficacy. Using romosozumab before an antiresorptive agent may be ideal for optimal bone density gain. When antiresorptive agents are used before romosozumab, bone density gain from romosozumab treatment is attenuated. However, cost and payer considerations need to be considered in treatment decisions, and more expensive osteoanabolic patients may not be appropriate for the initial treatment of all osteoporosis patients. Romosozumab may be a better choice than teriparatide when treatment is preceded by antiresorptive, especially in high-risk patients. When teriparatide is used after antiresorptive agents, there is a transient loss of bone mineral density in the hips. In contrast, with romosozumab, there was bone density gain, although attenuated. Romosozumab is well tolerated; 4%–5% of patients have injection site reactions in the ARCH and FRAME trials. There is a possibility that romosozumab may increase the risk of cardiovascular events. Therefore, caution is needed until further data are available.

Romosozumab and risk of cardiovascular disease

Findings in the ARCH study raised the concern about romosozumab and cardiovascular risk. Due to these concerns, romosozumab carries a black box warning per the United States Food and Drug Administration (FDA). Romosozumab should not be initiated in patients with myocardial infarction or stroke in the preceding year. Per the European Medicines Agency (EMA),[34] romosozumab is contraindicated in patients with history of myocardial infarction or stroke. The following sections summarize preclinical studies, genetic studies, and clinical trials examining the cardiovascular risk with romosozumab.

Preclinical data

Preclinical studies have found that sclerostin is expressed in the vasculature, usually within the vascular smooth muscle cells, and in aortic plaque.[35,36] However, sclerostin's role in the vasculature and if there is a relationship to the pathogenesis of atherosclerosis remains unclear.[37] Various hypotheses of the role of sclerostin have been postulated, including sclerostin expression in calcified blood vessels, which may represent a secondary phenomenon of the ossification process, where vascular smooth muscle cells transdifferentiate to an osteoblastic/osteocytic phenotype during the calcification process.[38,39] Others have postulated that sclerostin upregulation is a negative regulator for vascular calcification. Therefore, sclerostin may protect against vascular inflammation, aortic aneurysm, and atherosclerosis in selected animal models.[40–42] Consequently, inhibition of sclerostin by romosozumab could theoretically lead to increased vascular calcification.[37,43]

However, animal studies in rats and monkeys have not demonstrated an association between sclerostin inhibition and increased vascular calcification.[27,44,45] A 6-month repeat dose monkey toxicity study, with romosozumab up to 93-fold clinic exposure based on area under the concentration-time curve (AUC), did not note vascular effects.[20] There was no vascular mineralization in aged ovariectomized monkeys receiving one year of romosozumab at 22-fold clinical AUC exposure.[20] Along similar lines, a 6-month study of rats did not note vascular lesions with romosozumab exposure up to 39-fold clinical AUC exposure.[20] Notably, the process of vascular calcification occurs gradually over some time. This does not explain the ARCH study finding, where separation of the alendronate and romosozumab arms occurred within the first three months of the study.[28,30] AMGEN, the company filing for approval, performed additional studies to explore possible mechanisms where romosozumab would cause a rapid increase cardiovascular risk. This included an in vitro human platelet activation study. The study did not find a prothrombotic effect of romosozumab through platelet activation. In an in vitro vasoconstriction study, romosozumab did not induce vasoconstriction at approximately 10-fold greater than reported serum values in postmenopausal women.[20] In a study of the ApoE $-/-$ mouse model of atherogenesis, the administration of sclerostin antibody had no meaningful effects on the incidence and morphology of the plaque in the aorta.[28]

The association between serum level of sclerostin and surrogate markers of cardiovascular dysfunction/cardiovascular outcomes has been investigated and has yielded inconsistent findings.[42] The conflicting results were related to variations in study design, differences between study populations and animal models, and heterogeneous methods used to investigate this association.[42] For example, in a cohort of patients with chronic kidney disease, aortic calcifications were noted in patients with higher sclerostin levels. However, in multivariate analysis, the association was inversed.[46] Studies investigating the association of serum sclerostin and aortic valve, coronary, or aortic calcification

have yielded positive associations, negative associations, and no correlation.[42] Golledge and Thanigaimani reviewed 14 studies examining the association between serum sclerostin concentration and arterial stiffness or atherosclerosis severity. 12 studies reported positive associations, while one study reported a negative association, and one study reported no association.[42]

