Review Article

# Romosozumab: A New Anabolic Arrow in Quiver for Management of Osteoporosis

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## Abstract

The multifactorial disease of the elderly, characterized by accelerated bone loss and a high risk of fracture (even with trivial trauma), osteoporosis, is known to primarily affect postmenopausal women. Moreover, the precipitating factors for the same mainly are the hormonal and nutritional deficiency. Clinically, the most common fracture to be encountered is the vertebral compression fracture. Apart from exogenously supplementing calcium and Vitamin D, a diverse group of drugs (bisphosphonates, denosumab, teriparatide, strontium ranelate, raloxifene, and calcitonin) are available to manage the case of osteoporosis. The latest drug to be approved and included in this quiver is a sclerostin-targeting monoclonal antibody, romosozumab. This new drug appears to be promising in managing the postmenopausal patients of osteoporosis. Although the array of adverse effects is not well recognized, a black box warning has been issued for this drug in reference to contraindicated use in patients with comorbid myocardial infarction. The intent of the authors for this review is to discuss the pharmacological profile of romosozumab, with particular emphasis on supportive clinical trials as well as the adverse drug reactions associated with its use.

**Keywords:** Bone formation, bone resorption, fracture prevention, osteopenia, sclerostin

## Introduction

Osteoporosis is known to be associated with a severe loss of both bone mineral density (BMD) and protein, along with alteration in bone structure, thus resulting in not only the loss of bone strength but also increased risk of fractures as well. It is the most common bone-related disorder among the elderly, particularly in postmenopausal women.[1] About 30% of women are osteoporotic in Europe and the United States, and a similar rate has been found in India as well.[2,3] As of 2015, nearly 46 million Indian women were having osteoporosis.[4] Primary osteoporosis develops because of aging or postmenopausal estrogen deficiency, while secondary osteoporosis is multifactorial involving lifestyle changes, endocrine disorders, genetic diseases, or drugs. The condition is usually diagnosed accidentally as it remains silent until the patient encounters a fracture with or without preceding trauma, mostly involving vertebrae, proximal femur, and distal forearm. Dual X-ray absorptiometry assesses BMD and is indicated for confirming the diagnosis of osteoporosis.[5] Osteoporosis is confirmed with a T-score of <−2.5 standard deviation (SD), and a T-score (−1 and −2.5 SD) indicates osteopenia.[5] The concept behind the management of osteoporosis is to inhibit osteoclast-mediated bone resorption and stimulate osteoblast-mediated bone formation. While the majority of the drugs available for osteoporosis act primarily by inhibiting bone resorption, bone formation is rather suppressed as a secondary phenomenon. The currently available drugs for the management of osteoporosis are bisphosphonates, denosumab, teriparatide, strontium ranelate, raloxifene, and calcitonin.[6] However, with these drugs which mainly act as antiresorptive, the bone remodeling may be slowed down, but there is no significant decrease in the risk of developing fractures, thus creating an unmet need among the patients of osteoporosis who are on antiresorptive therapy.[7] Apart from that, it has been observed that the use of bisphosphonates in the Asian population was associated with the possibility of

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developing atypical fractures, and with zoledronate, there is a risk of developing symptomatic hypocalcemia and hypophosphatemia.[8,9] Romosozumab is the most recent drug approved for this indication. Further, the article will only focus on the pharmacology of romosozumab.

### Romosozumab (Evenity/AMG 785)

There is an unmet need for drugs that not only restore the bone structure but also decrease the risk of fracture among the patients of osteoporosis. To fulfill this requirement, drugs that can promote bone formation are desired. Romosozumab, the newest among antiosteoporotic agents developed by Amgen and UCB, seems to fulfill this unmet need. This monoclonal antibody (immunoglobulin G2) targets sclerostin, which is a crucial inhibitor of bone formation, and whose deficiency is known to result in sclerosteosis (usually manifesting as an abnormally high bone mass).[10] The mechanism by which this novel drug brings about its effect, i.e., inhibiting the bone loss and increasing the bone strength, is illustrated in Figure 1.[11] Apart from the depicted effects, it has been observed that romosozumab brings about an increase in the level of the marker for bone synthesis, i.e., procollagen type 1 N-telopeptide (P1NP), as well as it also causes a reduction in type 1 collagen C-telopeptide (CTX) which is a bone resorption marker.[12] At a dose of 210 mg, the drug achieves a maximum serum concentration (Cmax) of 5.8 mcg/mL. The median time to reach the maximum level is 5 days, with the volume of distribution being 3.9 L. It follows nonlinear pharmacokinetics; hence, following a higher dose administration, there occurs a disproportionate increase in serum concentration. The mean clearance of romosozumab is 0.38 mL/h/kg, with a half-life of 12.8 days. It gets metabolized by degrading into small peptides. The fallacy is that antibodies against romosozumab may lead to its decreased concentration[13] [Table 1].

