Pharmacological Therapy of Osteoporosis: What's New?

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Abstract: Osteoporosis and fragility fractures are relevant health issues because of their impact in terms of morbidity, mortality, and socioeconomic burden. Despite this alarming scenario, both underdiagnosis and undertreatment are common features of osteoporotic patients, particularly those who have already sustained a fragility fracture. Pharmacotherapy of osteoporosis is the main treatment option for these patients because of strong evidence about the efficacy of available drugs targeting bone metabolism. However, several issues can interfere with the effectiveness of anti-osteoporotic drugs in clinical practice, such as lack of awareness of both healthcare providers and patients, poor adherence to therapy, and safety in long-term treatment. Therefore, new therapeutic strategies have been proposed to overcome these problems, such as sequential therapy or emerging molecules mainly targeting the stimulation of bone formation. In particular, abaloparatide has been demonstrated to reduce major nonvertebral fracture risk compared with both placebo and teriparatide, although the European Medicines Agency (EMA) refused the marketing authorization because the benefits of this drug did not outweigh its risks. On the other side, EMA has recently approved romosozumab, a monoclonal antibody directed against sclerostin and the only available therapeutic option targeting Wnt signaling, as both bone-forming and antiresorptive intervention to treat osteoporosis and fragility fractures.

Keywords: osteoporosis, sequential therapy, antiresorptive drugs, bone anabolic drugs, abaloparatide, romosozumab

Introduction

In the last decades, the healthcare demand in developed countries has progressively increased along with the aging of the population. Osteoporosis is one of the main health problems, considering that fragility fractures result in significant increases in morbidity, mortality, as well as socioeconomic burden. In particular, osteoporosis affects about 18.5% and 10% of Italian women and men, respectively, and an annual incidence of over 400,000 fragility fractures has been estimated.¹ Moreover, the prevalence of osteoporosis in the Italian population is expected to increase by 25% in the next decades. Fragility fractures are a serious obstacle to healthy aging, compromising the independence and quality of life in the affected patients. Considering hip fractures only, over 500,000 elderly patients experienced these devastating traumas, leading to an increased hospitalization rate up to about 30% in Italy in a 6-year period.²

In Europe, osteoporotic fractures are the fourth leading cause of morbidity associated with chronic diseases, annually contributing to over 2.6 million disability-adjusted life years (DALYs) that is more than hypertensive heart disease and

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rheumatoid arthritis.³ In Italy, the loss of DALYs due to fragility fractures is estimated as higher than that associated with other chronic diseases, including stroke and chronic obstructive pulmonary disease (COPD).⁴ Moreover, the hospital costs of hip fragility fractures are comparable to or even higher than those reported for major cardiovascular diseases (strokes and acute myocardial infarctions, AMIs).⁵

Despite the relevance of these epidemiological data, along with the massive costs borne by the National Health Systems, underdiagnosis, and, above all, undertreatment remain two main issues in the field of osteoporosis management, particularly in the secondary prevention care. This last issue represents the leading target of several national and international initiatives aiming to increase knowledge about the appropriate approach to osteoporosis, particularly regarding the effectiveness of anti-osteoporotic drugs in preventing new fragility fractures.

Pharmacological therapy is the mainstay of interventions for patients with osteoporotic fractures. Indeed, commercially available anti-osteoporotic drugs are supported by substantial evidence of efficacy as well as a favorable safety profile. In particular, the number needed to treat (NNT) of bisphosphonates (BPs) for secondary prevention of low-trauma fracture is significantly lower (NNT 10) than that reported for statins in preventing major cardiovascular events (NNT 56).⁶

Despite strong evidence supporting anti-osteoporotic drugs for preventing fractures, several issues can interfere with their effectiveness in clinical practice.³

Bisphosphonates, most commonly used for osteoporosis treatment, can increase matrix mineralization and bone density up to a certain point, but they cannot restore lost structure or substantially improve bone micro-architecture, other than by the closing of resorption pits, giving their inability to stimulate osteoblast activity.⁷ Moreover, compliance and persistence to BP therapy are generally poor.⁸

Denosumab is an advancement in antiresorptive therapy especially for enhancing adherence and persistence to treatment⁹ as well as for a putative stimulation of osteoblastic activity in specific areas of cortical bone,¹⁰ as evidenced by animal studies, but not yet confirmed in humans.¹¹

Furthermore, the suppression of bone turnover caused by antiresorptive drugs may explain osteonecrosis of the jaw and atypical femoral fractures which can be observed in patients with high-dose or long-term treatment.

