

Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update

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Objective: The objective is to provide an update of the 2019 *Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline* for the pharmacological management of osteoporosis in postmenopausal women using romosozumab.

Conclusions: We reviewed findings from the meta-analysis and primary clinical trials assessing the efficacy of romosozumab, a monoclonal antibody targeting sclerostin, for the prevention of fractures and concluded that this agent can be considered a treatment option for postmenopausal women at very high risk for osteoporotic fracture. The romosozumab label has a boxed warning, recommending careful consideration by the treating clinician as to cardiovascular risk profile in the individual woman who might receive this agent, since clinical trial data from an active comparator study show an imbalance in serious cardiovascular adverse events between romosozumab and alendronate. (*J Clin Endocrinol Metab* 105: 587–594, 2020)

Key Words: postmenopausal women, osteoporosis, romosozumab, sclerostin, cardiovascular, guideline

The Guideline Update is a document that permits rapid and focused communication to guideline stakeholders in response to new developments that substantially impact the recommendations of an existing clinical practice guideline (e.g., important new drug approval or withdrawal, important new risks or harms). This Guideline Update is published in response to the recent approval of romosozumab by the United States Food and Drug Administration (FDA), the European Medicines Agency,

Health Canada and other agencies, and it represents a formal amendment to the Endocrine Society's recently published clinical practice guideline regarding the pharmacological management of postmenopausal osteoporosis (1).

The guideline for the management of postmenopausal osteoporosis is designed to provide the clinician with an evidence-based approach to the management of this condition. Several therapeutic options are available for the treatment of osteoporosis, and this framework presents evidence from clinical trials for the efficacy and

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Abbreviations: AFF, atypical femur fractures; ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BMD, bone mineral density; CI, confidence interval; FDA, Food and Drug Administration; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; HR, hazard ratio; MACE, major adverse cardiovascular events; ONJ, osteonecrosis of the jaw; OR, odds ratio; PTH, parathyroid hormone; RR, risk ratio.

