



Title	Effects after starting or switching from bisphosphonate to romosozumab or denosumab in Japanese postmenopausal patients
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Citation	Journal of Bone and Mineral Metabolism, 39(5), 868-875 <a href="https://doi.org/10.1007/s00774-021-01226-1">https://doi.org/10.1007/s00774-021-01226-1</a>
Issue Date	2021-09
Doc URL	<a href="http://hdl.handle.net/2115/86683">http://hdl.handle.net/2115/86683</a>
Rights	This is a post-peer-review, pre-copyedit version of an article published in Journal of Bone and Mineral Metabolism. The final authenticated version is available online at: <a href="http://dx.doi.org/10.1007/s00774-021-01226-1">http://dx.doi.org/10.1007/s00774-021-01226-1</a>
Type	article (author version)
File Information	J Bone Miner Metab 39 868-875.pdf



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1 **Effects after starting or switching from bisphosphonate to romosozumab or denosumab in**  
2 **Japanese postmenopausal patients**

3

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## 1 **Abstract**

### 2 *Purpose*

3 We aimed to investigate the longitudinal changes in bone metabolic markers and bone mineral  
4 density (BMD) after starting or switching from bisphosphonate (BP) to romosozumab (ROMO)  
5 or denosumab (DENO) therapies over 12 months and to determine predictors that establish  
6 associations with changes in BMD among the patients received the ROMO therapy.

### 7 *Methods*

8 Postmenopausal osteoporosis patients with a high risk of fracture—154 in total—were recruited;  
9 their therapies were switched to ROMO or DENO from BP/naïve or vitamin D (ND) (ND-  
10 ROMO: 43, BP-ROMO: 38, ND-DENO: 38, and BP-DENO: 35). Longitudinal changes in bone  
11 metabolic markers and BMD were evaluated.

### 12 *Results*

13 ROMO groups showed significant increases in BMD of the lumbar spine at 6 and 12 months and  
14 femoral neck at 12 months compared to the DENO groups. Although BP-ROMO showed  
15 significant increase in the lumbar spine BMD compared to BP-DENO, there were no significant  
16 differences in femoral neck and total hip BMDs between BP-ROMO and BP-DENO. Among the  
17 ROMO groups, % changes of BMD from baseline to 12 months were associated with bone  
18 metabolic markers at baseline and changes in TRACP-5b from baseline to 3 months.

### 19 *Conclusions*

20 ROMO continuously increased BMD for 12 months and performed better than DENO. On the  
21 other hand, effects of ROMO switched from BP on BMD of femoral neck and total hip were  
22 almost same with DENO. Bone metabolic markers at baseline and changes in TRACP-5b from  
23 baseline to 3 months may predict the efficacy of ROMO after 12 months of administration.

1

2 **Keywords:** postmenopausal osteoporosis, romosozumab, denosumab, bone metabolic marker

3

4 **Conflicts of interest/Competing interests**

5 Tomohiro Shimizu, Kosuke Arita, Eihiro Murota, Shigeto Hiratsuka, Ryo Fujita, Tsuyoshi

6 Asano, Masahiko Takahata and Norimasa Iwasaki declare that they have no conflict of interest.

7

## 1 **Introduction**

2           Osteoporosis is a chronic, progressive condition that requires long-term management. An  
3           estimated 9 million new osteoporosis-related fractures were reported worldwide in the year 2000  
4           [1], and 75 million people in the United States, Europe, and Japan are affected by osteoporosis [2].  
5           In 2010 there were estimated to be 158 million individuals at high fracture risk. Demographic  
6           shifts mean that this figure is likely to double by 2040 [3]. Patients with osteoporosis are usually  
7           treated with bisphosphonates (BP) as first-line therapy because of their high effectiveness, long-  
8           term benefits, and price considerations. In patients who are at high risk of fractures and patients  
9           who do not respond sufficiently, such as those who have a persistent low bone mineral density  
10          (BMD) or those who develop fractures regardless of BP therapy, starting or switching to potent  
11          therapies is the common clinical practice.

