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ROMOSOZUMAB IN THE SPOTLIGHT: A PARADIGM SHIFT IN THE TREATMENT OF OSTEOPOROTIC FRACTURES

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ABSTRACT

Osteoporosis is a prevalent metabolic bone disorder marked by decreased bone mass and deterioration of bone structure, leading to an increased risk of fractures, particularly in older adults. Traditional therapeutic approaches have primarily focused on inhibiting bone resorption; however, their ability to restore lost bone is limited. Romosozumab, a first-in-class monoclonal antibody targeting sclerostin, has introduced a novel dual-action mechanism that not only promotes bone formation but also inhibits resorption, offering a more comprehensive treatment strategy. This article explores the mechanism of action, clinical efficacy, and safety profile of romosozumab, with emphasis on pivotal clinical trials such as FRAME, ARCH, and BRIDGE. While the therapy has demonstrated significant improvements in bone mineral density and fracture risk reduction, its cardiovascular safety profile necessitates careful patient selection. Romosozumab represents a promising advancement for patients with severe osteoporosis, especially those who have not responded adequately to traditional therapies. Ongoing research continues to refine its place in long-term osteoporosis management.

I. INTRODUCTION

Osteoporosis is a chronic and progressive skeletal disorder that leads to a reduction in bone mass and degradation of bone microarchitecture, thereby increasing susceptibility to fragility fractures, particularly in the hip, vertebrae, and wrist. It affects over 200 million individuals worldwide, primarily postmenopausal women and elderly men, contributing significantly to morbidity, mortality, and economic burden on healthcare systems [1]. Often described as a "silent thief," osteoporosis develops insidiously, with bone loss occurring without overt symptoms until a fracture reveals the underlying pathology [1]. The rising global life expectancy and aging population are anticipated to further escalate the burden of osteoporosis, making effective and innovative treatments a public health priority.

For many years, clinical management primarily relied on antiresorptive therapies such as bisphosphonates and denosumab, which function by inhibiting osteoclast-mediated bone resorption, thereby slowing down bone loss [2]. While effective in reducing the risk of fracture, these agents are limited in their ability to rebuild lost

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bone or significantly improve compromised bone structure. To address this gap, anabolic treatments like teriparatide and abaloparatide have been introduced. These agents stimulate osteoblastic bone formation, offering hope for patients with severe disease. However, their clinical use is often constrained by cost, treatment duration limitations (usually 18–24 months), and potential adverse effects, including hypercalcemia and, in animal models, an increased risk of osteosarcoma [3]. A paradigm shift in bone biology occurred with the discovery of sclerostin, a glycoprotein secreted primarily by osteocytes. Sclerostin functions as a key negative regulator of bone formation, acting through the Wnt/β-catenin signaling pathway, which is essential for osteoblast proliferation, survival, and function [4]. By inhibiting this pathway, sclerostin suppresses osteoblast activity, thereby decreasing bone formation.

The physiological relevance of sclerostin was illuminated by rare genetic disorders like sclerosteosis and van Buchem disease, in which mutations in the SOST gene result in sclerostin deficiency, leading to high bone mass, increased skeletal strength, and low fracture incidence [5]. These insights laid the foundation for targeting sclerostin inhibition as a novel anabolic strategy. This scientific understanding culminated in the development of romosozumab, a humanized monoclonal antibody designed to neutralize sclerostin. Romosozumab exhibits a dual mechanism of action—it not only stimulates bone formation by enhancing Wnt signaling but also inhibits bone resorption, potentially through the suppression of RANKL-mediated osteoclastogenesis [6].

This unique pharmacological profile leads to rapid and substantial increases in bone mineral density (BMD) and has shown superior fracture risk reduction compared to conventional treatments. Romosozumab's clinical efficacy has been validated in three major Phase III randomized controlled trials—FRAME, ARCH, and BRIDGE—which demonstrated significant gains in BMD at both lumbar spine and hip sites, along with reductions in vertebral, clinical, and non-vertebral fractures across various patient populations [7].