Teriparatide, the most commonly used bone anabolic drug, stimulates bone formation before it enhances bone resorption, generating a period when it is maximally anabolic

(anabolic window), thus limiting further accrual of bone mass.¹² Novel routes of administration of this drug, such as oral, transdermal, and intranasal formulations, have been proposed and investigated in both animal models and humans, demonstrating to be effective and more tolerable than subcutaneous injections, and might potentially improve compliance to anabolic therapy.¹³ The availability of new formulations might be an additional factor for improving adherence and persistence to anti-osteoporosis therapy, also considering some limitations in the reliability of diagnostic tools to monitor the treatment response, such as the bone turnover markers (BTMs). Indeed, although BTMs might be useful in this context, their dosage is not justified for routine clinical evaluation.¹²

Furthermore, new therapeutic solutions have been proposed, such as the use of already available drugs in succession (sequential therapy) or new molecules mainly targeting the stimulation of bone formation (rather than decreasing bone resorption), therefore improving bone mass, structure, and ultimately skeletal strength.

Sequential Therapies

The therapeutic strategy of using anti-osteoporotic drugs with different mechanisms of action in a sequential administration mode based on the physiology of bone turnover has been proposed some time ago. A first attempt was made using cyclic administration of etidronate (the first studied BP) for 2 weeks followed by 76 days of calcium and vitamin D supplementation, in order to simulate the periods of osteoclast and osteoblast activity, respectively, within bone remodeling units, thus avoiding osteomalacia.¹⁴

In a modern view of the pharmacotherapy of osteoporosis, three combinations of drugs with predominantly antiresorptive properties with agents with prevailing anabolic activity can be proposed: 1) antiresorptive therapy first followed by an anabolic drug; 2) anabolic therapy first followed by an antiresorptive drug; or 3) co-administration of both antiresorptive and anabolic agents.

The first option is more frequently adopted in clinical practice because of supporting indications and costs. In particular, teriparatide use follows prolonged BP therapy that is often discontinued because of adverse events or the occurrence of a new fragility fracture. Patients receiving this treatment regimen usually experience a relevant reduction in bone turnover that blunts or delays the anabolic response to teriparatide and the consequent potential increase of bone mineral density (BMD).

Therefore, in the context of a positive sequential pattern of bone turnover modulation it would be advisable to start treatment with teriparatide followed by an antiresorptive drug (BPs or denosumab), although this therapeutic strategy undoubtedly goes against what is established by the regulatory bodies.¹⁵

In a pre-planned 2-year extension of a randomized controlled trial (RCT),¹⁶ it was demonstrated that patients switching from teriparatide to denosumab continued to report an increase of BMD mainly in the hip region, while those switching from denosumab to teriparatide reported bone loss. According to the available evidence, this therapeutic strategy seems to be the most effective for fracture prevention in osteoporotic patients.

On the other hand, simultaneous administration of a BP (alendronate) and teriparatide did not show a greater benefit over the single administration of these drugs,^{17,18} whereas the simultaneous administration of zoledronate and teriparatide led to a greater increase of hip BMD compared to that obtained with the administration of teriparatide or zoledronate alone.¹⁹ Moreover, the combined use of denosumab and teriparatide over a 2-year period significantly increases the BMD at both lumbar spine and femoral neck more than can be obtained with the single administration of both drugs.^{20,21} A possible explanation for these findings could be identified in the ability of denosumab to counteract the undeniable increase in bone resorption observed with teriparatide use, thus expanding the anabolic window and consequently enhancing the gain in bone density.

New Anabolic Drugs: Abaloparatide

Abaloparatide is a synthetic analog of a parathyroid hormone-related peptide (PTHrP) approved by the Food and Drug Administration (FDA) for clinical use in 2017.²² This drug binds to the same receptor of teriparatide, an agonist of PTH type 1 receptor (PTH1R).²³ This latter is a G-protein coupled receptor that acts with two different conformations: R° and RG.^{22,23} Pre-clinical studies showed that abaloparatide, bound with the same affinity to the RG conformation, but 80-fold weaker to the R° conformation than teriparatide.^{23,24} The strong binding affinity to the RG conformation results in a shorter increase in intracellular cAMP levels and higher anabolic activity of osteoblasts. It was hypothesized that this different mechanism of action may be responsible for the enhanced anabolic effect of abaloparatide.²⁵ Indeed, its use is associated with a lower magnitude of bone remodeling and eroded bone surface^{26–28}

thus reducing the early increase of intracortical remodeling and cortical porosity observed during PTH or teriparatide administration.²⁶