12          Romosozumab (ROMO) is a monoclonal antibody that binds to and inhibits sclerostin.  
13          ROMO therapy has a dual effect; it increases bone formation and decreases bone resorption [4,5].  
14          Because of this unique dual effect, the anabolic window, which determines the effects of  
15          osteoporosis treatment, is assumed to be larger for ROMO than for other osteoporosis treatments  
16          [6]. Large-cohort randomized control studies showed that ROMO was associated with increased  
17          bone mineral density and formation and decreased bone resorption and lower risk of vertebral  
18          fractures than the placebo at 12 months [5,7]. Furthermore, other randomized cohort studies  
19          showed that ROMO treatment for 12 months followed by alendronate treatment significantly  
20          lowered the risk of fractures than treatment with alendronate and teriparatide [8,9]. Contrarily,  
21          there is limited information comparing ROMO with denosumab (DENO), a human monoclonal  
22          antibody that targets the osteoclast differentiation factor/receptor activator of the NF- $\kappa$ B ligand  
23          [10].

1           Japan approved ROMO in March 2019 and was the first to do so. Recent clinical reports  
2   on Japanese patients with postmenopausal osteoporosis in the real-world setting also showed that  
3   ROMO was effective in increasing BMD and preventing fractures even after 4–6 months of  
4   treatment [11,12]. Although these reports showed that differences in prior treatment and early  
5   changes in bone turnover markers were associated with changes in BMD, there was still a paucity  
6   of information regarding the efficacy of ROMO until 12 months and its predictors in the real-world  
7   setting. Therefore, the current study aimed to investigate the longitudinal changes in bone  
8   metabolic markers and bone mineral density (BMD) after starting or switching from BP to ROMO  
9   or DENO therapies over 12 months and to determine predictors that establish associations with  
10  changes in BMD among the patients received the ROMO therapy. The hypotheses of this current  
11  study were that ROMO therapy could be one of most ideal treatment options for postmenopausal  
12  osteoporosis patients with high-risk fragility fracture and that bone metabolic markers before  
13  administration could be predictor for the therapeutic efficacy of ROMO.

14

## 15 **Materials and Methods**

### 16 *Study design and subjects*

17           This study was conducted in accordance with the ethical standards of the Declaration of  
18  Helsinki and approved by the Hokkaido University Hospital Institutional Review Board (#020-  
19  0188). A total of 327 patients with postmenopausal osteoporosis met the criteria defined by the  
20  Japanese guidelines for prevention and treatment of osteoporosis [13,14], who were at a high risk  
21  of fractures, were visited to our clinical team from January 2014 to December 2019. They were  
22  treated using DENO (60 mg, subcutaneously every 6 months), zoledronic acid (Zol) (5 mg,  
23  intravenous drip infusion), and ROMO (210 mg, subcutaneously every month) in combination