II. METHODOLOGY

1. Romosozumab: Clinical Trials and Efficacy

Romosozumab has emerged as a groundbreaking therapeutic agent in the field of osteoporosis management due to its distinct dual mode of action—enhancing bone formation while simultaneously inhibiting bone resorption [6]. This pharmacological profile marks a major shift from conventional osteoporosis therapies. Traditional antiresorptive drugs like bisphosphonates and denosumab primarily act by reducing bone turnover and slowing the breakdown of existing bone, thereby helping to stabilize or slightly increase bone mineral density (BMD) over time [2]. Conversely, anabolic agents such as teriparatide and abaloparatide focus on promoting new bone synthesis, yet they often stimulate bone resorption as well, which can diminish their net bone-gaining effect [3]. Romosozumab offers the best of both therapeutic classes by achieving a positive bone balance—enhancing formation while suppressing degradation—resulting in significant improvements in both BMD and structural integrity. Mechanistically, romosozumab is a humanized monoclonal IgG2 antibody

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specifically designed to target and inhibit sclerostin, a glycoprotein that is primarily secreted by osteocytes, the most abundant cells within the bone matrix. Sclerostin serves as a key negative regulator of bone formation by antagonizing the Wnt/β-catenin signaling pathway, which is essential for osteoblast proliferation, maturation, and survival [4]. When sclerostin binds to the LRP5/6 receptors on osteoblasts, it suppresses the downstream activation of Wnt signaling, thereby limiting bone formation. Romosozumab disrupts this inhibition by neutralizing sclerostin's activity, leading to upregulation of Wnt signaling, increased osteoblast differentiation, and stimulation of matrix production [4], [5].

In addition to its anabolic effects, romosozumab also indirectly modulates bone resorption. It downregulates the expression of RANKL (Receptor Activator of Nuclear Factor κB Ligand), a critical cytokine that promotes osteoclast formation and activity. By reducing RANKL levels, romosozumab decreases osteoclast-mediated bone breakdown, further contributing to a net gain in bone mass [5]. This complementary dual effect not only accelerates increases in BMD but also enhances bone microarchitecture and mechanical strength, significantly reducing the risk of both vertebral and non-vertebral fractures. Clinical trials have consistently demonstrated that patients receiving romosozumab exhibit greater improvements in BMD and faster fracture risk reduction than those treated with either antiresorptive or anabolic agents alone [6], [9].Because of these outcomes, romosozumab is increasingly recommended for individuals with severe osteoporosis, particularly those with multiple prior fractures or at imminent risk of future fractures, where a rapid therapeutic response is essential.

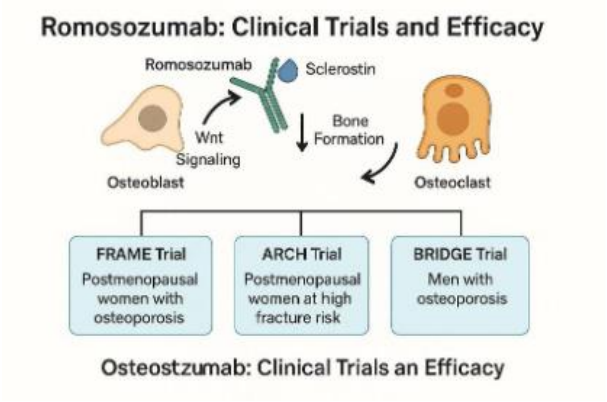


Fig (1): 3 Types of Clinical Trails

Despite its efficacy, careful consideration is warranted in patient selection, especially in those with a history of cardiovascular events, due to the observed increase in serious cardiovascular complications in some clinical studies. Nonetheless, when appropriately prescribed, romosozumab stands as a transformative intervention in the evolving landscape of osteoporosis treatment.