Similarly, conflicting results have been noted between the association of sclerostin and cardiovascular outcomes such as cardiovascular events and mortality. Some studies reported better cardiovascular survival,[47,48] while others predicted higher rates of adverse cardiovascular outcomes with higher levels of sclerostin.[49] Golledge and Thanigaimani reviewed nine studies examining the association between serum sclerostin and cardiovascular events. Four of the nine studies showed that higher sclerostin levels were associated with a significantly greater risk of cardiovascular events; four reported no significant association. In contrast, one study reported an inverse association between sclerostin concentration and risk of major cardiovascular and cerebrovascular events.[42] A meta-analysis of six observational studies showed that median or upper tertile sclerostin levels were not associated with a greater risk of MACE (hazard ratio 1.2, 95% confidence interval (CI) 0.75–1.93).[42] However, subanalysis in patients with chronic kidney disease demonstrated a statistically significant risk of cardiovascular events (HR 2.28, 95% CI 1.10–4.74). At the same time, higher serum sclerostin levels were not associated with a higher risk of cardiovascular events in healthy individuals.[42]

Genetic studies

No increased risk of cardiovascular disease has been noted in patients with sclerosteosis and van Buchem disease.[50] In a mouse model for sclerosteosis, the SOST gene knockout mouse showed increased bone density but did not demonstrate increased vascular calcification.[51] To investigate the role of sclerostin in cardiovascular events, investigators also evaluated human genetic data. Investigators examined genome-wide association studies in public databases to test for the association of single nucleotide polymorphisms (SNPs) that associate SOST RNA expression levels with BMD, stroke, or myocardial infarction. Investigators chose SNP rs2741856 because it has been reported to be strongly linked to the most significant BMD association at the SOST locus.[20] The more common c allele of the rs2741856 SNP was associated with increased bone mineral density, decreased risk of osteoporosis, and fracture with decreased sclerostin levels in the tibial artery, aorta, and coronary artery. Searching GWAS databases, which included Gene Atlas, Rapid GWAS, and Global Biobank Engine database, noted no detectable effect on the risk of myocardial infarction or stroke associated with the major allele C of SNP rs2741856.[20]

However, Bovijn et al. subsequently identified two independent genetic variants in the SOST locus associated with bone mineral density from a large-scale genome-wide association study of estimated heel bone mineral density. The two independent genetic variants were rs7209826 (A > G, G allele frequency in UK Biobank, 40%) and rs188810925 (G > A; A allele frequency 8%). The minor alleles rs7209826 (G allele), and rs188810925(A allele), were associated with lower sclerostin expression in various human tissues, including the tibial artery and aorta. These minor alleles of both SNPs were associated with higher bone mineral density and a lower risk of fracture. These minor alleles of both SNPs were associated with a higher risk of myocardial infarction and/or coronary revascularization and major adverse cardiovascular events. These alleles also had a positive association with diabetes and hypertension. The authors concluded that inhibition of sclerostin may be associated with increased cardiovascular risk and further evaluation of the cardiovascular safety of romosozumab is needed.[52]

Clinical trials

The FRAME trial was one of the largest studies to evaluate the efficacy of romosozumab in treating osteoporosis. There were no differences in serious cardiovascular adverse events in the FRAME trial (7180 patients). After 1 year of romosozumab treatment, adjudicated cardiovascular events were 1.1% in the placebo group compared to 1.2% in the romosozumab group (hazard ratio 1.0; 95% CI 0.66–1.50). At 24 months, when both groups were transitioned to denosumab, adjudicated serious cardiovascular events were 2.2% in the placebo–denosumab group and 2.3% in the romosozumab–denosumab group.[24]