In the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) phase III randomized control study, the authors observed that abaloparatide was able to reduce both vertebral (compared with placebo) and major nonvertebral (compared with both placebo and teriparatide) fracture risk.²⁸ Regarding the safety profile, common adverse events associated with abaloparatide use were back pain, arthralgia, upper respiratory infections, hypercalciuria, nausea, and dizziness.²⁸ Palpitations were also reported,²⁸ leading the European Medicines Agency (EMA) to refuse the marketing authorization because the benefits of this drug did not outweigh its risks.²⁹

Furthermore, although findings about fracture prevention are encouraging, the assertion that abaloparatide is more effective than teriparatide in reducing fracture risk seems somewhat questionable. In fact, a large number of patients reporting a fragility fracture in the placebo and teriparatide groups sustained the traumatic event during the first few weeks of treatment^{28,30} and the differences in fracture rates between the two treatment arms were minimal at 12 and 18 months.^{9,30,31} Moreover, the observations of both enhanced anabolic effect and lower bone resorption with abaloparatide use compared to teriparatide therapy have also been questioned.³¹

New Anabolic Drugs Targeting Wnt Signaling

A recent therapeutic option for the treatment of osteoporosis is the manipulation of the canonical Wnt pathway that is activated by the binding of a Wnt-protein ligand to a Frizzled family receptor which in turn mediates signal transduction in osteoblasts enhancing gene transcription.³²

Sclerostin, a glycoprotein secreted by osteocytes and encoded by the SOST gene [17q12-q21],³³ binds to the LRP-5/6 co-receptors, preventing the interactions between Wnt and its receptor, and thus causing phosphorylation and degradation of β -catenin.³⁴ In this way the Wnt target genes are not activated, consequently inhibiting osteoblast proliferation, differentiation, and function. Furthermore, sclerostin can increase RANKL-mediated osteoclast formation and activation.

The identification of genetic diseases due to impaired sclerostin expression and function, such as van Buchem disease and sclerosteosis,³⁵ characterized by a high bone

mass phenotype, has stimulated research for monoclonal antibodies directed against this protein with the aim of introducing an innovative therapeutic strategy for osteoporosis.

The pharmaceutical industry has recently developed three monoclonal antibodies against sclerostin: blosozumab (LY251546), setrusumab (BPS804), and romosozumab (AMG-785).

In a randomized, double-blind phase 2 clinical trial versus placebo including postmenopausal women with low BMD, blosozumab (180 mg every 4 weeks, Q4W, 180 mg every 2 weeks, Q2W, or 270 mg Q2W) demonstrated significant dose-related improvements of BMD at both lumbar spine and total hip after 1 year of treatment.³⁶ After 1-year of treatment discontinuation, the same population was investigated for BMD changes and incidence of delayed adverse events.³⁷ The authors reported that the BMD of the lumbar spine remained significantly greater than placebo in women treated with blosozumab at a dose of both 270 mg and 180 mg Q2W, and no adverse events occurred.

Pharmacodynamics and safety of setrusumab were investigated in a randomized phase 2a trial including adults with moderate osteogenesis imperfecta (OI) during 21 weeks of treatment at three escalating doses administered by intravenous infusions Q2W. In the 14 treated patients, P1NP, P1CP, BSAP, and OC increased by 84% ($p < 0.001$), 53% ($p = 0.003$), 59% ($p < 0.001$), and 44% ($p = 0.012$), respectively, with a reduction of CTX-1 by 44%.³⁸ Moreover, this neutralizing, anti-sclerostin antibody increased BMD of the lumbar spine by 4%, with a good safety profile as well as no treatment-related fractures. Setrusumab received the orphan drug designation for OI treatment from both the FDA and the EMA in 2016, and was also accepted into the EMA's Adaptive Pathways program and granted the PRiority Medicines (PRIME) designation.³⁹

Romosozumab is the first agent of its class to have completed phase III studies at a recommended dose of 210 mg subcutaneous injection monthly. Previously, experimental studies on rats and ovariectomized primates treated with romosozumab had shown significant increases in bone mass and strength, and phase 2 trials also demonstrated the efficacy and safety of different romosozumab dosages compared to placebo, alendronate, or teriparatide in postmenopausal osteoporotic women.