## Preclinical Studies

The antiosteoporotic activity of antibody against sclerostin (AMG 785) was assessed in different animal models of osteoporosis. These studies were conducted in ovariectomized rats for 12 months and cynomolgus monkeys for 6 months, and no major noxious effects were noted in rats and monkeys in doses up to 100 mg/kg.[14] Another study assessed the effect of transition from anti-sclerostin antibody to receptor activator of nuclear factor-κB ligand (RANKL) inhibitor in ovariectomized rats and demonstrated positive effects on bone formation and resorption, thus resulting in improved bone mass and strength which were sustained with the subsequent course of RANKL inhibitor osteoprotegerin.[15] Further lifetime carcinogenicity studies (up to 98 weeks) in rats did not show any carcinogenic potential of romosozumab in doses up to 19 times that of clinical exposure.[16] It has also not been found to affect fertility in rats (both males and females; <300 mg/kg); however, its mutagenic potential had not been assessed.[13]

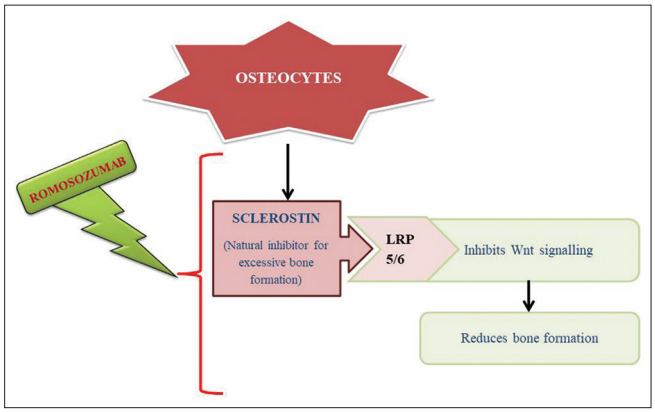


**Figure 1:** Mechanism of action of romosozumab. LRP: Low-density lipoprotein receptor, Wnt: Wingless-related integration site

## Clinical Studies

Following preclinical studies, AMG 785 underwent different phases of human studies. A total of 17 clinical trials have been conducted, among which a majority of the trials are complete (with the submission of results). Out of these 17 clinical trials conducted, 6 were Phase I trial,[17-22] 4 were Phase II,[23-26] and 7 were Phase III trials.[27-33] We will mainly focus on Phase III trials involving a maximum number of patients, simultaneously emphasizing the significant findings of Phase I and II trials, which may be of clinical interest and helpful in clinical practice. All the clinical trials have been enumerated in Annexure 1.

### Phase I trials

Most of the Phase I trials were conducted between 2008 and 2014 in the United States, involving 24–74 participants who were having osteopenia or osteoporosis and were observed for 85–169 days. It was evident in various Phase I studies of romosozumab that its use in healthy volunteers of either sex brought about rise and fall of bone formation and resorption markers respectively.[17,19] In the study involving patients of Stage 4 renal impairment and end-stage renal disease, 8 patients were enrolled in each group and observed for adverse events for 85 days. Two patients, one from each group, developed serious adverse events, i.e., anemia and mitral valve disease, respectively. Other than this, no serious adverse effect was reported.[21]

### Phase II trials

These studies were conducted in various parts of the world involving 252–419 patients who were having postmenopausal osteoporosis or looked for fracture healing and were observed for 5–12 months. In a crucial Phase II trial, 419 postmenopausal women with low bone mineral density (BMD) were assessed for responses of romosozumab.[24] The patients were randomized and received either romosozumab 70, 140, or 210 mg monthly, or in doses of 140 mg or 210 mg every 3 months, or placebo. The remaining participants were randomly administered alendronate 70 mg weekly, teriparatide 20 mcg subcutaneously daily/zoledronic acid 5 mg annually. The primary outcome was to look for percentage difference from baseline to 12 months in BMD of the lumbar spine for individuals in the romosozumab

