Is Romosozumab better than Teriparatide for the treatment of osteoporosis? A meta-analysis through a grade analysis of evidence

CURRENT STATUS: POSTED

Zhao-hui Liu
Tianjin Medical University

Jian-xiong Ma
Tianjin Hospital

Xiao-lei Sun
Tianjin Hospital

Shun Zhang
Tianjin Medical University

Ming-jie Kuang
Tianjin Medical University

Xin-long Ma  maxinlong5566@163.com
Corresponding Author

DOI:
10.21203/rs.2.13598/v1

SUBJECT AREAS
  Geriatrics & Gerontology

KEYWORDS
Romosozumab, Teriparatide, postmenopausal osteoporosis
Abstract

Background

Osteoporosis is a common systemic skeletal disease. With an ageing population, the socioeconomic effect of osteoporosis will remarkably improve. Romosozumab (EVENITYTM) is a new osteoanabolic drug, which is a humanised monoclonal antibody against sclerostin, and received its first global approval for the treatment of osteoporosis in patients at high risk of fracture in Japan on January 8, 2019. Teriparatide is the first osteoanabolic drug. However, there is no comprehensive analysis and systematic review about the efficacy and safety of the two treatment.

Method

Randomized controlled trials (RCTs) about our analysis were searched from electronic database, including Pubmed (1996 to June 2019), Embase (1980 to June 2019), Cochrane Library (CENTRAL, June 2019), Web of Science (1998 to June 2019) and others. Four studies were included in our meta-analysis.

Results

Four studies containing 1304 patients meet our selection criteria. Our result of analysis indicated that Romosozumab showed better effects in improving BMD of lumbar spine (month 6: MD=3.54, 95% CI 3.13, 3.94, P<0.00001; month 12: MD=4.93, 95% CI 4.21, 5.64, P<0.00001), total hip (month 6: MD=2.27, 95% CI 0.62, 3.91, P=0.007; month 12: MD=3.17, 95% CI 2.68, 3.65, P<0.00001) and femoral neck (month 6: MD=2.30, 95% CI 0.51, 4.08, P=0.01; month 12: MD=3.04, 95% CI 2.29, 3.78, P<0.00001). And the injection-site reaction was fewer (month 12: RR=2.84, 95% CI 1.22, 6.59, P=0.02). But there were no significant differences in the incidence of serious adverse events (month 12: RR=0.78, 95% CI 0.46, 1.33, P=0.37), and death (month 12: RR=0.61, 95% CI 0.08, 4.62, P=0.63).

Conclusion
Based on the available studies, our current results demonstrated that Romosozumab was better than Teriparatide both in terms of efficacy and side effects.

**Introduction**

Osteoporosis is identified as a systemic skeletal disorder characterized by low BMD and qualitative changes in microarchitecture of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture[1]. In elderly patients, Osteoporotic fracture (fragility fracture) is a catastrophic complication, which causes substantial morbidity and mortality[2]. This fracture often occurs in the spine, hip and wrist, but also affects other bones, such as humerus and radius[3]. Drugs for osteoporosis fall into two major categories, antiresorptive drugs and osteoanabolic drugs. Antiresorptive drugs for osteoporosis increase bone mineral density and prevent the progression of structural damage but may not restore bone structure[4]. However, osteoanabolic drugs can reverse microarchitectural deterioration of bone tissue and seem to be better. Now for osteoporosis treatment, the classic drug bisphosphonate represents the vast majority of prescriptions, and is conventional drugs. However, either by oral or intravenous administration, bisphosphonate is reported that atypical femoral fractures and osteonecrosis of jaw may be more common[5-8]. Teriparatide (brand name FOTTEO™), an N-terminal (1–34) fragment of human parathyroid hormone, is the first one osteoanabolic drug approved by Food and drug administration in 2003[9, 10]. It can significantly improve BMD. However, patients must inject this drug one time each day in their thigh or abdomen. Besides, After Teriparatide is discontinued, its benefits are quickly lost[11]. What’s worse, a study of the Forteo Patient Registry (FPR) anticipated that their on-going study will be able to detect a fourfold increase in the risk of osteosarcoma if one exists in 2024[12].
Sclerostin, a glycoprotein produced primarily by osteocytes, is encoded by the SOST gene, which can specifically block the canonical Wnt signaling[13, 14]. This pathway plays a pivotal role in promoting bone formation and regulating bone homeostasis[15][15]. Sclerostin increases the expression of RANKL and decreases that of OPG, resulting in bone absorption[16, 17]. Romosozumab, a humanized monoclonal anti-sclerostin antibody, is a new osteoanabolic drug that inhibits sclerostin with a dual effect on bone, increasing bone formation and decreasing bone resorption[4]. However, the efficacy and safety of this new drug are not well documented. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials of romosozumab and teriparatide to fully evaluate their effects in postmenopausal osteoporosis patients.