The efficacy of romosozumab in enhancing bone formation and preventing fragility fractures was assessed in several RCTs.⁴⁰

In the FRAME (Fracture Study in Postmenopausal Women with Osteoporosis, NCT01575834) trial,⁴¹

postmenopausal women with osteoporosis were randomly assigned to romosozumab subcutaneous injections (210 mg) or placebo monthly for 1 year; thereafter, patients in each group received denosumab (60 mg Q6M) in the 2nd year. After the first 12 months, the intervention group showed an incidence of vertebral fractures of 0.5% versus 1.8% in the placebo group (−73%), while a nonsignificant between-group difference was reported for nonvertebral fractures (1.6% in the romosozumab group vs 2.1% in the placebo group). At 24 months, the significantly lower incidence of vertebral fractures in women previously treated with romosozumab vs placebo group was confirmed (−75%). Adverse events reported in the FRAME trial include hyperostosis, cardiovascular events, osteoarthritis, and cancer, without a significant difference between romosozumab and placebo groups. On the other side, in the romosozumab group were reported one atypical femoral fracture and two cases of osteonecrosis of the jaw.

The ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk, NCT01631214) trial,⁴² including over 4000 women with a fragility fracture, compared the efficacy in terms of fracture risk reduction of 1-year treatment with subcutaneous injections of romosozumab (210 mg monthly) vs placebo, followed by 12 months of oral alendronate administration (70 mg weekly) in both groups. Considering the primary endpoints, the authors reported a significantly lower risk of incident vertebral fractures and clinical fractures (nonvertebral and symptomatic vertebral fracture) at 2-year follow-up (−48% and −27%, respectively) in romosozumab groups versus placebo. Moreover, women receiving romosozumab reported a significantly lower risk of hip fracture (−38%). On the other hand, during the first year of treatment, a higher percentage of serious cardiovascular adverse events were reported in the intervention group vs the alendronate group (2.5% vs 1.9%).

In the international multicenter STRUCTURE study (STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopausal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy), romosozumab was compared to teriparatide to investigate its efficacy in improving BMD in postmenopausal osteoporosis transitioning from BP treatment.⁴³ STRUCTURE data support superiority of romosozumab in terms of BMD gains of the lumbar spine, total hip, and femoral neck (9.8% vs 5.4%, 2.6% vs −0.6%, and 3.2% vs −0.2%, respectively).

The BRIDGE [A Double-blind Study to Compare the Safety and Efficacy of Romosozumab (AMG 785) Versus Placebo in Men With Osteoporosis, NCT02186171]⁴⁴ trial aimed to assess the efficacy and safety of romosozumab (210 mg subcutaneously monthly for 12 months) versus placebo in male osteoporosis, reporting significantly greater changes in the BMD of the lumbar spine (+10.9%) and total hip (+3%) in the intervention group. Moreover, cardiovascular events were not significantly higher with romosozumab use than placebo (4.9% vs 2.5%).

In the aforementioned trials, safety was generally comparable between groups. Common adverse events observed with romosozumab treatment were arthralgia (13%), nasopharyngitis (12.8%), back pain (10.5%), hypocalcemia (<0.1%), hypersensitivity (6.8%), injection-site reaction (5.2%), hyperostosis (0.5%), osteoarthritis (7.8%), osteonecrosis of the jaw (<0.1%), and atypical femoral fracture (<0.1%). An additional safety concern associated with romosozumab use is the potential tumorigenic effect by stimulating the Wnt pathways, considering that somatic mutations of the Wnt signaling are associated with several tumors.²⁵ Anyway, the risk of malignancy is reduced by the relatively specific expression of sclerostin by bone cells and the short duration of therapy. Moreover, the incidence of cancer in the FRAME study was 1.6% among romosozumab users compared to 1.9% in controls.⁴¹

Another issue of concern is the high incidence of cardiovascular (CV) events in patients treated with romosozumab. The incidence of these events is higher in males than females (4.9% vs 1.2%),^{41,44} and is probably related to a putative role of sclerostin in vascular remodeling and homeostasis.²⁵

Interestingly, approximately 20% of patients treated with romosozumab develop anti-romosozumab antibodies potentially neutralizing its effect.⁴²

Romosozumab use was recently approved in Japan and by the FDA,^{40,45} even if its use is not indicated in patients with a recent history of myocardial infarction or stroke.