**Table 1: Pharmacokinetic properties of romosozumab[13]**

| Pharmacokinetic parameters | Romosozumab (210 mg) |
|---|---|
| Cmax (mcg/mL) | 5.8 |
| Tmax (days) | 5 |
| Vd (L) | 3.9 |
| Cl (ml/h/kg) | 0.38 |
| $T_{1/2}$ (days) | 12.8 |

Cmax: Maximum concentration achieved, Tmax: Time at which maximum concentration achieved, Vd: Volume of distribution, Cl: Clearance, $T_{1/2}$: Half-life of drug in plasma

and placebo groups. The result of this study substantiated the findings of a Phase I trial, i.e., romosozumab led to a rise in the bone formation markers from baseline within a month, followed by a return to baseline after 2–6 months depending on the dose administered, while on the other hand, it decreased the bone resorption marker after 1 week, which remained below baseline during the therapy.[12] Romosozumab caused an increase in BMD at the spine and proximal femur, and the maximum increase was noted with a dose of 210 mg per month. Another similar study was conducted in Japan involving 252 osteoporotic postmenopausal women who were administered romosozumab in doses of 70 mg, 140 mg, and 210 mg monthly or placebo for 12 months. The primary aim was to look for the percentage change in BMD of the lumbar spine at 12 months. All these doses led to a remarkable improvement in BMD compared to the initial status and placebo group.[26] In another study (STARTT-Hip) involving 332 patients, who were looking for fracture healing from different parts of the world including India, romosozumab was given in four doses, i.e.,70 mg, 140 mg, or 210 mg or placebo subcutaneously on day 1 and at 2, 6, and 12 weeks. The primary aim was to assess functional healing over weeks 6–20 for the romosozumab and placebo groups. The results were not encouraging for fracture healing; hence, for this condition, the trial was discontinued.[23]

## Phase III trials

Three significant trials have been discussed in detail.

### *Fracture study in postmenopausal women with osteoporosis[29]*

The clinical trial Fracture study in postmenopausal women with osteoporosis was a randomized, double-blind trial involving 7180 ambulatory postmenopausal women aged between 55 and 90 years with a T score of –2.5 to –3.5 at the femoral neck, who monthly received either romosozumab 210 mg subcutaneously or placebo for 12 months, followed by an open-label therapy for another 12 months with denosumab 60 mg given every 6 months for 12 months. The primary outcome was to observe for 12 months the incidence of vertebral fracture, which was later modified to the percentage of participants with a new vertebral fracture through months 12 and 24. At 12 months, the risk of new vertebral fractures was decreased by 73% (the incidence of vertebral fractures was 0.5% and 1.8% in the groups receiving romosozumab and placebo, respectively $P<0.001$). Most fractures in the romosozumab group occurred in the first 6 months of treatment. Clinical fractures were also reduced by 36% at 1 year in the romosozumab group relative to the placebo; fracture incidence was 2.5% and 1.6% in the placebo and romosozumab groups, respectively ($P = 0.008$). The incidence of nonvertebral fractures was similar to the placebo group ($P = 0.10$). Moreover, at 2 years, the incidence of vertebral fractures was significantly less in the group, which initially received romosozumab (0.6%) than the placebo group (2.5%) ($P < 0.001$). BMD started increasing by 6 months, and at 1 year, the difference from baseline in BMD was more in the romosozumab group compared to the placebo ($P < 0.001$). The rise in BMD was noticed in the following order lumbar spine >total hip >femoral neck, i.e., 13.3%, 6.9%, and 5.9%, respectively, compared to the placebo. BMD was found to significantly increase further between 12 and 24 months after the transition into denosumab compared to placebo ($P < 0.001$). The level of P1NP increased initially; however, it returned to the starting value at 9 months. At 12 months, bone resorption maker β-CTX level remained below compared to the placebo. The all-cause mortality rate was 0.7% and 0.8%in the placebo and romosozumab groups, respectively. The incidence of adverse events was 8.3% and 9.1% in the placebo and romosozumab groups, respectively, while the injection site reactions were more common in the romosozumab group than the placebo (5.2% vs. 2.9%). The most common adverse effects reported with romosozumab (>10% than placebo) were arthralgia and nasopharyngitis, and arthralgia was the most common cause of discontinuation of romosozumab. Serious adverse events reported during the trial were 9.6% and 8.7% in the romosozumab and placebo groups, respectively. Adjudicated serious cardiovascular events were relatively more common in romosozumab than placebo (1.2% vs. 1.1%). Other adverse events that were less common but are of clinical interest in the romosozumab group were atypical femoral fracture (one case), osteonecrosis of the jaw (two cases), and hypocalcemia (one case).