Materials And Methods

2.1. Literature search

The way to identify relevant studies was to use “Romosozumab ,” “Teriparatide” and “postmenopausal osteoporosis” as key words with Boolean operators “AND” or “OR” in electronic databases including PubMed, Embase, the Cochrane Library, Web of Science and the Cochrane Controlled Trials Register up to June 2019 . Only randomized controlled trials (RCTs) performed on human beings were included in our studies. The Flow chart of the trial selection process was presented in the figure of flow chart (Fig. 1). We also used the PRISMA guidelines[18] , GRADE system[19] and Cochrane Handbook[20] to assess the quality of the included studies to make sure the data reliable and veritable.

2.2. Selection criteria

Trials were included on condition that they met the PICOS (population, intervention, comparator, outcome, study design) criteria.

Population: Female patients with postmenopausal osteoporosis
Intervention: Romosozumab

Comparator: Teriparatide

Outcomes: The primary outcomes included the following: the percentage change of lumbar spine and total hip from baseline in bone mineral density at month 6 and month 12 in each group. The secondary outcomes contained the following: the percentage change of femoral neck from baseline in bone mineral density at month 6 and month 12 in each group and the incidence of adverse events at month 12 in each group.

Study design: RCT

2.3. Data extraction

A standard data extraction form was used to collect the relevant data from included studies. Two reviewers collected available data from included studies independently, and any disagreement between the two reviewers was judged by a third reviewer. The relevant data included authors, published dates, intervention types, age, sample size, outcomes, duration of follow-up and reference type. Baseline characteristics of included trials were presented in Table 1. Data on BMD were obtained from the data presented in tables or figures if no direct data were available from the article text.

2.4. Risk of bias assessment

According to the Cochrane Handbook for Systematic Reviews of Interventions[20], the methodological quality and basis of the included literature were assessed as follows: randomization, allocation concealment, blind method, selective reporting, incomplete outcome data, and other bias (Figs. 2 and 3).

2.5. Grading quality of evidence

We used GRADE system to evaluate the level of the evidence and strength of recommendations for included outcomes. GRADE software was used to evaluate the evidence of included outcomes. Initially, RCTs were considered as high confidence in an
estimate of effect and cohort studies were considered as low confidence in an estimate of effect. Reasons that might decrease the level of confidence include limitations, inconsistency, indirectness, and imprecision, and publication bias. Reasons that might raise the level of confidence include large effect, plausible confounding, dose-response. The GRADE evidence was divided into the following categories: (1) High-quality evidence, which indicated that further research was unlikely to change the confidence in an estimate of effect; (2) Moderate-quality evidence, which indicated that further research was likely to have an important impact on confidence in an estimate of effect and may change the estimate; (3) Low-quality evidence, which indicated that further research was likely to have an important impact on confidence in an estimate of effect and was likely to change the estimate; and (4) Very low-equality evidence, which indicated that we were very uncertain about the results. The results of the GRADE analysis were presented in Table 2.

2.6. Statistical analysis and data synthesis

Meta-analyses were performed with Review Manager Software for Windows (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The mean difference (MD) was used to assess continuous outcomes in month 6 and 12, such as BMD of different parts, with a 95% confidence interval (CI). Relative risks with a 95% CI were used to assess dichotomous outcomes, such as AEs. The inverse variance and Mantel-Haenszel methods were used to combine separate statistics. If P values were <0.05, the results were considered statistically significant.

2.7. Investigation of heterogeneity and publication bias

Statistical heterogeneity of the included studies was evaluated using the chi-square test in accordance with the values of P and I^2. If the values of I^2 < 50%, the heterogeneity might not be important. A fixed-effects model was used to assess these outcomes. If I^2
was between 50% and 100%, it could represent substantial heterogeneity. We used random-effects model to evaluate these outcomes. Thresholds for the interpretation of $I^2$ can be misleading, since the importance of inconsistency depends on several factors. Therefore, subgroup analysis or sensitivity analysis was performed to interpret the potential source of heterogeneity. Because of only four studies included, publication bias test were not necessary.