However, the smaller ARCH study (4093 patients) noted concerns of cardiovascular disease in patients receiving romosozumab. It was noted that in the first year, a higher frequency of serious cardiovascular adverse events occurred (50 patients in the romosozumab group versus 38 in the alendronate group; odds ratio 1.31; 95% CI 0.85–2.00). Further analysis showed that increased risk of cardiovascular events was related to increased cardiac ischemic events and cerebrovascular events. Sixteen patients in the romosozumab group and six in the alendronate group (odds ratio 2.65; 95% CI 1.03–6.77) developed cardiac ischemic events. Sixteen patients in the romosozumab group compared with 7 patients in the alendronate group had cerebrovascular events (odds ratio 2.27; 95% CI 0.93–5.22). Heart failure, noncoronary revascularization, and peripheral vascular events not requiring revascularization were lower in the romosozumab group.[30]

In the smaller BRIDGE study studying the efficacy of romosozumab in men, numerically higher adjudicated cardiovascular events were noted. In the BRIDGE study, 245 men with osteoporosis were randomized 2:1 to receive

romosozumab or placebo for 12 months. Although the primary endpoint of gain in bone density compared with placebo was met, investigators noted a numerical increase in positively adjudicated cardiovascular serious events: 8 patients in the romosozumab group (4.9%) and two patients in the placebo (2.5%).[53] There was an increased risk of cardiovascular events and cerebrovascular events. Conclusions drawn from the BRIDGE trial regarding cardiovascular events are limited due to the very few cardiovascular events reported.

Interpretation of clinical trial data

While the imbalance of severe adverse cardiovascular events in the ARCH and BRIDGE study is concerning, cardiovascular outcome data in these studies must be interpreted cautiously. Severe adverse vascular events are defined as death, cardiac ischemic events (myocardial infarction, angina requiring hospitalization, coronary revascularization), cerebrovascular events (stroke, transient ischemic attack), noncoronary revascularization, hospitalization of heart failure, and peripheral vascular event not requiring revascularization.[28] The FDA noted that these clinical trials were designed to assess fracture efficacy and not to evaluate cardiovascular safety. Because of this, baseline data regarding measures of cardiovascular risk and data regarding adverse cardiovascular events were not rigorously collected. Post hoc analysis after the imbalance of serious cardiovascular events was noted is limited due to a lack of rigorously collected data needed to assess cardiovascular risk and outcomes. Furthermore, the numbers of severe cardiovascular events in the trials were low, as they were not powered to assess cardiovascular outcomes.[28] Very few numbers of cardiovascular events led to wide CIs of risk estimates, leading to uncertainty in assessing the true risk of cardiovascular events attributable to romosozumab use.
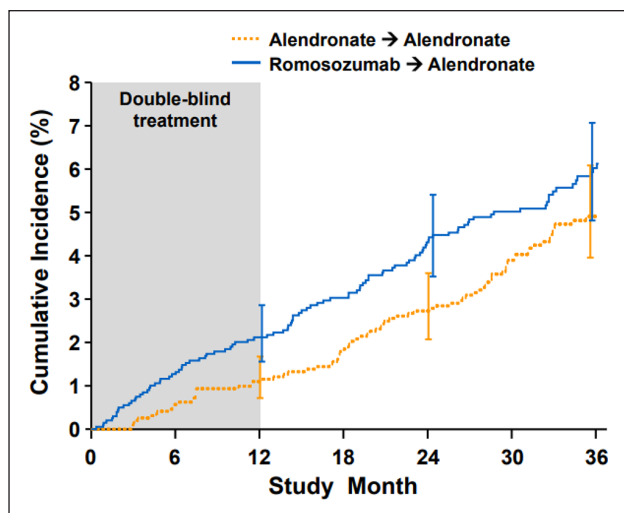
Regarding cardiovascular risk factors of the patients in ARCH, BRIDGE, and FRAME, patients in the ARCH study had a mean age of 74. The mean age for patients in the FRAME was 71, and BRIDGE was 71.5. Patients in the ARCH had higher rates of hypertension, consistent with the older population. Patients in ARCH had the highest proportion of previous cardiovascular disease (73%), as compared with FRAME (66%) and BRIDGE (65%).[28,54] Although there were differences between trials, cardiovascular risk factors, age, and use of cardiovascular-related baseline medications were similar between treatment groups in each study.[28] Almost 90% of patients in the ARCH and BRIDGE trial who had a cardiovascular event in the ARCH trial had a history of cardiovascular disease or one or more cardiovascular risk factors.[54]