### *Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk[31]*

The clinical trial Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) was a double-blind, randomized trial involving 4093 postmenopausal women with osteoporosis and fragility fracture, which was conducted in 270 centers in 41 countries. Women who were mobile and 55–90 years of age and fulfill ≥1 of the below-mentioned criteria, i.e., T-score of ≤ −2.5 at the femoral neck or complete hip, ≥1 moderate or severe vertebral fractures, ≥2 mild vertebral fractures, ≤−2 at the femoral neck or total hip either ≥2 vertebral fractures (moderate/severe), or a proximal femur fracture encountered before randomization (3–24 months), were included in the trial. The primary endpoints were incidence of clinical fracture or new vertebral fracture in 24 months, later modified to the percentage of participants with a new vertebral fracture in 24 months, and percentage of patients with a clinical fracture at primary analysis after completing

month 24 visit. The patients were allotted randomly in a ratio of 1:1 and received romosozumab (210 mg once monthly subcutaneous) or weekly oral alendronate (70 mg) for 12 months, followed by alendronate in both the groups. At 24 months, the risk of new vertebral fractures was decreased by 48% ($P < 0.001$) in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group. The incidence of clinical fractures was also reduced by 27% in the romosozumab-to-alendronate group ($P < 0.001$). Nonvertebral fractures and hip fractures were reduced by 19% and 38%, respectively, in the romosozumab-to-alendronate group ($P = 0.04$ and 0.02, respectively). The combination of romosozumab for the first 12 months, followed by subsequent administration of alendronate, led to a reduced risk of fracture as compared to alendronate alone in postmenopausal females with osteoporosis and with high risk for fracture. The occurrence of serious adverse events at the end of the double-blind period, i.e., 12 months, was 1.8% and 12.8% in the alendronate and romosozumab groups, respectively. The most usual adverse reactions noted were nasopharyngitis and back pain, while injection site reactions were more common in the romosozumab group (4.4% vs. 2.6%). The incidence of adjudicated cardiovascular adverse events was more in the romosozumab group as compared to the alendronate group (2.5% vs. 1.9%). The adverse cardiovascular events in the romosozumab and alendronate groups, respectively, were cardiac ischemic events (0.8% vs. 0.3%), cerebrovascular event (0.8% vs. 0.3%), death (0.8% vs. 0.6%), and heart failure (0.2% vs. 0.4%). At the end of the double-blind period, osteonecrosis of the jaw and atypical femoral fracture were not observed in either group, however, after the open-label period, these were observed in both the groups. The study ARCH has certainly seemed superior to the previous one as it involved an active comparator. Both the trials are compared in Table 2.

### *BRIDGE*[32]

This Phase III double-blind, placebo-controlled trial assessed the efficacy of romosozumab in men with osteoporosis. A total of 245 men who were 55–90 years old with BMD, T-score ≤−2.5 at lumbar spine, femoral neck, or total hip or T-score ≤−1.5 with history of fragility fracture (vertebral/nonvertebral) were included in the study. The primary endpoint was the mean change in BMD from baseline to endpoint. The romosozumab group showed a greater increase in mean BMD