Results

3.1. Search results

Initially, 198 citations were identified from electronic databases, of which 169 records were excluded by primary screening. After reading the full text of all remaining 29 studies in detail, 25 studies were also excluded according to the inclusion and exclusion criteria. Finally, 4 RCTs[21-24] were included. But only two studies[23, 24] had the data measured in month 6 and the data of femoral neck BMD. The characteristics of included studies were summarized in Table 1.

3.2. Primary outcome

The BMD of lumbar spine and total hip were the primary outcome in our meta-analysis, which were used to evaluate the therapeutic effect of osteoporosis. The treatment period were divided into two subgroups (month 6 and 12).

3.2.1. BMD of lumbar spine

Four studies assessed lumbar spine BMD of 620 patients through month 12 and 514 patients through month 6. Compared with Teriparatide, Romosozumab significantly improved the BMD (month 6: MD=3.54, 95% CI [3.13, 3.94], $P<0.00001$; month 12: MD=4.93, 95% CI [4.21, 5.64], $P<0.00001$; Fig. 4)
3.2.2. BMD of total hip

Four studies assessed total hip BMD of 570 patients through month 12 and 514 patients through month 6. Compared with Teriparatide, Romosozumab significantly improved the BMD (month 6: MD=2.27, 95% CI [0.62, 3.91], P=0.007; month 12: MD=3.17, 95% CI [2.68, 3.65], P<0.00001; Fig. 5).

3.3. Secondary outcome

3.3.1. BMD of femoral neck

The BMD of femoral neck was reported in two studies[23, 24], including 514 patients in month 6 and the same sample size in month 12. The percentage change from baseline in the group of Romosozumab was significantly improved (month 6: MD=2.30, 95% CI [0.51, 4.08], P=0.01; month 12: MD=3.04, 95% CI [2.29, 3.78], P<0.00001; Fig. 6).

3.3.2. Adverse events

There were also two studies[23, 24] evaluating the incidence adverse events. The common points of interest were serious adverse event, death and injection-site reaction. No significant differences were found between the two group in the incidence of serious adverse events (month 12: RR=0.78, 95% CI [0.46, 1.33], P=0.37), and death (month 12: RR=0.61, 95% CI [0.08, 4.62], P=0.63). However, Romosozumab could significantly alleviate the local response (month 12: RR=2.84, 95% CI [1.22, 6.59], P=0.02; Fig. 7).

Discussion

4.1. Summary of evidence

According to our study, Romosozumab can significantly increase the BMD of lumbar spine, total hip and femoral neck, with a lower incidence of injection-site reaction. And those differences all have statistical significance (P<0.05). There is no difference in the incidence of death and other serious adverse events. Fewer adverse events (P<0.05) and
longer half-life may improve the compliance of patients and reduce the loss of benefits.

4.2. Limitations

Our meta-analysis has several limitations[1] there were only 4 RCTs in our meta-analysis, the sample size of included studies was small (N=1304). (2) In regard to the significant heterogeneity of LS BMD ($I^2=86\%$) and TH BMD ($I^2=84\%$), although we used a random effect model, we tried to find the source of heterogeneity. When we excluded the study of Keaveny et al, the heterogeneity of LS BMD ($I^2=71\%$) reduced at a level; When we excluded the study of Langdahl et al or McClung et al, the heterogeneity of TH BMD ($I^2=0$) reduced significantly. Therefore, we thought those excluded studies might be the source. The heterogeneity of FN BMD ($I^2=99\%$ in month 6, $I^2=94\%$ in month 12) could not be analyzed, because there were only 2 RCTs included. (3) Some original data could not be directly acquired. (4) The follow-up period was too short in included trials, so some AEs might not be revealed. The effectiveness and safety needed longer follow-up time to be confirmed. (5) Only English publications were included in our meta-analysis.

Conclusions

With an ageing population, Osteoporosis, especially the most common postmenopausal osteoporosis has brought great economic burden to the global public health, and also seriously affects the quality of life of patients themselves[25, 26]. In America, age-related fractures are projected to increase nationally to over 3 million fractures in 2025[27]. The process of ageing in women is associated with an increase in the rate of bone remodelling in both cancellous and cortical bone, combined with a negative remodeling balance, resulting in bone loss and disruption of bone microarchitecture[1]. It is generally believed that the key to the treatment of osteoporosis is to restore the dynamic balance of bone metabolism, and the signal pathway between cells has become a key to
research[28]. With the emergence of new signaling pathways, new types of avenues targeting them are also emerging, such as Melatonin[29].