The flow diagram Illustrates the progression of clinical evidence supporting the efficacy of romosozumab in osteoporosis treatment. Beginning with its overarching mechanism of action—stimulating bone formation and reducing bone resorption—the diagram highlights three pivotal trials. The FRAME trial demonstrated significant reductions in fracture incidence among postmenopausal women. Building upon this, the ARCH trial showed that romosozumab outperformed alendronate in preventing fractures in high-risk patients. Lastly, the BRIDGE trial extended these findings to male patients, confirming the drug's consistent effects across genders. Together, these studies establish romosozumab as a transformative option in osteoporosis therapy.

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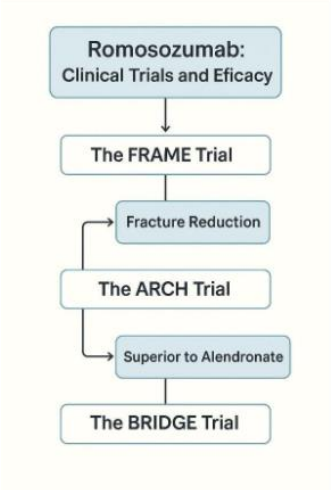


Fig (2): Flow diagram of the research

2. The FRAME Trial

The FRAME (Fracture Study in Postmenopausal Women with Osteoporosis) trial stands as a cornerstone in the clinical validation of romosozumab's efficacy in treating osteoporosis. Conducted as a Phase III, randomized, double-blind, placebo-controlled trial, it aimed to evaluate the ability of romosozumab to reduce the risk of osteoporotic fractures and to improve bone mineral density (BMD) in postmenopausal women—a population particularly vulnerable to fragility fractures due to hormonal changes that accelerate bone loss [8]. This large-scale international study enrolled 7,180 postmenopausal women, aged 55 to 85 years, who had low BMD (defined by a T-score of ≤–2.5 at the total hip or femoral neck) but were otherwise in good health. Notably, many of these women had not experienced prior fractures, differentiating this trial from other studies targeting high-risk populations. Participants were randomized to receive either 210 mg of romosozumab or placebo via subcutaneous injection every month for 12 months, followed by open-label treatment with denosumab for another 12 months in both groups [8]. The trial's primary endpoint was the reduction in the incidence of new vertebral fractures at 12 months, with secondary endpoints including changes in BMD and nonvertebral fracture rates. The findings were both clinically and statistically significant. At the end of the first year, romosozumab treatment led to a 73% reduction in new vertebral fractures compared to placebo (0.5% vs. 1.8%)—an effect that was observed as early as six months into the treatment. Furthermore, BMD at the lumbar spine increased by 13.3%, and BMD at the total hip rose by 6.9%, representing one of the largest gains observed with any osteoporosis medication over a similar duration [8].

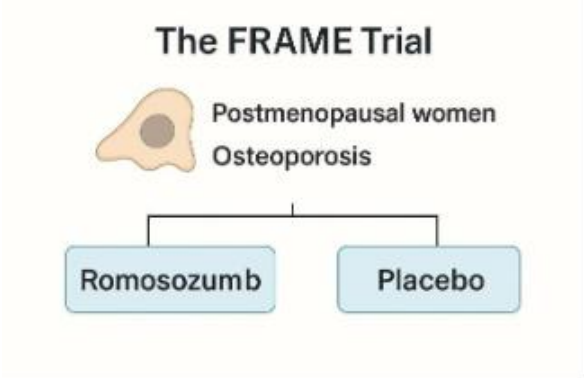


Fig (3): Frame Trail

These improvements in bone density and fracture protection illustrate romosozumab's powerful anabolic effect, achieved more rapidly and effectively than conventional osteoporosis treatments. Importantly, the transition to denosumab in the second year of treatment maintained and further enhanced these gains, supporting a therapeutic strategy of initial bone building followed by antiresorptive maintenance. Another critical insight from FRAME was the safety profile of romosozumab in this relatively lower-risk population. The study did not observe a

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significant imbalance in cardiovascular events between the treatment and placebo groups, which contributed to the overall favorable risk-benefit ratio in this trial population [8].