**Table 2: Characteristics of important Phase III clinical trials of romosozumab**

| Characteristics | FRAME NCT01575834[29] | ARCH NCT01631214[31] |
|---|---|---|
| Condition | Postmenopausal women with T-score of 2.5-3.5 | Postmenopausal osteoporosis |
| Age (years, mean±SD) | RMZ: 70.9±7.0 | RMZ: 74.4±7.5 |
| | PLA: 70.8±6.9 | ALD: 74.2±7.5 |
| Intervention | RMZ: 210(mg) QM, SC / PLA for 12 months followed by denosumab 60(mg) SC Q6M for next 12 months | RMZ: 210 (mg) QM SC injections and ALD 70 (mg) once a week (oral) for 12 months, followed by alendronate for at least another 12 months in both groups |
| Number of participants | RMZ: 3589 | RMZ: 2046 |
| | PLA: 3591 | ALD: 2047 |
| Time frame (months) | 24 | 24 |
| Endpoints | Incidences of | Cumulative incidences of |
| | New vertebral fractures | New vertebral fractures |
| | Clinical fractures | Clinical fractures |
| | Nonvertebral fractures (at 12 months and at 24 months) | Nonvertebral fractures (at 24 months) |
| Results | At 12 months, incidences of | At 24 months, incidences of |
| | New vertebral fractures | New vertebral fractures |
| | RMZ: 0.5% | RMZ: 6.2% |
| | PLA: 1.8% | ALD: 11.9% |
| | Clinical fractures | Clinical fractures |
| | RMZ: 1.6% | RMZ: 9.7% |
| | PLA: 2.5% | ALD: 13% |
| | Nonvertebral fractures | Nonvertebral fractures |
| | RMZ: 1.6% | RMZ: 8.7% |
| | PLA: 2.1% | ALD: 10.6% |
| Most common adverse events | Arthralgia | Back pain |
| | RMZ: 13% | RMZ: 9.1% |
| | PLA: 12% | ALD: 11.3% |
| | Nasopharyngitis | Nasopharyngitis |
| | RMZ: 12.8% | RMZ: 10.4% |
| | PLA: 12.2% | ALD: 10.8% |

ARCH: Active-controlled fracture study in postmenopausal women with osteoporosis at high risk. FRAME: Fracture study in postmenopausal women with osteoporosis. SC: Subcutaneous, QM: Once monthly, Q3M: Once in 3 months, Q6M: Once in 6 months, RMZ: Romosozumab, PLA: Placebo, ALD: Alendronate

at 12 months as compared to the placebo at lumbar spine (12.1% vs. 1.2%, $P < 0.001$), femoral neck (2.2% vs. −2%, $P < 0.001$), and total hip (2.5% vs. −0.5%, $P < 0.001$). The significant increase in BMD was evident as early as 6 months at all three sites. Injection site reactions had more incidences in the romosozumab group (5.5% vs. 3.7%). The incidence of serious adverse events was more in the romosozumab group compared to the placebo (12.9% vs. 12.3%). Adjudicated serious cardiac adverse effects were higher in the romosozumab group compared to the placebo (4.9% vs. 2.5%) including cardiac ischemia (1.8% vs. 0%) and cerebrovascular events (1.8% vs. 1.2%). Hypocalcemia, atypical fracture of the femur, and osteonecrosis of the jaw were not reported.

## Contraindications and Precautions

Romosozumab must not be given to patients with a history of myocardial infarction or stroke in the previous 12 months, and it must be stopped if the patient encounters any of such incidents during treatment.[34] The drug must be avoided in case of hypocalcemia or with a history of hypersensitivity. Atypical subtrochanteric fracture, diaphyseal femoral fracture, and osteonecrosis of the jaw have been reported in the clinical trials, and these adverse effects should always be kept in mind while prescribing this drug, as well as the patients should be educated about the same. On the one hand, the drug proves to be advantageous, as no dose adjustment is required if patients have renal impairment, and on the other hand, its use is still not recommended in pregnant or lactating women and the pediatric population.[13]

## Conclusion

Romosozumab was approved on April 9, 2019, for the treatment of osteoporosis in postmenopausal women at a considerable fracture risk. Its availability in the market will fulfill the unmet need of those drugs which stimulate bone formation as well as retard bone resorption simultaneously. However, once the drug gets marketed, it will become due responsibility of the manufacturer as well as the vigilance program of respective countries, to keep this drug under surveillance for any undiscovered effects. Because of the adverse effect profile, which is yet to be discovered, and the black box warning issued to this drug, its use should be cautious and under supervision.