The real-life challenge, however, roots in the long therapeutic procedure for osteoporosis. Today, generally speaking, women still have a long life expectancy, possibly 30 years or more after menopause and their fracture risk increases exponentially with age. There is few clinical extension trials for over 10 years for the treatment of osteoporosis, especially those of antiresorptive therapies. Additionally, serious adverse effects such as osteonecrosis of the jaw and atypical femoral fractures have been related to extended antiresorptive therapy, raising concerns of increased risks due to continuous inhibition of bone resorption. Osteoanabolic therapy is currently limited to 24 months of Teriparatide treatment[2].

There are two major categories of drugs for osteoporosis, antiresorptive drugs and osteoanabolic drugs. The former inhibit the recruitment and activity of osteoclasts, and probably do not fully correct the negative remodeling balance. The latter have anabolic skeletal effects, which can be achieved through changes in bone remodelling, bone modelling or a combination of the two[1]. Except Teriparatide, there is another osteoanabolic drug, Abaloparatide (brand name Tymlos™). It was approved by FDA on 28 April 2017. Abaloparatide is a synthetic analogue of PTHrP, which can increase bone mass in animals[30] and in human[31]. But patients still need daily subcutaneous injections like Teriparatide. For a long time, Abaloparatide injected subcutaneously in rats resulted in dose and time dependent formation of osteosarcomas, with a comparable response to h-PTH (1-34) at similar exposure[32]. Although Abaloparatide can reduce hypercalcaemia, its registration was denied in Europe on the grounds of concerns about its effectiveness in reducing nonvertebral fractures, and increases in heart rate and palpitations[1]. EMA’s Committee for Medicinal Products for Human Use (CHMP) thought some data from study
sites of Abaloparatide were not reliable and had to be excluded as the study had not been conducted in compliance with ‘good clinical practice’ (GCP) at those sites[33]. After enough clinical trials in postmenopausal women with osteoporosis[34-39], Romosozumab (EVENITY™) has been proved to be safe and effect, then approved by FDA in 2019[40].

There is a new avenue for the treatment of osteoporosis. Dating back to 1979, Frost first proposed the concept of sequential therapy for osteoporosis[41]. However, relevant DATA-Switch studies do not attach enough attention until now and have shown better outcomes than monotherapy [42-47]. Similarly, there are few similar researches on Romosozumab. Compared with monotherapy, the transition from Romosozumab to other antiresorptive drugs may further increase bone mineral density in postmenopausal osteoporotic women.

Through bone-targeting systems to deliver siRNA is also a new method for osteoporosis, and it has already been examined in a preclinical study[48].

In summary, all the current drugs for osteoporosis more or less have some side effects or lack efficacy, and an very ideal osteoporosis therapy has not yet been developed. Other than drugs, good nutrition, regular physical activity, avoiding harmful lifestyle habits and fall prevention are recommended for all patients at risk of osteoporosis and should be taken into the equal value as medical treatment [49].

In our study, compared with Teriparatide, Romosozumab had better effectiveness for the treatment of osteoporosis, especially in increasing the BMD of lumbar spine, total hip and femoral neck, decreasing the incidence of injection-site reaction. But on the grounds of the concerns about small sample size, incomplete data and heterogeneity for RCTs included, we need more studies to demonstrate our results.

Abbreviations

CI: Confidence interval; MD: Mean difference; OR: Odds ratio; NOS: Newcastle Ottawa
Ethics approval and consent to participate
This article is not involved in ethical requirements.

Consent for publication
The manuscript is approved for publication by all the authors.

Availability of data and materials
All data generated or analyzed during this study are available from all the included studies from those databases mentioned in the abstract.

Acknowledgements and founding
National Natural Science Foundation of China (NO. 81871777).

Competing interests
Zhaohui Liu, Jianxiong Ma, Xiaolei Sun, Shun Zhang, Mingjie Kuang and Xinlong Ma declare that they have no conflict of interest.

Authors’ contributions
Zhaohui Liu and Jianxiong Ma are contributed equally for this article. Mingjie Kuang and Xinlong Ma are the co-corresponding authors of this paper.

Authors’ information
* These authors contributed equally
†Correspondence to Xin-long Ma and Ming-jie Kuang.