3. The ARCH Trial

The ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture) trial was designed to evaluate romosozumab's efficacy in a more clinically severe population—postmenopausal women with a documented history of fragility fractures, placing them at very high risk for future fractures. This study was crucial in assessing romosozumab's real-world therapeutic potential in patients requiring urgent and effective skeletal reinforcement [9]. Unlike the FRAME trial, which studied treatment-naïve women without prior fractures, the ARCH trial adopted an active-comparator design rather than a placebo-controlled model. It randomized 4,093 postmenopausal women aged 55–90 years to receive either romosozumab (210 mg subcutaneously once monthly for 12 months) followed by alendronate (70 mg weekly) for another 12 months, or alendronate alone for the entire 24-month period [9]. Alendronate, a potent bisphosphonate, was selected as the comparator because of its established anti-fracture efficacy and widespread use in osteoporosis care. The trial's primary endpoint was the incidence of new vertebral fractures at 24 months, with secondary endpoints assessing clinical fractures, nonvertebral fractures, and changes in BMD. Romosozumab demonstrated superior outcomes across multiple domains. At the end of the first year, women in the romosozumab group had achieved a 13.7% increase in lumbar spine BMD and a 6.3% increase at the total hip, significantly greater than those in the alendronate group. Over the full 24-month period, romosozumab followed by alendronate resulted in a 48% reduction in new vertebral fractures, 27% reduction in clinical fractures, and 19% reduction in nonvertebral fractures compared to continuous alendronate alone [9].

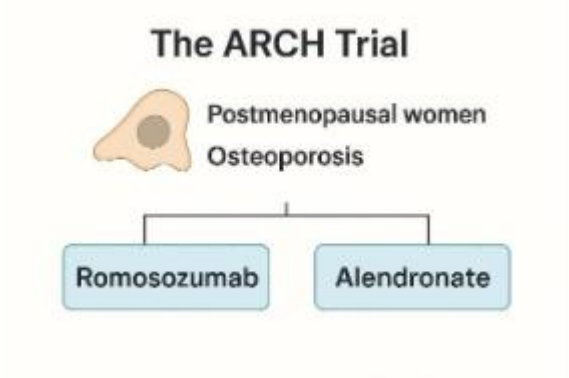


Fig (4): Arch Trail

These results highlight romosozumab's ability to deliver rapid skeletal benefits that are both greater in magnitude and faster in onset than conventional antiresorptive therapy. The data supports a sequential treatment strategy: initiating with an anabolic agent to rebuild bone rapidly, followed by an antiresorptive to maintain the achieved gains. However, despite the striking efficacy results, the ARCH trial brought to light an important safety concern. The incidence of serious cardiovascular adverse events (MACE) was modestly higher in the romosozumab group compared to the alendronate group—2.5% vs. 1.9%, respectively. This imbalance, although not statistically conclusive in terms of causality, led to significant

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regulatory scrutiny. The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued warnings and required precautionary labeling, advising that romosozumab should not be used in patients with a recent history of myocardial infarction or stroke, and that clinicians should carefully assess cardiovascular risk before prescribing [10].

4. The BRIDGE Trial

While osteoporosis has traditionally been associated with postmenopausal women, it also affects a significant number of men—an often underdiagnosed and undertreated population. The BRIDGE (Bone Research in Gents) trial was a landmark Phase III, double-blind, placebo-controlled clinical trial specifically designed to evaluate the efficacy and safety of romosozumab in men with osteoporosis—a demographic largely excluded from previous anabolic bone treatment studies [7].

This study enrolled 245 men aged 55 to 90 years who had either low bone mineral density (BMD) (T-score ≤ −2.5 at the lumbar spine or hip) or a history of low-trauma fractures. Subjects were randomized to receive 210 mg of romosozumab or placebo once monthly via subcutaneous injection for a period of 12 months. The primary endpoint was the percent change in BMD at the lumbar spine from baseline at 12 months, with secondary endpoints including changes at other skeletal sites and assessments of safety [7].