LIST OF RECOMMENDATIONS

RECOMMENDATIONS	GRADE
1. Who to Treat	
1.1 We recommend treating postmenopausal women at high risk of fractures, especially those who have experienced a recent fracture, with pharmacological therapies, as the benefits outweigh the risks.	(1 ⊕⊕⊕⊕)
2. Bisphosphonates	
2.1 In postmenopausal women at high risk of fractures, we recommend initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) to reduce fracture risk. Technical remark: Ibandronate is not recommended to reduce nonvertebral or hip fracture risk.	(1 ⊕⊕⊕⊕)
2.2 In postmenopausal women with osteoporosis who are taking bisphosphonates, we recommend that fracture risk be reassessed after 3 to 5 years, and women who remain at high risk of fractures should continue therapy, whereas those who are at low-to-moderate risk of fractures should be considered for a “bisphosphonate holiday.” Technical remark: A bisphosphonate holiday is operationally defined as a temporary discontinuation of bisphosphonate for up to 5 years. This period may be longer depending on the bone mineral density and clinical circumstances of the individual patient. The evidence is stronger for retention of benefits during a holiday for alendronate and zoledronic acid where there are randomized extension trials. A shorter reassessment period of 3 years is more appropriate for annual intravenous zoledronic acid (5 mg) based on evidence from research control trials showing residual effects after 3 years of annual use. Once a bisphosphonate holiday is initiated, reassess fracture risk at 2- to 4-year intervals and consider reinitiating osteoporosis therapy earlier than the 5-year suggested maximum if there is a significant decline in bone mineral density, an intervening fracture, or other factors that alter the clinical risk status.	(1 ⊕⊕⊕⊕)
3. Denosumab	
3.1 In postmenopausal women with osteoporosis who are at high risk for osteoporotic fractures, we recommend using denosumab as an alternative initial treatment. Technical remark: The recommended dosage is 60 mg subcutaneously every 6 months. The effects of denosumab on bone remodeling, reflected in bone turnover markers, reverse after 6 months if the drug is not taken on schedule. Thus, a drug holiday or treatment interruption is not recommended with this agent.	(1 ⊕⊕⊕⊕)
3.2 In postmenopausal women with osteoporosis who are taking denosumab, we suggest that the fracture risk be reassessed after 5 to 10 years and that women who remain at high risk of fractures should either continue denosumab or be treated with other osteoporosis therapies.	(2 ⊕⊕⊕⊕)
3.3 In postmenopausal women with osteoporosis taking denosumab, administration of denosumab should not be delayed or stopped without subsequent antiresorptive (eg, bisphosphonate, hormone therapy, or selective estrogen receptor modulator) or other therapy administered in order to prevent a rebound in bone turnover and to decrease the risk of rapid bone mineral density loss and an increased risk of fracture.	(Ungraded Good Practice Statement)
4. Teriparatide and Abaloparatide (Parathyroid Hormone and Parathyroid Hormone-Related Protein Analogs)	
4.1 In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe or multiple vertebral fractures, we recommend teriparatide or abaloparatide treatment for up to 2 years for the reduction of vertebral and nonvertebral fractures.	(1 ⊕⊕⊕⊕)
4.2 In postmenopausal women with osteoporosis who have completed a course of teriparatide or abaloparatide, we recommend treatment with antiresorptive osteoporosis therapies to maintain bone density gains.	(1 ⊕⊕⊕⊕)
UPDATE A (2020). Romosozumab	
A.1 In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe osteoporosis (ie, low T-score < -2.5 and fractures) or multiple vertebral fractures, we recommend romosozumab treatment for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures. Technical remark: The recommended dosage is 210 mg monthly by subcutaneous injection for 12 months. Women at high risk of cardiovascular disease and stroke should not be considered for romosozumab pending further studies on cardiovascular risk associated with this treatment. High risk includes prior myocardial infarction or stroke.	(1 ⊕⊕⊕⊕)
A.2 In postmenopausal women with osteoporosis who have completed a course of romosozumab, we recommend treatment with antiresorptive osteoporosis therapies to maintain bone mineral density gains and reduce fracture risk.	(1 ⊕⊕⊕⊕)
5. Selective Estrogen Receptor Modulators	
5.1. In postmenopausal women with osteoporosis at high risk of fracture and with the patient characteristics below, we recommend raloxifene or bazedoxifene to reduce the risk of vertebral fractures. Patient characteristics: With a low risk of deep vein thrombosis and for whom bisphosphonates or denosumab are not appropriate or with a high risk of breast cancer.	(1 ⊕⊕⊕⊕)
6. Menopausal Hormone Therapy and Tibolone	

LIST OF RECOMMENDATIONS

RECOMMENDATIONS	GRADE
6.1 In postmenopausal women at high risk of fracture and with the patient characteristics below, we suggest menopausal hormone therapy, using estrogen-only therapy in women with hysterectomy, to prevent all types of fractures. Patient characteristics: Under 60 years of age or < 10 years past menopause; at low risk of deep vein thrombosis; those in whom bisphosphonates or denosumab are not appropriate; with bothersome vasomotor symptoms; with additional climacteric symptoms; without contraindications; without prior myocardial infarction or stroke; without breast cancer; willing to take menopausal hormone therapy.	(2 ⊕⊕⊕⊕)
6.2 In postmenopausal women with osteoporosis at high risk of fracture and with the patient characteristics below, we suggest tibolone to prevent vertebral and nonvertebral fractures. Patient characteristics: Under 60 years of age or < 10 years past menopause; with a low risk of deep vein thrombosis; those in whom bisphosphonates or denosumab are not appropriate; with bothersome vasomotor symptoms; with additional climacteric symptoms; without contraindications; without prior myocardial infarction or stroke or high risk for cardiovascular disease; without breast cancer; willing to take tibolone. Technical remark: Tibolone is not available in the United States or Canada.	(2 ⊕⊕⊕⊕)
7. Calcitonin	
7.1 In postmenopausal women at high risk of fracture with osteoporosis, we suggest that nasal spray calcitonin be prescribed only in women who cannot tolerate raloxifene, bisphosphonates, estrogen, denosumab, tibolone, abaloparatide, or teriparatide or for whom these therapies are not considered appropriate.	(2 ⊕○○○)
8. Calcium and Vitamin D	
8.1 In postmenopausal women with low bone mineral density and at high risk of fractures with osteoporosis, we suggest that calcium and vitamin D be used as an adjunct to osteoporosis therapies.	(2⊕⊕○○)
8.2 In postmenopausal women at high risk of fracture with osteoporosis who cannot tolerate bisphosphonates, estrogen, selective estrogen response modulators, denosumab, tibolone, teriparatide, and abaloparatide, we recommend daily calcium and vitamin D supplementation to prevent hip fractures.	(1 ⊕⊕⊕⊕)
11. Monitoring	
11.1 In postmenopausal women with a low bone mineral density and at high risk of fractures who are being treated for osteoporosis, we suggest monitoring the bone mineral density by dual-energy X-ray absorptiometry at the spine and hip every 1 to 3 years to assess the response to treatment. Technical remark: Monitoring bone turnover markers (serum C-terminal crosslinking telopeptide for antiresorptive therapy or procollagen type N-terminal propeptide for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy.	(2 ⊕○○○)