Conclusions

Osteoporosis and related fractures are a serious health and social problem due to the high morbidity and mortality in older people. Nowadays it is possible to identify in a precise way the osteoporotic patients at risk of fracture and to treat them in order to prevent both the first and subsequent fragility fractures with drugs that are supported by strong evidence. Nevertheless, in almost all countries, high-risk patients, such as those who have already suffered a fragility fracture, are not properly investigated and almost never treated with

anti-osteoporotic drugs. The introduction of new pharmacological approaches is essential to solve some critical issues in the management of osteoporosis and related fractures, such as compliance and persistence to prolonged treatments, long-term efficacy in reducing the risk of new fractures, and safety.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Tarantino U, Capone A, Planta M, et al. The incidence of hip, forearm, humeral, ankle, and vertebral fragility fractures in Italy: results from a 3-year multicenter study. *Arthritis Res Ther*. 2010;12(6):R226. doi:10.1186/ar3213
2. Piscitelli P, Gimigliano F, Gatto S, et al. Hip fractures in Italy: 2000–2005 extension study. *Osteoporos Int*. 2010;21(8):1323–1330. doi:10.1007/s00198-009-1084-x
3. Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*. 2013;8(1–2):136. doi:10.1007/s11657-013-0136-1
4. Institute for Health Metrics and Evaluation (IHME) (2016) GBD compare data visualization. Available from: <https://vizhub.healthdata.org/gbd-compare/>. Accessed April 23, 2019.
5. Piscitelli P, Iolascon G, Argentiero A, et al. Incidence and costs of hip fractures vs strokes and acute myocardial infarction in Italy: comparative analysis based on national hospitalization records. *Clin Interv Aging*. 2012;7:575–583. doi:10.2147/CIA.S36828
6. Black DM, Kelly MP, Genant HK, et al. Fracture intervention trial steering committee; HORIZON pivotal fracture trial steering committee. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med*. 2010;362(19):1761–1771. doi:10.1056/NEJMoa1001086
7. Pazianas M, van der Geest S, Miller P. Bisphosphonates and bone quality. *Bonekey Rep*. 2014;7(3):529.
8. Iolascon G, Gimigliano F, Moretti A, et al. Rates and reasons for lack of persistence with anti-osteoporotic drugs: analysis of the Campania region database. *Clin Cases Miner Bone Metab*. 2016;13(2):127–130. doi:10.11138/ccmbm/2016.13.2.127
9. Migliaccio S, Francomano D, Romagnoli E, et al. Persistence with denosumab therapy in women affected by osteoporosis with fragility fractures: a multicenter observational real practice study in Italy. *J Endocrinol Invest*. 2017;40(12):1321–1326. doi:10.1007/s40618-017-0701-3
10. Iolascon G, Napolano R, Gioia M, et al. The contribution of cortical and trabecular tissues to bone strength: insights from denosumab studies. *Clin Cases Miner Bone Metab*. 2013;10(1):47–51. doi:10.11138/ccmbm/2013.10.1.047
11. Ominsky M, Libanati C, Niu Q, et al. Sustained modeling-based bone formation during adulthood in cynomolgus monkeys may contribute to continuous BMD gains with denosumab. *J Bone Miner Res*. 2015;30(7):1280–1289. doi:10.1002/jbmr.2480