## Take-Home Message

1. This novel anti-sclerostin monoclonal antibody, romosozumab, promotes bone formation which leads to a rapid and persistent increase in BMD.
2. Romosozumab prevents vertebral, clinical, and nonvertebral fractures.
3. It is possibly superior to alendronate; however, more studies are required to strengthen the finding.
4. A black box warning issued regarding its use in cardiac patients gives a dent to its reputation.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

1. Tian L, Yang R, Wei L, Liu J, Yang Y, Shao F, *et al*. Prevalence of osteoporosis and related lifestyle and metabolic factors of postmenopausal women and elderly men: A cross-sectional study in Gansu province, Northwestern of China. Medicine (Baltimore) 2017;96:e8294.
2. Sozen T, Ozsik L, Basaran NC. An overview and management of osteoporosis. Enr J Rheumatol 2017;4:46-56.
3. Mithal A, Bansal B, Kyer CS, Ebeling P. The Asia-pacific regional audit-epidemiology, costs, and burden of osteoporosis in India 2013: A report of international osteoporosis foundation. Indian J Endocrinol Metab 2014;18:449-54.
4. Khadilkar AV, MAndik RM. Epidemiology and treatment of osteoporosis in women: An Indian perspective. Int J Womens Health 2015;7:841-50.
5. Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. Chronic Dis Transl Med 2015;1:9-13.
6. Tu KN, Lie JD, Wan CK, Cameron M, Austel AG, Nguyen JK, *et al*. Osteoporosis: A review of treatment options. P T 2018;43:92-104.
7. Ramchand SK, Seeman E. Advances and unmet needs in the therapeutics of bone fragility. Front Endocrinol (Lausanne) 2018;9:505.
8. Black DM, Geiger EJ, Eastell R, Vittinghoff E, Li BH, Ryan DS, *et al*. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. N Engl J Med 2020;383:743-53.
9. Kaur U, Chakrabarti SS, Gambhir IS. Zoledronate induced hypocalcemia and hypophosphatemia in osteoporosis: A cause of concern. Curr Drug Safety 2016;11:267-69.
10. van Lierop AH, Appelman-Dijkstra NM, Papapoulos SE. Sclerostin deficiency in humans. Bone 2017;96:51-62.
11. Joiner DM, Ke J, Zhong Z, Xu HE, Williams BO. LRP5 and LRP6 in development and disease. Trends Endocrinol Metab 2013;24:31-9.
12. Ishibashi H, Crittenden DB, Miyauchi A, Libanati C, Maddox J, Fan M, *et al*. Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study. Bone 2017;103:209-15.
13. Highlights of Prescribing Information (romosozumab). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761062s000lbl.pdf. [Last accessed on 2020 Jan 10].
14. Ominsky MS, Boyd SK, Varela A, Jolette J, Felx M, Doyle N, *et al*. Romosozumab improves bone mass and strength while maintaining bone quality in ovariectomized cynomolgus monkeys. J Bone Miner Res 2017;32:788-801.
15. Ominsky MS, Boyce RW, Li X, Ke HZ. Effects of sclerostin antibodies in animal models of osteoporosis. Bone 2017;96:63-75.
16. Chouinard L, Felx M, Mellal N, Varela A, Mann P, Jolette J, *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;81:212-22.
17. Padhi D, Allison M, Kivitz AJ, Gutierrez MJ, Stouch B, Wang C, *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;54:168-78.
18. A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Effect of AMG 785 on Parameters of Bone Quality of the Forearm Using pQCT in Postmenopausal Women With Low Bone Mineral Density. Available from: https://clinicaltrials.gov/ct2/show/NCT00950950. [Last accessed on 2020 Jan 10].
19. Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. J Bone Miner Res 2011;26:19-26.
20. A Randomized, Double-Blind, Placebo-Controlled, Single-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG785 in Healthy Postmenopausal Japanese Women. Available from: https://clinicaltrials.gov/ct2/show/