safety of these interventions. An algorithm is presented to guide clinicians in the most appropriate therapeutic choices when discussing clinical decision making with the patient (1).

Since the development of the Guideline, several regulatory agencies have approved romosozumab, a new type of anabolic agent for the treatment of osteoporosis that differs from teriparatide and abaloparatide in its mechanism of action. Unlike the latter drugs which work directly through the parathyroid hormone (PTH) type 1 receptor, romosozumab works by blocking the actions of sclerostin, an inhibitor of bone formation that binds to the low-density lipoprotein receptor-related protein (LRP)5/6 component of the LRP5/6-frizzled co-receptor complex that mediates Wnt signaling (2). The introduction of romosozumab to the clinical armamentarium necessitates this update to the osteoporosis guidelines. This development gives providers an additional osteoporosis treatment option to

consider, particularly in women with multiple vertebral fractures and low bone mineral density (BMD), as indicated by the algorithm and also in the approval documents from the FDA and Health Canada. Discussion about the efficacy and safety of this drug is contained within the Guideline Update and is based on a systematic review of the clinical trials for romosozumab (3–5).

Romosozumab

A.1 In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe osteoporosis (this is supposed to be “i.e.,” low T-score < –2.5 and fractures) or multiple vertebral fractures, we recommend romosozumab treatment for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures. (1|⊕⊕⊕⊕)

Technical Remarks:

- The recommended dosage is 210 mg monthly by subcutaneous injection for 12 months.

- *Women at high risk of cardiovascular disease or stroke should not be considered for romosozumab pending further studies on cardiovascular risk associated with this treatment. High risk includes prior myocardial infarction or stroke.*

A.2 In postmenopausal women with osteoporosis who have completed a course of romosozumab, we recommend treatment with antiresorptive osteoporosis therapies to maintain bone mineral density gains and reduce fracture risk. (1⊕⊕⊕⊕)

Evidence

Romosozumab is an anabolic agent that increases bone formation and also reduces bone resorption. It is administered once monthly for 1 year and produces marked increases in spine and hip BMD, almost certainly as a result of an early increase in bone modeling. Romosozumab should be considered as a first-line therapy in patients with multiple vertebral fractures or hip fracture and BMD in the osteoporotic range (this is supposed to be “i.e.,” severe osteoporosis). This agent also could be considered in individuals who have failed antiresorptive treatments. [Figure 1](#) is an updated algorithm for the management of postmenopausal osteoporosis.

Two large phase 3 trials of romosozumab were conducted to test its efficacy in vertebral and nonvertebral fracture risk reduction ([3](#), [5](#)). Neither was powered to show an effect on hip fracture risk. In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial, 7180 postmenopausal women were treated with monthly injections of romosozumab or placebo. An analysis that compared romosozumab with placebo using a direct approach ([3](#)) rather than a network approach ([4](#)) showed a 73% reduction in the risk of vertebral fractures (risk ratio [RR], 0.27; 95% confidence interval [CI], 0.16–0.47) but no significant effect on the risk of hip or nonvertebral fractures. Romosozumab and placebo treatments were followed by 12 months with the antiresorptive agent denosumab to maintain/increase the gains in BMD. At 24 months, those treated with romosozumab followed by denosumab demonstrated a 75% lower risk for new vertebral fractures (RR, 0.25; 95% CI, 0.16–0.40). In the follow-up extension to the FRAME study, which investigated an additional year of denosumab treatment, similar significant reductions in relative risk and increases in spine and hip BMD with the initial therapy with romosozumab were sustained at 36 months ([6](#)).