In their meta-analysis of the ARCH, BRIDGE, and FRAME trial, the FDA indicated that the incidence of positively adjudicated cardiovascular severe adverse events during the 12-month double-blind treatment period was higher in the romosozumab group (hazard ratio 1.17 CI 0.88–1.56). For meta-analysis of the three studies' overall study periods, the hazard ratio for positively adjudicated cardiovascular severe adverse events was 1.06 (95% CI 0.89–1.25). Major Adverse Cardiac Event (MACE) composite endpoint is a vital endpoint used to evaluate cardiovascular risk in clinical trials. Duke Clinical Research Institute and Myocardial Infarction Study Group (TIMI) adjudicated MACE events with similar results. MACE comprises only cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, removing noncoronary vascular events and heart failure from severe adverse cardiovascular events.[55] MACE events were increased in the ARCH trial at 12 months, hazard ratio of 1.87 (95% CI 1.11–1.34), with an increased risk of serious myocardial infarction and stroke (Table 2 and Figure 4). The FRAME trial did not show an imbalance regarding MACE events at 12 months (Table 2 and Figure 4). A meta-analysis of the ARCH, FRAME, and BRIDGE studies showed that the hazard ratio for MACE was 1.38 (95% CI 0.96–1.99). ARCH and FRAME studies showed no imbalance in MACE for the overall study periods (Table 2). A meta-analysis from the three studies, ARCH, FRAME, and BRIDGE, showed a hazard ratio of 1.14 (95% CI 0.94–1.39). Along the same lines, Bovijn et al.[52] performed a meta-analysis of the results of the ARCH, BRIDGE, and FRAME trial showing that although the odds ratios were in favor of cardiovascular events (OR 1.54, 95% CI 0.90–2.65), cerebrovascular events (OR 1.44, 95% CI 0.80–2.58), MACE (OR 1.39, 95% CI 0.98–1.98) and serious cardiovascular events (OR 1.21, 95% CI 0.90–1.63). However, these were not statistically significant.

Increased cardiovascular risk with romosozumab in the ARCH trial: possible explanations

Several possibilities could explain the increased cardiovascular events in the ARCH trial. Three main possibilities have been raised (1) an actual increased risk of cardiovascular risk with romosozumab, (2) cardioprotective effects of alendronate, and (3) Type 1 error where the increased cardiovascular events were due to chance. Cummings et al. analyzed the pattern of cardiovascular events in the ARCH trial over time (Figure 5). There were no cardiovascular events in the alendronate group during the first 3 months, with fewer cardiovascular events in the remainder of the 12 months. The rate of cardiovascular events then increases steadily in parallel with the romosozumab group (Figure 5). This pattern is not consistent with what one would expect to see if romosozumab caused increased cardiovascular events; one would expect the separation of rates between two groups from the beginning.[55] Furthermore, rates of cardiovascular events would

Figure 5. Cumulative incidence of cardiovascular events in the ARCH study.
Accessed at https://www.fda.gov/advisory-committees/advisory-committee-calendar/january-16-2019-meeting-bone-reproductive-and-urologic-drugs-advisory-committee-meeting-announcement; Amgen presentation: Cardiovascular Safety.

decrease when romosozumab was stopped in year 2 of treatment, but this was not observed.