1 Tianjin Medical University, Tianjin 300052, People's Republic of China

2 Biomechanics Labs of Orthopaedics Institute, Tianjin Hospital, Tianjin 300050, People's
Republic of China

3 Tianjin Hospital, Tianjin 300211, People's Republic of China

4 Tianjin Hospital, Tianjin University 300211, People's Republic of China

**Corresponding author:**

Ming-jie Kuang, Tianjin Medical University, Tianjin 300052, People's Republic of China, e-mail: doctorkmj@tmu.edu.cn, phone number: +86-13602179865

Xin-long Ma, Tianjin Hospital, Tianjin 300211, People's Republic of China, e-mail: maxinlong5566@163.com, phone number: +86-15031729187

**References**

1. Compston JE, McClung MR, Leslie WD: *Osteoporosis*. *The Lancet* 2019, **393**(10169):364-376.

2. Hofbauer LC, Rachner TD: *More DATA to guide sequential osteoporosis therapy*. *LANCET* 2015, **386**(9999):1116-1118.

3. Rachner TD, Khosla S, Hofbauer LC: *Osteoporosis: now and the future*. *The Lancet* 2011, **377**(9773):1276-1287.

4. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, Langdahl BL, Reginster JY, Zanchetta JR, Wasserman SM et al: *Romosozumab in postmenopausal women with low bone mineral density*. *N Engl J Med* 2014, **370**(5):412-420.

5. Watts NB, Diab DL: *Long-term use of bisphosphonates in osteoporosis*. *J Clin Endocrinol Metab* 2010, **95**(4):1555-1565.

6. Shane E: *Evolving data about subtrochanteric fractures and bisphosphonates*. *N Engl J Med* 2010, **362**(19):1825-1827.

7. Harvey NC, McCloskey E, Kanis JA, Compston J, Cooper C: *Bisphosphonates in...*
8. Whitaker M, Guo J, Kehoe T, Benson G: Bisphosphonates for osteoporosis--where do we go from here? *N Engl J Med* 2012, **366**(22):2048-2051.

9. **Forteo approved for osteoporosis treatment.** *FDA Consum* 2003, **37**(2):4.

10. FDA: **FORTEO ™**. In. 2002:

    https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21318_forteo_lbl.pdf;

11. Black DM, Rosen CJ: **Clinical Practice. Postmenopausal Osteoporosis.** *N Engl J Med* 2016, **374**(3):254-262.

12. Gilsenan A, Harding A, Kellier-Steele N, Harris D, Midkiff K, Andrews E: **The Forteo Patient Registry linkage to multiple state cancer registries: study design and results from the first 8 years.** *Osteoporos Int* 2018, **29**(10):2335-2343.

13. McClung MR: **Romosozumab for the treatment of osteoporosis.** *Osteoporosis and Sarcopenia* 2018, **4**(1):11-15.

14. Semenov M, Tamai K, He X: **SOST is a ligand for LRP5/LRP6 and a Wnt signaling inhibitor.** *J BIOL CHEM* 2005, **280**(29):26770-26775.

15. Baron R, Kneissel M: **WNT signaling in bone homeostasis and disease: from human mutations to treatments.** *NAT MED* 2013, **19**(2):179-192.

16. Tu X, Delgado-Calle J, Condon KW, Maycas M, Zhang H, Carlesso N, Taketo MM, Burr DB, Plotkin LI, Bellido T: **Osteocytes mediate the anabolic actions of canonical Wnt/beta-catenin signaling in bone.** *Proc Natl Acad Sci U S A* 2015, **112**(5):E478-E486.

17. Fijalkowski I, Geets E, Steenackers E, Van Hoof V, Ramos FJ, Mortier G, Fortuna AM, Van Hul W, Boudin E: **A Novel Domain-Specific Mutation in a Sclerosteosis Patient Suggests a Role of LRP4 as an Anchor for Sclerostin in Human Bone.**
18. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. INT J SURG 2010, 8(5):336-341.

19. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008, 336(7650):924-926.

20. Becker L (ed.): Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.4; 2011.

21. Genant HK, Engelke K, Bolognese MA, Mautalen C, Brown JP, Recknor C, Goemaere S, Fuerst T, Yang YC, Grauer A et al: Effects of Romosozumab Compared With Teriparatide on Bone Density and Mass at the Spine and Hip in Postmenopausal Women With Low Bone Mass. J BONE MINER RES 2017, 32(1):181-187.

22. Keaveny TM, Crittenden DB, Bolognese MA, Genant HK, Engelke K, Oliveri B, Brown JP, Langdahl BL, Yan C, Grauer A et al: Greater Gains in Spine and Hip Strength for Romosozumab Compared With Teriparatide in Postmenopausal Women With Low Bone Mass. J BONE MINER RES 2017, 32(9):1956-1962.

23. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK 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.

24. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, Langdahl BL, Reginster JY, Zanchetta JR, Wasserman SM et al: Romosozumab in
postmenopausal women with low bone mineral density. *N Engl J Med* 2014, 370(5):412-420.

25. Borgstrom F, Lekander I, Ivergard M, Strom O, Svedbom A, Alekna V, Bianchi ML, Clark P, Curiel MD, Dimai HP et al: **The International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS)--quality of life during the first 4 months after fracture.** *Osteoporos Int* 2013, 24(3):811-823.

26. Marques A, Lourenco O, Da SJ: **The burden of osteoporotic hip fractures in Portugal: costs, health related quality of life and mortality.** *Osteoporos Int* 2015, 26(11):2623-2630.

27. Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LR: **Trends in fracture incidence: a population-based study over 20 years.** *J Bone Miner Res* 2014, 29(3):581-589.

28. Plotkin LI, Bellido T: **Osteocytic signalling pathways as therapeutic targets for bone fragility.** *Nat Rev Endocrinol* 2016, 12(10):593-605.

29. Li T, Jiang S, Lu C, Yang W, Yang Z, Hu W, Xin Z, Yang Y: **Melatonin: Another avenue for treating osteoporosis?** *J Pineal Res* 2019, 66(2):e12548.

30. Bahar H, Gallacher K, Downall J, Nelson CA, Shomali M, Hattersley G: **Six Weeks of Daily Abaloparatide Treatment Increased Vertebral and Femoral Bone Mineral Density, Microarchitecture and Strength in Ovariectomized Osteopenic Rats.** *Calcif Tissue Int* 2016, 99(5):489-499.

31. Leder BZ, O'Dea LS, Zanchetta JR, Kumar P, Banks K, McKay K, Lyttle CR, Hattersley G: **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.

32. Jolette J, Attalla B, Varela A, Long GG, Mellal N, Trimm S, Smith SY, Ominsky MS,
Hattersley G: **Comparing the incidence of bone tumors in rats chronically exposed to the selective PTH type 1 receptor agonist abaloparatide or PTH(1-34).** *Regul Toxicol Pharmacol* 2017, **86**:356-365.

33. Brennan Z: **EMA’s CHMP Rejects Two Drugs Approved by US FDA in 2017.** In.; 2018.

34. Cosman F, Crittenden DB, Ferrari S, Lewiecki EM, Jaller-Raad J, Zerbini C, Milmont CE, Meisner PD, Libanati C, Grauer A: **Romosozumab FRAME Study: A Post Hoc Analysis of the Role of Regional Background Fracture Risk on Nonvertebral Fracture Outcome.** *J Bone Miner Res* 2018, **33**(8):1407-1416.

35. Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD, Miyauchi A, Maddox J, Chen L, Horlait S: **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.

36. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A: **Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis.** *N Engl J Med* 2017, **377**(15):1417-1427.

37. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK 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.

38. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A et al: **Romosozumab Treatment in Postmenopausal Women with Osteoporosis.** *N Engl J Med* 2016, **375**(16):1532-1543.
39. 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**(1):19-26.

40. Markham A: **Romosozumab: First Global Approval.** *DRUGS* 2019, **79**(4):471-476.

41. Frost HM: **Treatment of osteoporoses by manipulation of coherent bone cell populations.** *Clin Orthop Relat Res* 1979(143):227-244.

42. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, Burnett-Bowie SA: **Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial.** *Lancet* 2015, **386**(9999):1147-1155.

43. Tsai JN, Nishiyama KK, Lin D, Yuan A, Lee H, Bouxsein ML, Leder BZ: **Effects of Denosumab and Teriparatide Transitions on Bone Microarchitecture and Estimated Strength: the DATA-Switch HR-pQCT study.** *J Bone Miner Res* 2017, **32**(10):2001-2009.

44. Leder BZ, Tsai JN, Jiang LA, Lee H: **Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: The Denosumab and Teriparatide Follow-up study (DATA-Follow-up).** *Bone* 2017, **98**:54-58.

45. Tsai JN, Jiang LA, Lee H, Hans D, Leder BZ: **Effects of Teriparatide, Denosumab, or Both on Spine Trabecular Microarchitecture in DATA-Switch: a Randomized Controlled Trial.** *J Clin Densitom* 2017, **20**(4):507-512.