In the trial, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High

Risk (ARCH) (n = 4093), 1 year of treatment with romosozumab followed by 1 year of alendronate was compared with 2 years of treatment with alendronate in postmenopausal women at high risk of fracture ([5](#)). The ARCH trial showed that romosozumab/alendronate as compared with alendronate/alendronate resulted in a 48% reduction in the risk of vertebral fractures at 24 months (RR, 0.52; 95% CI, 0.40–0.66), a 38% reduction in the risk of hip fractures at 24 months (hazard ratio [HR], 0.62; 95% CI, 0.42–0.92), and a 19% reduction in the risk of nonvertebral fractures at 24 months (HR, 0.81; 95% CI, 0.66–0.99).

Adverse events

Adverse events from the FRAME and ARCH trials included the first 12 months of each study, which was the romosozumab treatment period. In FRAME, there were no imbalances in major adverse cardiovascular events (MACE) or in cardiovascular serious adverse events ([7](#)). In ARCH, there were imbalances in MACE in the first year of the trial with 50 patients in the romosozumab-treated group vs 38 patients in the alendronate-treated group having these events (odds ratio [OR], 1.31; 95% CI, 0.85–2.00) ([5](#), [7](#)). There was a total of 2040 women receiving romosozumab and 2014 receiving alendronate in year 1 of ARCH who were included in the safety analysis ([5](#)). Regarding specific events, there were 12 cardiovascular deaths in the alendronate group and 17 in the romosozumab group (HR, 1.42; 95% CI, 0.68–2.97) ([5](#), [7](#)). There were 6 vs 16 cardiac ischemic events in the alendronate- vs romosozumab-treated groups, respectively (OR, 2.65; 95% CI, 1.03–6.77) ([5](#)). There were 7 vs 16 cerebrovascular events in the alendronate- vs romosozumab-treated groups, respectively (OR, 2.27; 95% CI, 0.93–5.22) ([5](#)). The absolute numbers and OR and HR differ slightly in the FDA Briefing Document and in the Prescribing Information ([8](#)) compared with data reported from the trial ([5](#)). In the ARCH trial with alendronate as the control arm, these differences in adverse events raised the possibility that alendronate might reduce cardiovascular events and that the effects of romosozumab on cardiovascular risk may not be significant ([9](#)). The issue related to alendronate remains uncertain at this time. Although the numbers of serious cardiovascular events overall are small and the CIs are wide, the boxed warning on the label for romosozumab in the United States and Canada cautions its use in patients at risk of myocardial infarction, stroke, and cardiovascular death.

Drugs that decrease bone resorption have been associated with 2 adverse events on bone, namely osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFFs). During the 12-month, double-blind portion