The possibility of the cardioprotective effects of alendronate has been raised as a possible explanation of the finding in the ARCH trial. Retrospective cohort studies have suggested the possibility of a cardioprotective effect of bisphosphonates. However, there does not seem to be a plausible biologic mechanism where alendronate could cause an acute reduction in cardiovascular events in the first 3 months.[55–57] While a network meta-analysis of the ARCH and FRAME by the FDA also suggested this possibility with a hazard ratio of 0.55 (95% CI 0.27–1.14) for alendronate versus placebo, this was not statistically significant. Two meta-analyses have found no association of effect of bisphosphonates on the risk of cardiovascular events, with a hazard ratio of 1.03 (95% CI 0.91–1.17),[58] and 0.98 (0.84–1.14).[59] The largest randomized trial of alendronate compared to placebo did not show the effect of alendronate over 3 years on cardiovascular events (relative risk = 0.99; 95% CI 0.80–1.22).

The hazard ratio of cardiovascular event risk from the FDA network meta-analysis of 0.55 for bisphosphonates compared with placebo was well below the lower range of 95% CI of the aforementioned bisphosphonates and cardiovascular risk meta-analysis (0.91, 0.81, 0.80), suggesting a high likelihood that the lower rate of cardiovascular events in the ARCH study was due to chance.[55] A type 1 error for the association of romosozumab with increased cardiovascular events risk is possible. The FDA examined baseline rates of myocardial infarction and strokes in similar populations. While noting the results were heterogeneous with a wide range, the incidence rates of myocardial

infarction and stroke in the ARCH and BRIDGE studies fall within the expected baseline rates of similar populations.[28] The FDA[20,28] also noted in the ARCH study that incidence rates in year 1 on alendronate were 1.09% lower than in years 2 and 3, regardless of treatment group (1.63%–2.25%).

In summary, there is conflicting data regarding romosozumab and increased cardiovascular risk. There is a high level of uncertainty in assessing the romosozumab cardiovascular risk due to current data being inadequate from various limitations. While there are other possible explanations for increased cardiovascular events noted in the ARCH study with romosozumab, there is a possibility that romosozumab may increase the risk of cardiovascular events. Therefore, caution is needed when using romosozumab. Studies have shown romosozumab to be a potent osteoanabolic agent with remarkable antifracture efficacy. Avoiding romosozumab in the highest risk patients with cardiovascular risk (myocardial infarction, stroke within 1 year) may be a prudent approach where high fracture risk patients with low cardiovascular risk may benefit from romosozumab treatment. Discussing the cardiovascular disease risk with patients, an individualized approach with shared decision making weighing the fracture prevention benefit versus cardiovascular risk is essential. To draw a more definitive conclusion in the future, a more appropriately powered noninferiority study design may be necessary to evaluate the cardiovascular risk with romosozumab.[54]

As a postmarketing requirement, the FDA has recommended a 5-year observational feasibility study. A comparative safety study may follow. Subsequent pharmacovigilance analysis of the United States FDA Adverse Event Reporting System (FAERS) has shown an increased risk of MACE events with romosozumab. This was primarily driven by significant disproportionality measures in Japanese reports.[60] This study reported 59.5% of cases from Japan. Of the 206 reported MACE outcomes, 164 originated from Japan. Notably, Japan was the first country to authorize romosozumab use and initially did not include a safety warning for cardiovascular use (Japan placed safety warnings for romosozumab in September 2019). In Japan, romosozumab use is not restricted to postmenopausal women and can be used in men. It was noted that Japanese patients were older and more likely male.[60] Also reported were a higher proportion of patients who were on cardioprotective drugs.[60] The results support current safety warnings from the United States FDA and European Medicines Agency to avoid romosozumab in patients with higher cardiovascular risk.[60]

Limitations

This article was a narrative review of romosozumab's efficacy in osteoporosis treatment and its possible association with increased cardiovascular risk. Narrative reviews are limited due to bias and subjectivity in study inclusion

determination.[61] Narrative reviews are less standardized as compared with systematic reviews.[61] Nevertheless, we have made our best effort to present the data and various viewpoints in a balanced and comprehensive fashion to provide up-to-date information and insights to clinicians to facilitate patient care and clinical decision making.