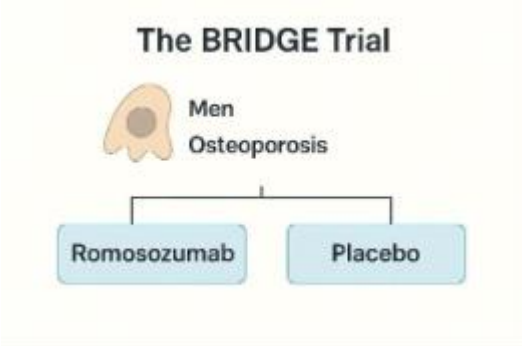


Fig (5): Bridge Trail

The results of the BRIDGE trial were both statistically and clinically significant. At the end of 12 months, men treated with romosozumab experienced a 12.1% increase in lumbar spine BMD and a 2.5% increase at the total hip, compared to negligible gains in the placebo group. Improvements were also seen in BMD at the femoral neck, though to a lesser extent. These results closely mirrored the BMD gains observed in postmenopausal women in the FRAME and ARCH trials, suggesting that romosozumab's mechanism of action is equally effective across genders [7].

Table 1: BMD Increases Observed in Romosozumab Trials

Trial	Lumbar Spine BMD Increase (%)	Total Hip BMD Increase (%)
FRAME	13.3	6.9
ARCH	13.7	6.3
BRIDGE	12.1	2.5

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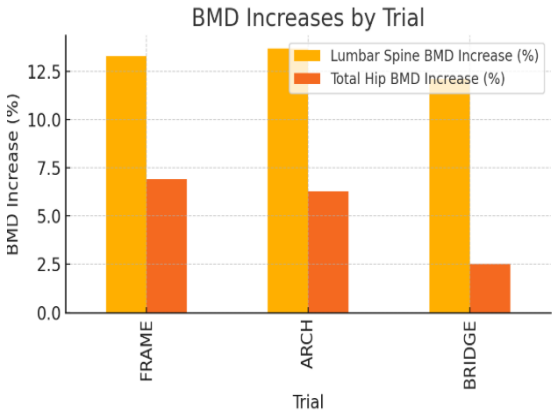


Fig (6): Comparison of lumbar spine and total hip BMD increases across FRAME, ARCH, and BRIDGE trials.

III. CONCLUSION

Romosozumab marks a transformative step forward in the therapeutic landscape of osteoporosis. Unlike traditional treatments that primarily aim to slow bone loss, romosozumab introduces a dual-action mechanism that actively stimulates bone formation while concurrently suppressing bone resorption. This pharmacological innovation offers a more holistic and aggressive approach to restoring skeletal strength, particularly in patients at high or imminent risk of fragility fractures. Its ability to deliver rapid and substantial improvements in bone mineral density—especially at clinically critical sites such as the lumbar spine and hip—positions it as one of the most potent agents available for osteoporosis management. The clinical evidence from large-scale trials has consistently demonstrated romosozumab's efficacy in reducing both vertebral and non-vertebral fracture risks within a relatively short treatment window. Furthermore, its effectiveness across different patient populations, including both women and men with osteoporosis, underscores its broad therapeutic potential and represent an important step toward addressing gender disparities in osteoporosis research and treatment. Despite its impressive clinical benefits, the use of romosozumab is not without limitations. The emergence of a possible signal for cardiovascular adverse events has led to regulatory precautions, emphasizing the importance of careful patient selection and monitoring. It is crucial that healthcare providers weigh the benefits of rapid bone-building effects against potential risks, especially in individuals with a recent history of cardiovascular disease. Looking ahead, romosozumab opens new avenues for personalized osteoporosis treatment strategies. Research is now focusing on optimizing its use in sequential therapy—initiating treatment with romosozumab to quickly rebuild bone, followed by long-term maintenance with antiresorptive agents to preserve those gains. Additionally, ongoing studies aim to better define the long-term safety profile of romosozumab, as well as its potential role in combination therapies.

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