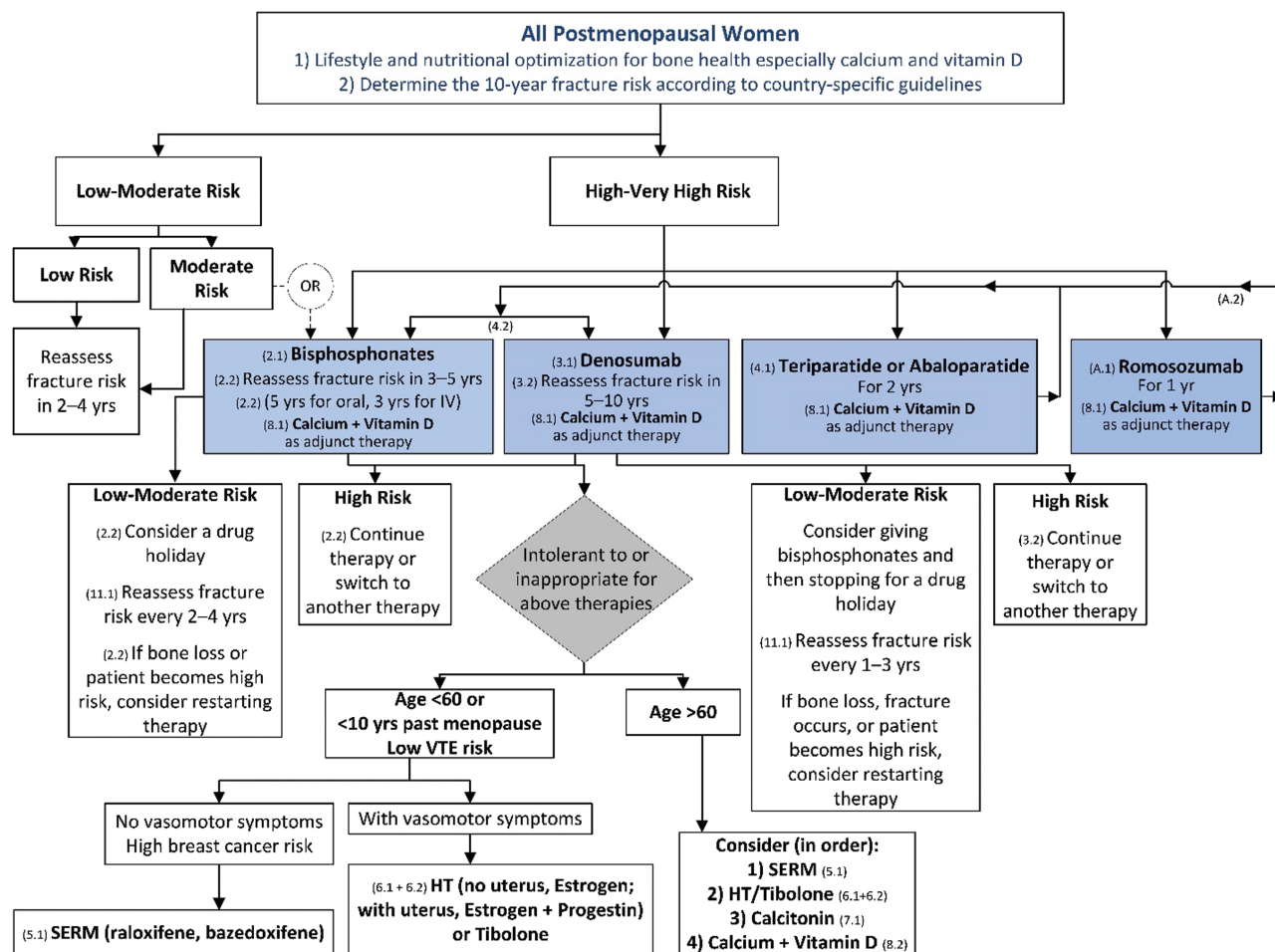


Figure 1. Updated algorithm for management of postmenopausal osteoporosis. Note: We considered that a determination of fracture risk would include measurement of lumbar spine and hip BMD and inserting femoral neck BMD value into the fracture risk assessment (FRAX) tool. Using that FRAX algorithm, we define the following risk categories: (1) *low risk* includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above -1.0 , a 10-year hip fracture risk $< 3\%$, and 10-year risk of major osteoporotic fractures $< 20\%$; (2) *moderate risk* includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above -2.5 , and 10-year hip fracture risk $< 3\%$ or risk of major osteoporotic fractures $< 20\%$; (3) *high risk* includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of ≤ -2.5 or below, or 10-year hip fracture risk $\geq 3\%$, or risk of major osteoporotic fracture risk $\geq 20\%$; and (4) *very high risk* includes multiple spine fractures and a BMD T-score at the hip or spine of ≤ -2.5 or below.

of FRAME, there was 1 case of ONJ in a participant receiving romosozumab and none in participants receiving placebo (3, 7). An additional case of ONJ occurred in 1 participant during the denosumab phase of FRAME, who had previously received romosozumab (3, 7). In ARCH, there were no cases of ONJ during the 12-month, double-blind treatment period (first year) (5, 7). During the second year of ARCH, there were 2 cases of ONJ—1 in the alendronate-alone group and 1 in the group who received romosozumab followed by alendronate (5, 7).

