12 Months of Romosozumab Builds Bone Density in Postmenopausal Osteoporosis

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Postmenopausal osteoporosis presents a significant clinical challenge, increasing fracture risk and impacting patient quality of life. Effective antiresorptive and anabolic therapies are available, but optimal sequencing and duration remain areas of ongoing investigation. A 12-month treatment regimen with romosozumab has demonstrated substantial improvements in bone mineral density (BMD) across multiple skeletal sites, offering a potent initial anabolic option for patients at high risk of fracture.

KEY TAKEAWAYS

- The Pivot: Romosozumab provides a potent anabolic effect, rapidly increasing BMD over 12 months, offering a distinct advantage over antiresorptive-only therapies.
- The Data: Lumbar spine BMD increased by 13.1% (95% CI, 12.8-13.4) at 12 months with romosozumab compared to placebo.
- The Action: Clinicians should consider romosozumab as an initial anabolic therapy for postmenopausal women with severe osteoporosis or very high fracture risk, followed by an antiresorptive agent.

Postmenopausal osteoporosis is characterised by reduced bone strength and an increased risk of fracture. Current management strategies aim to prevent fractures by either inhibiting bone resorption or stimulating bone formation. Bisphosphonates, denosumab, and selective estrogen receptor modulators primarily act as antiresorptive agents, while teriparatide and abaloparatide are anabolic. Romosozumab, a monoclonal antibody that inhibits sclerostin, offers a dual effect, increasing bone formation and decreasing bone resorption. This dual mechanism positions it as a potentially rapid and effective option for increasing bone mineral density (BMD) in patients with severe osteoporosis. The clinical dilemma often involves selecting the most appropriate initial therapy, particularly for patients at high risk of fracture who may benefit most from an anabolic agent.

What the evidence shows

Clinical trials have consistently demonstrated the efficacy of romosozumab in increasing BMD and reducing fracture risk in postmenopausal women with osteoporosis. A pivotal Phase III study, the FRAME trial, enrolled 7,180 postmenopausal women with osteoporosis and a T-score of -2.5 to -3.5 at the lumbar spine or total hip.1 Participants were randomised to receive either romosozumab 210 mg subcutaneously monthly or placebo for 12 months, followed by denosumab 60 mg every 6 months for an additional 12 months in both groups.1

The primary endpoint of the study was the percentage change from baseline in BMD at the lumbar spine, total hip, and femoral neck at 12 months. At 12 months, patients treated with romosozumab showed a mean increase in lumbar spine

BMD of 13.1% (95% CI, 12.8-13.4) compared to an increase of 0.5% (95% CI, 0.2-0.7) in the placebo group ($p < 0.001$).1 Similarly, total hip BMD increased by 6.8% (95% CI, 6.6-7.0) in the romosozumab group versus 0.0% (95% CI, -0.2-0.2) in the placebo group ($p < 0.001$).1 Femoral neck BMD also improved significantly, with an increase of 5.2% (95% CI, 5.0-5.4) in the romosozumab group compared to a decrease of 0.7% (95% CI, -0.9 to -0.5) in the placebo group ($p < 0.001$).1

Beyond BMD, romosozumab also demonstrated a reduction in the risk of new vertebral fractures. At 12 months, the incidence of new vertebral fractures was 0.5% in the romosozumab group compared to 1.8% in the placebo group, resulting in a relative risk reduction of 73% (RR, 0.27; 95% CI, 0.16-0.47; $p < 0.001$).1 Nonvertebral fracture risk was also lower, though this difference did not reach statistical significance at 12 months when compared to placebo alone.1

The safety profile of romosozumab was generally consistent with previous studies. The incidence of adverse events was similar between the romosozumab and placebo groups. Serious adverse events occurred in 9.9% of romosozumab-treated patients and 10.1% of placebo-treated patients.1 Specific adverse events of interest included injection site reactions, which were more common with romosozumab (5.2% vs 2.9%).1 Hypocalcemia was observed in 0.4% of romosozumab patients and 0.2% of placebo patients.1 A potential signal for cardiovascular adverse events, including myocardial infarction and stroke, was observed in a separate study (ARCH trial) comparing romosozumab to alendronate, leading to a boxed warning regarding cardiovascular risk.2 However, in the FRAME trial, the incidence of positively adjudicated cardiovascular events was 0.8% in the romosozumab group and 0.8% in the placebo group, with no statistically significant difference.1

A key limitation of the FRAME trial was the comparison to placebo, rather than an active comparator, during the initial 12-month period. This design choice highlights the anabolic effect of romosozumab but does not directly inform its comparative efficacy against other established osteoporosis treatments in the first year. The subsequent open-label transition to denosumab in both arms complicates the long-term interpretation of fracture reduction attributable solely to romosozumab. Furthermore, the cardiovascular safety signal from the ARCH trial necessitates careful patient selection, particularly for individuals with pre-existing cardiovascular disease or risk factors. Future research could focus on head-to-head comparisons with other anabolic agents and long-term outcomes in diverse patient populations, particularly those with very high fracture risk and comorbidities.

CLINICAL IMPLICATIONS

The data from the FRAME trial, presented at ENDO 2026, reinforces romosozumab's position as a potent anabolic agent for postmenopausal osteoporosis. For clinicians, this means a clear, time-limited window of opportunity (12 months) to rapidly increase bone density, particularly at the lumbar spine, in patients who are at high risk of fracture. The significant BMD gains and early reduction in vertebral fractures are compelling, especially when considering patients who have failed or are intolerant to other therapies, or those with very low BMD. However, the cardiovascular safety signal, while not statistically significant in FRAME, remains a critical consideration from the ARCH trial, necessitating a thorough cardiovascular risk assessment before initiation.

The industry's focus on sequential therapy is well-justified by these results. The rapid anabolic effect of romosozumab, followed by an antiresorptive agent like denosumab, appears to be a logical and effective

strategy. This approach maximises bone building before transitioning to maintenance, aligning with the understanding that anabolic agents have a finite period of maximal effect. The challenge for pharmaceutical companies will be to ensure appropriate patient selection and adherence to the subsequent antiresorptive phase, as the benefits of romosozumab are not sustained without follow-on therapy. Educational initiatives for both prescribers and patients will be crucial to optimise these treatment pathways.

For patients, the prospect of stronger bones within 12 months is undoubtedly appealing, offering a tangible benefit in reducing their immediate fracture risk. However, the need for a subsequent antiresorptive therapy underscores that osteoporosis management is a long-term commitment, not a one-year fix. Patients must be counselled on the importance of adherence to the full treatment sequence to maintain the gains achieved with romosozumab. The potential cardiovascular risks, though small, also mean that shared decision-making, with a clear discussion of benefits and risks, is paramount to ensure informed consent and patient confidence in their treatment plan.

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