NCT01101061. [Last accessed on 2020 Jan 12].
21. A Phase 1, Open-Label, Single-Dose Study of Romosozumab (AMG 785) Administered Subcutaneously to Healthy Subjects and Subjects With Stage 4 RenalImpairment or Stage 5 Renal Impairment Requiring Hemodialysis. Available from: https://clinicaltrials.gov/ct2/show/NCT01833754. [Last accessed on 2019 Oct 10].
22. An Open-label, Randomized Study to Estimate the Percent Change From Baseline in Lumbar Spine Bone Mineral Density After 3 Months of AMG 785Administration in Postmenopausal Women With Low Bone Mineral Density Previously Treated with Alendronate. Available from: https://clinicaltrials.gov/ct2/show/NCT01588509. [Last accessed on 2020 Jan 12].
23. A Multi-center, Randomized, Double-blind, Placebo-controlled Study to Determine the Efficacy, Safety, and Tolerability of AMG 785 in Adults With a Fresh Unilateral Hip Fracture, Status Post Surgical Fixation. Available from: https://clinicaltrials.gov/ct2/show/NCT01081678. [Last accessed on 2020 Jan 10].
24. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, *et al*. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 2014;370:412-20.
25. A Multi-center, Randomized, Double Blind, Placebo-Controlled Study of AMG 785 in Skeletally Mature Adults with a Fresh Unilateral Tibial Diaphyseal Fracture Status Post Definitive Fracture Fixation with an Intramedullary Nail. Available from: https://clinicaltrials.gov/ct2/show/NCT00907296. [Last accessed on 2020 Jan 15].
26. A Randomized, Double-Blind, Placebo-Controlled, Multi-Dose Phase 2 Study to Evaluate the Efficacy, Safety and Tolerability of Romosozumab in the Treatment of Japanese Women with Postmenopausal Osteoporosis. Available from: https://clinicaltrials.gov/ct2/show/NCT01992159. [Last accessed on 2020 Jan 15].
27. A Randomized, Multicenter, Open-label, Parallel Group Study in Postmenopausal Women with Osteoporosis to Evaluate the Noninferiority of Subject Administered Romosozumab Via Autoinjector/Pen vs. healthcare Provider-Administered Romosozumab Via Prefilled Syringe. Available from: https://clinicaltrials.gov/ct2/show/NCT03432533. [Last accessed on 2020 Jan 15].
28. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, *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;390:1585-94.
29. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, *et al*. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375:1532-43.
30. A Multicenter, Randomized, Multiple-dose Phase 3 Study to Evaluate the Non-Inferiority of Romosozumab at a 90 mg/mL Concentration Compared with a 70mg/mL Concentration in Postmenopausal Women with Osteoporosis. Available from: https://clinicaltrials.gov/ct2/show/NCT02016716. [Last accessed on 2020 Jan 15].
31. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, *et al*. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417-27.
32. Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD, *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;103:3183-93.
33. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Study to Compare the Efficacy and Safety of Romosozumab with Placebo in PostmenopausalSouth Korean Women With Osteoporosis. Available from: https://clinicaltrials.gov/ct2/show/NCT02791516. [Last accessed on 2020 Jan 15].
34. FDA Approves Romosozumab for Fracture Prevention in Osteoporosis. Available from: https://rheumatology.medicinematters.com/osteoporosis/romosozumab/fda-approves-romosozumab-for-fracture-prevention-in-osteoporosis/16649130. [Last accessed on 2020 Jan 25].