One AFF occurred in a patient who received romosozumab in FRAME (3, 7). During the ARCH trial, 6 AFFs occurred in the second year of the trial, 4 in the alendronate-only group, and 2 in the group who received romosozumab followed by alendronate (5, 7). One additional participant developed an AFF after withdrawal

from the trial (treatment with romosozumab for 12 months followed by alendronate for 2.5 years) (7).

Injection-site reactions were observed in 3% of placebo-treated and 5% of romosozumab-treated patients in FRAME, with few subjects discontinuing therapy (7). Similar rates of these reactions were seen in the ARCH trial.

Neoplasms were carefully assessed in these trials because of the known role of the Wnt signaling pathway, targeted by this therapy, in regulating cell proliferation. Overall romosozumab treatment was not judged to contribute to new tumor development in these trials.

Balance of benefits and harms

In general, once-monthly injections of subcutaneous romosozumab were well tolerated. The overall safety events in postmenopausal women were balanced between the

treatment groups in both the placebo-controlled and the alendronate-controlled trials. In both, injection-site reactions occurred in 5% or less of subjects receiving romosozumab (7). ONJ and AFFs occurred infrequently (*see Adverse Events*). In the ARCH trial, MACE were more common in the romosozumab arm than the alendronate arm. MACE is a composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (*see Adverse Events*). This led to a boxed warning on the label for romosozumab in the United States and Canada, which needs to be carefully considered in making treatment decisions.

Values and preferences

A systematic review of patient preference studies reported that patients do not mind getting injections if they are not given frequently (10).

Remarks

BMD rose substantially during romosozumab treatment in contrast with the control group in both trials. In FRAME at 12 months, the difference in BMD between romosozumab and placebo was 13.3% (spine), 6.9% (total hip), and 5.2% (femoral neck). Most of the difference is due to the effect of romosozumab as the changes were 0%, 0%, and –0.7% at these same sites in the placebo-treated group (3). In ARCH at 12 months, BMD significantly increased with romosozumab by 13.7% (spine), 6.2% (total hip), and 4.9% (femoral neck), compared with a BMD increase with alendronate of 5.0% (spine), 2.8% (total hip), and 1.7% (femoral neck) (5). In ARCH at 24 months, BMD significantly increased with romosozumab plus alendronate by 15.2% (spine), 7.1% (total hip), and 5.9% (femoral neck), compared with a BMD increase with alendronate alone of 7.1% (spine), 3.4% (total hip), and 2.2% (femoral neck).

In a head-to-head comparison of teriparatide and romosozumab given at their licensed doses to postmenopausal women with osteoporosis for 12 months, BMD significantly increased with romosozumab by 11.3% (spine), 4.1% (total hip), and 3.7% (femoral neck), compared with BMD increases with teriparatide of 7.1% (spine), 1.3% (total hip), and 1.1% (femoral neck) (11). Similar results were obtained in postmenopausal women previously treated with bisphosphonates and then randomized to the licensed dose of romosozumab (12). Hypercalcemia occurred more often in the teriparatide group (10%) than in the romosozumab group (< 1%) (12). Thus, romosozumab may be more potent than teriparatide in its effect on BMD, at least at 12 months. The treatment course is 12 months for romosozumab, rather than the 18- to 24-month course for teriparatide, as the anabolic effect is more rapid. Both drugs should be followed by an

antiresorptive agent to prevent the accelerated bone loss that occurs with stopping these anabolic treatments.

Methodology

Throughout the Guideline Update development process, Writing Committee composition and activities remained faithful to the Conflict of Interest Policy & Procedures for Endocrine Society Clinical Practice Guidelines (1). The new recommendations offered herein were created using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (13, 14), as described in the recently published clinical practice guideline (1). The final version of this Guideline Update was also informed by a comment review period, which provided an opportunity for internal and external stakeholders to review the draft and offer feedback. These stakeholders included Endocrine Society members, the Society's Clinical Guidelines Committee, and a representative of the Board of Directors. The draft also was subject to an expert review, undertaken by an individual with expertise in the topic, without relevant conflicts of interest, and external to the Writing Committee, Clinical Guidelines Committee, and Board of Directors.