Summary

Increased understanding of the Wnt signaling pathway has allowed the development of romosozumab, one of the most potent osteoanabolic agents to date for the treatment of osteoporosis. The Wnt signaling pathway is essential in bone formation, while sclerostin is a natural inhibitor of the Wnt signaling pathway. Romosozumab is a monoclonal antibody that binds to and inhibits sclerostin. The Wnt signaling pathway is then activated, leading to increased bone formation and decreased bone resorption, a unique uncoupling effect that leads to a sizable osteoanabolic window. As one of the most potent osteoanabolics, the introduction of romosozumab has significantly increased our ability to treat osteoporosis. Studies have provided invaluable information on optimally using romosozumab in combination with other osteoporosis medications. Romosozumab should be considered in patients at very high risk for fracture. Further studies are needed to clarify the safety of romosozumab, especially concerning cardiovascular events. Caution is required when using romosozumab, and it is prudent to avoid use in patients at high cardiovascular risk until further data are available.

Declarations

Ethics approval and consent to participate

Not applicable, this is a review article.

Consent for publication

All authors have agreed to the publication of this article.

Author contribution

Sian Yik Lim: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review and editing.

Acknowledgments

Not applicable.

Funding

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and material

Not applicable.

ORCID iD

Sian Yik Lim ⓘD https://orcid.org/0000-0003-4886-9007

References

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001; 285(6): 785–795.

2. International Osteoporosis Foundation (IOF). Epidemiology of osteoporosis and fragility fractures, 4 June 2022, https://www.osteoporosis.foundation/facts-statistics/epidemiology-of-osteoporosis-and-fragility-fractures

3. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. Epub ahead of print 28 April 2022. DOI: 10.1007/s00198-021-05900-y.

4. Eastell R, O'Neill TW, Hofbauer LC, et al. Postmenopausal osteoporosis. *Nat Rev Dis Primers* 2016; 2: 16069.

5. Lim SY and Bolster MB. Current approaches to osteoporosis treatment. *Curr Opin Rheumatol* 2015; 27(3): 216–224.

6. McClung MR. Role of bone-forming agents in the management of osteoporosis. *Aging Clin Exp Res* 2021; 33(4): 775–791.

7. Moester MJ, Papapoulos SE, Löwik CW, et al. Sclerostin: current knowledge and future perspectives. *Calcif Tissue Int* 2010; 87(2): 99–107.

8. Balemans W, Ebeling M, Patel N, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet* 2001; 10(5): 537–543.

9. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract* 2020; 26(suppl. 1): 1–46.

10. Baron R, Gori F and Leder BZ. Chapter 19: sclerostin inhibition in the treatment of osteoporosis. In: Leder BZ and Wein MN (eds) *Osteoporosis* (Contemporary endocrinology). Cham: Springer Nature, 2020, pp. 375–389.

11. MacDonald BT, Tamai K and He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Dev Cell* 2009; 17(1): 9–26.

12. Deal C. Potential new drug targets for osteoporosis. *Nat Clin Pract Rheumatol* 2009; 5(1): 20–27.

13. Lim SY and Bolster MB. Profile of romosozumab and its potential in the management of osteoporosis. *Drug Des Devel Ther* 2017; 11: 1221–1231.

14. Canalis E. Wnt signalling in osteoporosis: mechanisms and novel therapeutic approaches. *Nat Rev Endocrinol* 2013; 9(10): 575–583.

15. Shahi M, Peymani A and Sahmani M. Regulation of bone metabolism. *Rep Biochem Mol Biol* 2017; 5(2): 73–82.

16. Kahn M. Can we safely target the WNT pathway? *Nat Rev Drug Discov* 2014; 13(7): 513–532.

17. Padhi D, Allison M, Kivitz AJ, et al. Multiple doses of sclerostin antibody romosozumab in healthy men and postmenopausal women with low bone mass: a randomized,

double-blind, placebo-controlled study. *J Clin Pharmacol* 2014; 54(2): 168–178.

18. Padhi D, Jang G, Stouch B, et al. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *J Bone Miner Res* 2011; 26(1): 19–26.