**Annexure 1: Details of various clinical trials of romosozumab**

| Condition | Intervention | Phase | Number of participants | Randomized/ masking | Time frame for primary outcome measure | Country | Clinical trial identifier |
|---|---|---|---|---|---|---|---|
| Postmenopausal osteopenia | AMG 785: 1 mg/kg SC every 2 weeks, 6 doses<br>AMG 785: 3 mg/kg every 4 weeks, 3 doses<br>AMG 785: 2 mg/kg every 2 weeks, 6 doses<br>AMG 785: 2 mg/kg every 4 weeks, 3 doses | I | 48 | Yes/double | Up to day 169 | N/A | NCT01825785[17] |
| Osteopenia | AMG 785: 3 mg/kg or placebo SC of every 4 weeks for 3 months | I | 24 | Yes/double | Up to day 169 | N/A | NCT00950950[18] |
| Osteopenia | Women: One dose of AMG 785: 0.1, 0.3, 1, 3, 5, or 10 mg/kg SC or 1 or 5 mg/kg IV or placebo SC or IV<br>Men: One dose of AMG 785: 1 or 5 mg/kg SC or IV or placebo | I | 74 | Yes/double | Up to day 85 | N/A | NCT01059435[19] |
| Osteopenia | AMG 785: Single dose of 1 mg/kg, 3 mg/kg, or 5 mg/kg or placebo<br>Non-Japanese women: 3 mg/kg | I | 31 | Yes/double | Up to day 85 | N/A | NCT01101061[20] |
| Osteoporosis healthy participants and patients with Stage 4 and 5 renal impairment | Romosozumab<br>Single dose: 210 mg S/C. Three arms of participants. Each received the same dose | I | 24 | No/none | Up to day 85 | United States | NCT01833754[21] |
| Osteoporosis | AMG 785: Two doses 140 mg and 210 mg SC once a month for 3 months | I | 60 | No/none | Baseline and day 85 | United States | NCT01588509[22] |
| Fracture healing | | II | 332 | Yes/quadruple | Week 6, 12, 16, 20 | Europe, India, North America, Latin America, Australia, New Zealand, Hong Kong | NCT01081678[23] |
| Low BMD Postmenopausal osteoporosis | Romosozumab: 70 mg QM, 140 mg QM, or 210 mg Q3M. Alendronate: 70 mg once a week<br>Denosumab: 60 mg SC Q6M. Teriparatide: 20 mcg QD for 12 months<br>Zoledronic acid 5 mg IV annually | II | 419 | Yes/quadruple | 12 months | Europe, North America, Argentina | NCT00896532[24] |
| Fracture healing | Romosozumab: Two, three, or four doses of 70 mg, 140 mg, or 210 mg or four doses of placebo, SC on day 1 and at 2, 6, and 12 weeks | II | 402 | Yes/quadruple | 52 weeks | 66 centers in Europe, India, North America, Australia, New Zealand, Hong Kong, Mexico | NCT00907296[25] |
| Postmenopausal osteoporosis | Romosozumab: 70, 140, and 210 mg QM or placebo SC for 12 months | II | 252 | Yes/quadruple | 12 months | Japan | NCT01992159[26] |
| Postmenopausal osteoporosis | Romosozumab 210 mg SC, QM either by HCP or self-administration | III | 260 | Yes/none | 6 months | Poland, United Kingdom, United States | NCT03432533[27] |
| Postmenopausal osteoporosis | Romosozumab 210 mg, SC, QM, or teriparatide 20 mcg/day SC for 12 months | III | 436 | Yes/none | 12 months | Europe, North America, Latin America | NCT01796301[28] |

*Contd...*

**Annexure 1: Contd...**

| Condition | Intervention | Phase | Number of participants | Randomized/ masking | Time frame for primary outcome measure | Country | Clinical trial identifier |
|---|---|---|---|---|---|---|---|
| Postmenopausal osteoporosis | Romosozumab 210 mg QM SC injections and placebo alendronate 70 mg once a week (oral) for 12 months followed by alendronate (oral) for at least another 12 months (until end of study)<br>Oral alendronate and placebo AMG 785 subcutaneous injections for 12 months, followed by open-label alendronate (oral) for at least another 12 months (until end of study) | III | 4093 | Yes/quadruple | 24 months | 270 center countries | NCT01631214[29] |
| Postmenopausal osteoporosis | Romosozumab formulation<br>A 90 mg/ml or B 70 mg/ml or placebo | III | 294 | Yes/double | 6 months | Poland, Czech Republic, US | NCT02016716[30] |
| Postmenopausal osteoporosis | Romosozumab: 210 mg QM, SC or placebo for 12 months, followed by SC denosumab 60 mg SC, Q6M for 24 months | III | 7180 | Yes/quadruple | 12 months | Europe, North America, Latin America, Japan, Asia, Australia, New Zealand | NCT01575834[31] |
| Osteoporosis in men | Romosozumab: 210 mg monthly SC injection of or placebo for 12 months | III | 245 | Yes/triple | 12 months | Europe, North America, Latin America, Japan | NCT02186171[32] |
| Postmenopausal osteoporosis | Romosozumab and placebo: QM for 6 months. Dose: Not mentioned | III | 67 | Yes/triple | 6 months | South Korea | NCT02791516[33] |

SC: Subcutaneous, QM: Once monthly, Q3M: Once in 3 months, Q6M: Once in 6 months, HCP: Health care provider