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Additional Information

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Disclosure Summary: Please see Appendix for author conflicts.

References

1. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society* clinical practice guideline. *J Clin Endocrinol Metab*. 2019;**104**(5):1595–1622.
2. Holdsworth G, Roberts SJ, Ke HZ. Novel actions of sclerostin on bone. *J Mol Endocrinol*. 2019;**62**(2):R167–R185.
3. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;**375**(16):1532–1543.
4. Barrionuevo P, Kapoor E, Asi N, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *J Clin Endocrinol Metab*. 2019;**104**(5):1623–1630.
5. 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.
6. Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, et al. One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study. *J Bone Miner Res*. 2019;**34**(3):419–428.
7. Food and Drug Administration. FDA Briefing Document: Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee. 2019; <https://www.fda.gov/media/121257/download>. Accessed September 20, 2019.
8. Amgen. Evenity prescribing information. 2019; https://www.pi.amgen.com/-/media/amgen/repositorysites/pi-amgen-com/evenity/evenity_pi_hcp_english.ashx. Accessed December 3, 2019.
9. Kang JH, Keller JJ, Lin HC. Bisphosphonates reduced the risk of acute myocardial infarction: a 2-year follow-up study. *Osteoporos Int*. 2013;**24**(1):271–277.
10. Barrionuevo P, Gionfriddo MR, Castaneda-Guarderas A, et al. Women's values and preferences regarding osteoporosis treatments: a systematic review. *J Clin Endocrinol Metab*. 2019;**104**(5):1631–1636.
11. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2014;**370**(5):412–420.
12. 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.
13. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;**64**(4):383–394.
14. Guyatt GH, Oxman AD, Vist GE, et al.; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;**336**(7650):924–926.

Appendix – Relevant Conflict of Interests of Osteoporosis Guideline Update Writing Committee

Task Force Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/Family Info
Clifford Rosen, MD, Chair	Maine Medical Center Research Institute Senior Scientist Director	None	None	None	None	None
Dennis Black, PhD	University of California San Francisco Professor in Residence, Division of Clinical Trials & Multicenter Studies	None	None	None	None	None
Angela Cheung, MD, PhD	University Health Network, University of Toronto Director, Osteoporosis Program	-IOF CSA, Member	-JSCD Canadian Panel -CIHR, reviewer and grantee -Osteoporosis Canada, Clinical Guidelines member	-Amgen, Advisory Board -Alexion, Advisory Board	-Clementia -Regeneron -Mereo	None
Richard Eastell, MD, FRCP, FRCPI, FRCPEdin, FRCPath, FMedSci	The University of Sheffield Sheffield Teaching Hospitals NHS Trust Professor and Head of the Academic Unit of Bone Metabolism Director of the Mellanby Centre for Bone Research	-ECTS, member -ASBMR, member	None	-Alexion, consultant -Bone, Senior Editor -D-Star, consultant -FNIH, consultant -GSK Nutrition, consultant -Immuno-diagnostic Systems, consultant -Nittobo, consultant -Roche Diagnostics, consultant -Sandoz consultant -Mereo, consultant -Abbvie, consultant -Samsung, consultant -Haoma Medica, consultant -CL Bio, consultant -Biocon, consultant -Lyramid, consultant -Viking, consultant	-Amgen, grant awardee -Alexion, grant awardee -Nittobo, grant awardee -Roche Diagnostics, grant awardee, -Medical Research Council, grant awardee -Royal Osteoporosis Society, grant awardee -Arthritis Research UK, grant awardee -National Institute for Health Research, Senior Investigator Emeritus -European Union, grant awardee	None
M. Hassan Murad, MD, MPH	The Mayo Clinic Professor of Medicine	None	None	None	None	None
Dolores Shoback, MD	University of California San Francisco and Professor	ASBMR member	None	-SHIRE/Takeda, consultant -Ascendis, consultant -Bridge Bio, consultant -Secretary -Treasurer, Endocrine Society		None