46. Tsai J, Jiang L, Lee H, Hans D, Leder B: **Combination treatment with teriparatide and denosumab improves spine trabecular microarchitecture in data-switch: A randomized controlled trial.** *J Bone Miner Res* 2017, **32**:S110.

47. Uihlein A, Burnett-Bowie SA, Neer R, Tuck P, Wallace P, Bouxsein M, Leder B: **Effect
of denosumab (DMAB) and teriparatide (TPTD) transitions on peripheral bone mineral density (BMD) and microarchitecture: The DATA-Switch HR-pQCT study. *J Bone Miner Res* 2015, 30.

48. Stapleton M, Sawamoto K, Almeciga-Diaz CJ, Mackenzie WG, Mason RW, Orii T, Tomatsu S: *Development of Bone Targeting Drugs. INT J MOL SCI* 2017, 18(7).

49. Chen LR, Ko NY, Chen KH: *Medical Treatment for Osteoporosis: From Molecular to Clinical Opinions. INT J MOL SCI* 2019, 20(9).

**Tables**

**Table 1** Characteristics of included randomized controlled trials

| Study (year) | Intervention | Age (years, mean±SD) | Number of patients with LS BMD | Number of patients with TH BMD | Number of patients with FN BMD | Outcomes | Follow-up (months) | Reference type |
|--------------|--------------|-----------------------|--------------------------------|-------------------------------|-------------------------------|----------|-------------------|----------------|
| Genant 2017  | Romosozumab 210mg per month Teriparatide 20μg per day | 64.3±4.7 65.8±5.7 | 24 30 | 9 19 | — | BMD changes at LS, TH, FN; incidence of AEs | 12 | RCT |
| Keaveny 2017 | Romosozumab 210mg per month Teriparatide 20μg per day | 64.3 ±4.7 65.8 ±5.7 | 24 28 | 9 19 | — | BMD changes at LS, TH, FN; incidence of AEs | 12 | RCT |
| Langdahl 2017 | Romosozumab 210mg per month Teriparatide 20μg per day | 71.8±7.4 71.2±7.7 | 206 209 | 206 209 | 206 209 | BMD changes at LS, TH, FN; incidence of AEs | 12 | RCT |
| McClung 2014 | Romosozumab 210mg per month Teriparatide 20μg per day | 66.3±6.5 66.8±5.7 | 49 46 | 49 46 | 49 46 | BMD changes at LS, TH, FN; incidence of AEs | 12 | RCT |

**Table 2** The GRADE evidence quality for each outcome
| No of studies | Design | Decrease quality of evidence | Increase quality of evidence |
|---------------|--------|------------------------------|-----------------------------|
|               |        | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect |
| Lumbar spine  | RCT    | no          | serious       | no           | no          | likely          | large        |
| month 6       |        |             |               |             |             |                 |              |
| Lumbar spine  | RCT    | no          | serious       | no           | no          | likely          | large        |
| month 12      |        |             |               |             |             |                 |              |
| Total hip     | RCT    | no          | very serious  | no           | no          | likely          | large        |
| month 6       |        |             |               |             |             |                 |              |
| Total hip     | RCT    | no          | serious       | no           | no          | likely          | large        |
| month 12      |        |             |               |             |             |                 |              |
| Femoral neck  | RCT    | no          | very serious  | no           | no          | likely          | large        |
| month 6       |        |             |               |             |             |                 |              |
| Femoral neck  | RCT    | no          | very serious  | no           | no          | likely          | large        |
| month 12      |        |             |               |             |             |                 |              |
| Incidence of  | RCT    | no          | no            | no           | no          | likely          | no           |
| SAEs          |        |             |               |             |             |                 |              |
| Incidence of  | RCT    | no          | no            | no           | no          | likely          | no           |
| death         |        |             |               |             |             |                 |              |
| Incidence of  | RCT    | no          | no            | no           | no          | likely          | large        |
| Injection-site|        |             |               |             |             |                 |              |
| reaction      |        |             |               |             |             |                 |              |