19. Miller SA, St Onge EL and Whalen KL. Romosozumab: a novel agent in the treatment for postmenopausal osteoporosis. *J Pharm Technol* 2021; 37(1): 45–52.

20. United States Food and Drug Administration (FDA). FDA briefing document: meeting of the bone, reproductive and urologic drugs advisory committee, 16 January 2019 (BLA 761062 Romosozumab, Amgen, Inc.), 2019, https://www.fda.gov/media/121257/download (accessed 6 November 2022).

21. Zhao L, Ji P, Li Z, et al. The antibody drug absorption following subcutaneous or intramuscular administration and its mathematical description by coupling physiologically based absorption process with the conventional compartment pharmacokinetic model. *J Clin Pharmacol* 2013; 53(3): 314–325.

22. Ryman JT and Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol* 2017; 6(9): 576–588.

23. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2014; 370(5): 412–420.

24. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016; 375: 1532–1543.

25. United States Food and Drug Administration (FDA). Denosumab product insert-indications and usage, 2013, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125320s094lbl.pdf

26. Cosman F, Crittenden DB, Ferrari S, et al. Romosozumab FRAME study: a post hoc analysis of the role of regional background fracture risk on nonvertebral fracture outcome. *J Bone Miner Res* 2018; 33(8): 1407–1416.

27. Ominsky MS, Boyd SK, Varela A, et al. Romosozumab improves bone mass and strength while maintaining bone quality in ovariectomized cynomolgus monkeys. *J Bone Miner Res* 2017; 32(4): 788–801.

28. United States Food and Drug Administration (FDA). Division of bone, reproductive and urologic products, office of drug evaluation III multidisciplinary review and evaluation document, 9 July 2018, https://www.fda.gov/advisory-committees/advisory-committee-calendar/january-16-2019-meeting-bone-reproductive-and-urologic-drugs-advisory-committee-meeting-announcement (accessed 19 June 2022).

29. Brown JP, Engelke K, Keaveny TM, et al. Romosozumab improves lumbar spine bone mass and bone strength parameters relative to alendronate in postmenopausal women: results from the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) trial. *J Bone Miner Res* 2021; 36(11): 2139–2152.

30. 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.

31. Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet* 2017; 390(10102): 1585–1594.

32. Cosman F, Kendler DL, Langdahl BL, et al. Romosozumab and antiresorptive treatment: the importance of treatment sequence. *Osteoporos Int* 2022; 33(6): 1243–1256.

33. Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. *J Clin Endocrinol Metab* 2020; 105(3): dgaa048.

34. European Medicines Agency (EMA). Evenity, INN-romosozumab, https://www.ema.europa.eu/en/documents/product-information/evenity-epar-product-information_en.pdf (accessed 14 August 2022).

35. Didangelos A, Yin X, Mandal K, et al. Proteomics characterization of extracellular space components in the human aorta. *Mol Cell Proteomics* 2010; 9(9): 2048–2062.

36. Catalano A, Bellone F, Morabito N, et al. Sclerostin and vascular pathophysiology. *Int J Mol Sci* 2020; 21(13): 4779.

37. Langdahl BL, Hofbauer LC and Forfar JC. Cardiovascular safety and sclerostin inhibition. *J Clin Endocrinol Metab* 2021; 106(7): 1845–1853.

38. Zhu D, Mackenzie NC, Millán JL, et al. The appearance and modulation of osteocyte marker expression during calcification of vascular smooth muscle cells. *PLoS One* 2011; 6(5): e19595.

39. Hofbauer LC, Brueck CC, Shanahan CM, et al. Vascular calcification and osteoporosis—from clinical observation towards molecular understanding. *Osteoporos Int* 2007; 18(3): 251–259.

40. Donham C, Chicana B, Robling AG, et al. Sclerostin depletion induces inflammation in the bone marrow of mice. *Int J Mol Sci* 2021; 22(17): 9111.

41. Krishna SM, Seto SW, Jose RJ, et al. Wnt signaling pathway inhibitor sclerostin inhibits angiotensin II-induced aortic aneurysm and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2017; 37(3): 553–566.