12. Tarantino U, Iolascon G, Cianferotti L, et al. Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology. *J Orthop Traumatol*. 2017;18(Suppl 1):3–36. doi:10.1007/s10195-017-0474-7
13. Kim KM, Lee SY, Rhee Y. Influence of dosing interval and administration on the bone metabolism, skeletal effects, and clinical efficacy of parathyroid hormone in treating osteoporosis: a narrative review. *JBM R Plus*. 2017;1(1):36–45. doi:10.1002/jbm4.10005
14. Masud T, Mulcahy B, Thompson AV, et al. Effects of cyclical etidronate combined with calcitriol versus cyclical etidronate alone on spine and femoral neck bone mineral density in postmenopausal osteoporotic women. *Ann Rheum Dis*. 1998;57(6):346–349. doi:10.1136/ard.57.6.346
15. Agenzia Italiana del Farmaco. Modifiche alla Nota 79 di cui alla Determinazione del 7 giugno 2011. Available from: http://www.agenziafarmaco.gov.it/sites/default/files/Determinazione_n_589-2015-Modifiche_alla_Nota_79.pdf. Accessed April 27, 2019.
16. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-switch study): extension of a randomised controlled trial. *Lancet*. 2015;386(9999):1147–1155. doi:10.1016/S0140-6736(15)61120-5
17. Black DM, Greenspan SL, Ensrud KE, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med*. 2003;349(13):1207–1215. doi:10.1056/NEJMoa031975
18. Finkelstein JS, Hayes A, Hunzelman JL, et al. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med*. 2003;349(13):1216–1226. doi:10.1056/NEJMoa035725
19. Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1–34)] in postmenopausal osteoporosis. *J Bone Miner Res*. 2011;26(3):503–511. doi:10.1002/jbmr.238
20. Leder BZ, Tsai JN, Uihlein AV, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab*. 2014;99(5):1694–1700. doi:10.1210/jc.2013-4440
21. Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet*. 2013;382(9886):50–56. doi:10.1016/S0140-6736(13)60856-9
22. Chew CK, Clarke BL. Abaloparatide: recombinant human PTHrP (1–34) anabolic therapy for osteoporosis. *Maturitas*. 2017;97:53–60. doi:10.1016/j.maturitas.2016.12.003
23. Russow G, Jahn D, Appelt J, et al. Anabolic therapies in osteoporosis and bone regeneration. *Int J Mol Sci*. 2018;20(1):E83. doi:10.3390/ijms20010083
24. Hattersley G, Dean T, Corbin BA, et al. Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signaling. *Endocrinology*. 2016;157(1):141–149. doi:10.1210/en.2015-1726
25. Canalis E. Management of endocrine disease: novel anabolic treatments for osteoporosis. *Eur J Endocrinol*. 2018;178(2):R33–R44. doi:10.1530/EJE-17-0920
26. Moreira CA, Fitzpatrick LA, Wang Y, et al. Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: the ACTIVE Phase 3 trial. *Bone*. 2017;97:314–319. doi:10.1016/j.bone.2016.11.004
27. Leder BZ, O’dea LS, Zanchetta JR, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2015;100(2):697–706. doi:10.1210/jc.2014-3718
28. Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA*. 2016;316(7):722–733. doi:10.1001/jama.2016.11136
29. Available from: https://www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-eladynos-abaloparatide_en.pdf. Accessed April 27, 2019.
30. Ramchand SK, Seeman E. Advances and unmet needs in the therapeutics of bone fragility. *Front Endocrinol (Lausanne)*. 2018;9:505. doi:10.3389/fendo.2018.00505
31. Martin TJ, Seeman E. Abaloparatide is an anabolic, but does it spare resorption? *J Bone Miner Res*. 2017;32(1):11–16. doi:10.1002/jbmr.3042
32. Gaur T, Lengner CJ, Hovhannisyan H, et al. Canonical WNT signaling promotes osteogenesis by directly stimulating Runx2 gene expression. *J Biol Chem*. 2005;280(39):33132–33140. doi:10.1074/jbc.M500608200
33. Canalis E. Skeletal growth factors. In: Marcus R, Feldman D, Nelson D, Rosen C, editors. *Osteoporosis*. 3rd ed. San Diego: Academic Press; 2007:529–546.
34. Li X, Zhang Y, Kang H, et al. Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. *J Biol Chem*. 2005;280(20):19883–19887. doi:10.1074/jbc.M413274200
35. 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;10:537–543. doi:10.1093/hmg/10.5.537
36. Recker RR, Benson CT, Matsumoto T, et al. A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density. *J Bone Miner Res*. 2015;30(2):216–224. doi:10.1002/jbmr.2351
37. Recknor CP, Recker RR, Benson CT, et al. The effect of discontinuing treatment with blosozumab: follow-up results of a phase 2 randomized clinical trial in postmenopausal women with low bone mineral density. *J Bone Miner Res*. 2015;30(9):1717–1725. doi:10.1002/jbmr.v30.9
38. Glorieux FH, Devogelaer JP, Durigova M, et al. BPS804 anti-sclerostin antibody in adults with moderate osteogenesis imperfecta: results of a randomized phase 2a trial. *J Bone Miner Res*. 2017;32(7):1496–1504. doi:10.1002/jbmr.3143
39. Available from: <https://www.mereobiopharma.com/pipeline/bps-804-setrusumab/>. Accessed April 30, 2019.
40. Markham A. Romosozumab: first global approval. *Drugs*. 2019;79(4):471–476. doi:10.1007/s40265-019-01072-6
41. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532–1543. doi:10.1056/NEJMoa1607948
42. 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. doi:10.1056/NEJMoa1708322
43. 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. doi:10.1016/S0140-6736(17)31613-6
44. 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. doi:10.1210/jc.2017-02163
45. Available from: <https://www.amgen.com/media/news-releases/2019/04/fda-approves-evenity-romosozumabaqg-for-the-treatment-of-osteoporosis-in-postmenopausal-women-at-high-risk-for-fracture/>. Accessed December 11, 2019.

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