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and

**Very low quality:** We are very uncertain about the estimate.

**Figures**
Figure 1

the Flow Chart
Figure 2

Risk of bias graph
Figure 3

Risk of bias summary
### Figure 4

A forest plot diagram of lobar spine BMD

| Study or Subgroup | Mean (SD) | Total | Mean (SD) | Total | Mean Difference (95% CI) | Weight |
|-------------------|-----------|-------|-----------|-------|--------------------------|--------|
| 6.1.1 6 month     | 7.2 (3.3) | 250   | 5.5 (2.1) | 209   | 21.9% (3.0, 3.8)         | 120    |
| McClung 2014      | 5.2 (1.0) | 50    | 4.2 (0.8) | 49    | 9.4% (3.2, 2.6)          | 40     |
| Heterogeneity     | Tau² = 0.07, χ² = 14.2, df = 1 (P = 0.0001); I² = 76% |        |           |       |                          |        |
| Test for overall effect | Z = 17.24 (P = 0.00001) |        |           |       |                          |        |
| 6.1.2 12 month    | 6.3 (1.3) | 239   | 4.9 (1.6) | 229   | 14.3% (5.1, 1.4)         | 120    |
| Kenna 2014        | 27.3 (4.5) | 50   | 18.5 (2.8) | 50    | 4.0% (3.0, 2.4)          | 40     |
| McClung 2014      | 6.2 (1.0) | 50    | 4.2 (0.8) | 49    | 9.4% (3.2, 2.6)          | 40     |
| Subgroup (95% CI) |           |       |           |       |                          |        |
| Heterogeneity     | Tau² = 0.07, χ² = 20.8, df = 2 (P = 0.0001); I² = 66% |        |           |       |                          |        |
| Test for overall effect | Z = 13.63 (P = 0.00001) |        |           |       |                          |        |
| Total             | 12.6 (1.0) | 574   | 8.9 (1.5) | 497   | 100.9% (19.8, 1.4)       | 324    |
| Heterogeneity     | Tau² = 0.26, χ² = 122.37, df = 6 (P = 0.0001); I² = 50% |        |           |       |                          |        |
| Test for overall effect | Z = 18.61 (P = 0.00001) |        |           |       |                          |        |
| Test for subgroup differences | CHE = 10.95, df = 1 (P = 0.0089); I² = 60.9% |        |           |       |                          |        |
### Figure 5

A forest plot diagram of total hip BMD

| Study or Subgroup | Mean (SD) Total | Mean (SD) Total | N, Random, 95% CI | Mean Difference (95% CI) |
|-------------------|----------------|----------------|------------------|--------------------------|
| **6.1 1.6 month** |                |                |                  |                          |
| Langdell 2017     | 2.3 (0.8)      | 259            | 239              | 22.2%                    | 3.10 (2.12, 3.18) |
| McClung 2014      | 1.7 (0.2)      | 308            | 49               | 20.3%                    | 1.42 (1.15, 1.69) |
| Global (95% CI)   | 256            | 238            | 43.1%            |                          | 2.27 (2.02, 2.51) |
| Heterogeneity: Tau^2 = 1.49; Chi^2 = 140.74; df = 1 (P = 0.00001); I^2 = 99% | | | | |
| Test for overall effect: Z = 2.79 (P = 0.007) | | | | |

| **6.1 12 month**  |                |                |                  |                          |
| Garnett 2017      | 2.9 (1.6)      | 9              | 19               | 12.2%                    | 3.10 (1.00, 4.21) |
| Khasanov 2017     | 2.5 (3.2)      | 9              | 19               | 3.0%                     | 4.26 (1.59, 6.94) |
| Langdell 2017     | 2.9 (0.5)      | 208            | 309              | 22.2%                    | 3.40 (3.31, 3.49) |
| McClung 2014      | 4.1 (0.9)      | 50             | 49               | 21.0%                    | 2.62 (2.07, 3.17) |
| Global (95% CI)   | 274            | 286            | 36.9%            |                          | 3.17 (2.68, 3.66) |
| Heterogeneity: Tau^2 = 0.14; Chi^2 = 13.84; df = 0 (P = 0.002); I^2 = 64% | | | | |
| Test for overall effect: Z = 12.19 (P = 0.00001) | | | | |

| **Total (95% CI)** | 536            | 554            | 100.5%           |                          |
| Heterogeneity: Tau^2 = 0.27; Chi^2 = 205.11; df = 6 (P = 0.00001); I^2 = 99% | | | | |
| Test for overall effect: Z = 31.44 (P = 0.00001) | | | | |
| Test for autonomous difference: Chi^2 = 1.68; df = 1 (P = 0.20); I^2 = 8.9% | | | | |
Figure 6

A forest plot diagram of femoral neck BMD
Figure 7
A forest plot diagram of adverse events

Supplementary Files
This is a list of supplementary files associated with the primary manuscript. Click to download.
PRISMA 2009 checklist.pdf