42. Golledge J and Thanigaimani S. Role of sclerostin in cardiovascular disease. *Arterioscler Thromb Vasc Biol* 2022; 42: e187–e202.

43. De Mare A, Maudsley S, Azmi A, et al. Sclerostin as regulatory molecule in vascular media calcification and the bone-vascular axis. *Toxins* 2019; 11(7): 428.

44. Hamann C, Rauner M, Höhna Y, et al. Sclerostin antibody treatment improves bone mass, bone strength, and bone defect regeneration in rats with type 2 diabetes mellitus. *J Bone Miner Res* 2013; 28(3): 627–638.

45. Chouinard L, Felx M, Mellal N, et al. Carcinogenicity risk assessment of romosozumab: a review of scientific weight-of-evidence and findings in a rat lifetime pharmacology study. *Regul Toxicol Pharmacol* 2016; 81: 212–222.

46. Claes KJ, Viaene L, Heye S, et al. Sclerostin: another vascular calcification inhibitor? *J Clin Endocrinol Metab* 2013; 98(8): 3221–3228.

47. Viaene L, Behets GJ, Claes K, et al. Sclerostin: another bone-related protein related to all-cause mortality in haemodialysis? *Nephrol Dial Transplant* 2013; 28(12): 3024–3030.

48. Drechsler C, Evenepoel P, Vervloet MG, et al. High levels of circulating sclerostin are associated with better cardiovascular survival in incident dialysis patients: results

from the NECOSAD study. *Nephrol Dial Transplant* 2015; 30(2): 288–293.

49. Gong L, Zheng D, Yuan J, et al. Elevated levels of serum sclerostin are linked to adverse cardiovascular outcomes in peritoneal dialysis patients. *Int Urol Nephrol* 2018; 50(5): 955–961.

50. Van Lierop AH, Appelman-Dijkstra NM and Papapoulos SE. Sclerostin deficiency in humans. *Bone* 2017; 96: 51–62.

51. Li X, Ominsky MS, Niu QT, et al. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. *J Bone Miner Res* 2008; 23(6): 860–869.

52. Bovijn J, Krebs K, Chen CY, et al. Evaluating the cardiovascular safety of sclerostin inhibition using evidence from meta-analysis of clinical trials and human genetics. *Sci Transl Med* 2020; 12(549): eaay6570.

53. Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab* 2018; 103(9): 3183–3193.

54. Fixen C and Tunoa J. Romosozumab: a review of efficacy, safety, and cardiovascular risk. *Curr Osteoporos Rep* 2021; 19(1): 15–22.

55. Cummings SR and McCulloch C. Explanations for the difference in rates of cardiovascular events in a trial of alendronate and romosozumab. *Osteoporos Int* 2020; 31(6): 1019–1021.

56. Kang JH, Keller JJ and Lin HC. Bisphosphonates reduced the risk of acute myocardial infarction: a 2-year follow-up study. *Osteoporos Int* 2013; 24(1): 271–277.

57. Sing CW, Wong AY, Kiel DP, et al. Association of alendronate and risk of cardiovascular events in patients with hip fracture. *J Bone Miner Res* 2018; 33(8): 1422–1434.

58. Kranenburg G, Bartstra JW, Weijmans M, et al. Bisphosphonates for cardiovascular risk reduction: a systematic review and meta-analysis. *Atherosclerosis* 2016; 252: 106–115.

59. Kim DH, Rogers JR, Fulchino LA, et al. Bisphosphonates and risk of cardiovascular events: a meta-analysis. *PLoS One* 2015; 10(4): e0122646.

60. Kvist AV, Faruque J, Vallejo-Yague E, et al. Cardiovascular safety profile of romosozumab: a pharmacovigilance analysis of the US Food and Drug Administration adverse event reporting system (FAERS). *J Clin Med* 2021; 10: 1660.

61. Greenhalgh T, Thorne S and Malterud K. Time to challenge the spurious hierarchy of systematic over narrative reviews? *Eur J Clin Invest* 2018; 48(6): e12931.