1 with a daily oral active vitamin D by our clinical team from January 2014 to December 2019  
2 (Fig. 1). A high risk of fracture was defined by 1) BMD < - 2.5 of SD (standard deviation) and  
3 one or more fragility fractures, 2) lumbar BMD < - 3.3 of SD [15,16], 3) two or more fragility  
4 fractures [15,17], or 4) semi-quantitative evaluation [18] of existing grade 3 vertebral fracture  
5 [17]. The patients were treated with DENO from January 2014 to December 2016, Zol from  
6 January 2017 to February 2019, and ROMO from March to December 2019, unless the patients  
7 hoped the other therapy. The switch from BPs to the abovementioned treatments showed no  
8 increase in BMD. Patients 1) treated with Zol (Zol group); 2) switched from selective estrogen  
9 receptor modulator, teriparatide, and DENO (ROMO group); 3) with a history of angina,  
10 cerebral, or myocardial infarction; 4) < 50 years old; 5) who were male; and 6) with severe  
11 chronic kidney disease (stage 4 and 5), and 7) with abnormal serum levels of albumin-corrected  
12 calcium (Ca) (< 8.3 or > 10.3 mg/dL) at baseline, were excluded from the study. Ten of the 112  
13 patients treated with ROMO from March to December 2019 dropped out before 12 months—five  
14 due to infection with the novel coronavirus, one moved cities, one suffered a cancer recurrence  
15 and switched to DENO treatment, and the other three due to unknown reasons. In this current  
16 study, we retrospectively investigated 73 patients treated with DENO from January 2014 to  
17 December 2016 and 81 patients treated with ROMO from March to December 2019. The  
18 following baseline clinical information was obtained: the levels of albumin-corrected Ca, bone  
19 metabolic markers, 25-dihydroxy vitamin D [25(OH)D], intact parathyroid hormone (PTH), and  
20 liver and renal function from the analysis of blood samples. BMD was evaluated using dual-  
21 energy X-ray absorptiometry (DXA); X-rays of the whole spine and full length of the lower  
22 limbs were obtained for evaluating previous fragility fractures and risk factors for atypical  
23 femoral fractures. The levels of serum albumin-adjusted calcium (Ca), total type I procollagen

1 N-propeptide (P1NP), and tartrate-resistant acid phosphatase 5b (TRACP 5b) were monitored at  
2 3, 6, and 12 months after starting or switching to ROMO. Monitoring of serum Ca and  
3 inflammatory reactions was started after 1 or 2 weeks of DENO and ROMO administration to  
4 evaluate changes in Ca levels and assess side effects.

#### 5 ***BMD assessment***

6 Areal BMD of the lumbar spine (LS; L2–L4), femoral neck (FN), and total hip (TH) was  
7 assessed at baseline and 6 and 12 months after treatment, using Horizon® DXA Bone  
8 Densitometer (Hologic Discovery A, Inc., Tokyo, Japan). Regions of severe scoliosis, previous  
9 vertebral fracture, and postoperative sites were excluded from BMD measurements; at least two  
10 of the L2–L4 lumbar vertebrae had to be evaluated for BMD [19]. Subjects were excluded from  
11 the BMD assessment if the area was fractured or operated on during the study.

#### 12 ***Statistical analysis***

13 Statistical comparisons between the groups were performed using unpaired *t*-test  
14 (durations of pretreatment), or two-way analysis of variance with the Bonferroni test for post hoc  
15 comparisons. Spearman's correlation coefficients were calculated, and linear regression models  
16 adjusted for age, body mass index (BMI), pretreatment with BPs and active vitamin D, history of  
17 fragility fractures, and 25(OH)D levels were established to determine the associations with %  
18 changes in BMD between the baseline and 12 months. All statistical analyses were performed  
19 using the Statistical Package for the Social Sciences (SPSS Statistics version 23.0) (IBM  
20 Corporation, Armonk, NY, USA) with the significance level set at 0.05.

21

#### 22 ***Results***



## 1 *Clinical characteristics*

2           Table 1 shows the baseline characteristics. The number of patients who switched from  
3 naïve or vitamin D to ROMO (ND-ROMO), BPs to ROMO (BP-ROMO), ND to DENO (ND-  
4 DENO), and BPs to DENO (BP-DENO) was 43, 38, 38, and 35, respectively. Two-way ANOVA  
5 showed statistically significant differences in mean BMI values between treatments (ROMO vs  
6 DENO) ( $P = 0.016$ ) and pretreatments (ND vs BP) ( $P = 0.031$ ). No interaction was detected  
7 between pretreatment and treatment values ( $P = 0.173$ ). Post hoc Bonferroni tests showed that  
8 the mean BMI of patients was significantly higher in the ND-ROMO group than in the BP-  
9 ROMO group ( $P = 0.019$ ). The mean duration of pretreatment with BP-DENO was significantly  
10 higher than that of pretreatment with BP-ROMO ( $P = 0.015$ ). A total of 21 patients in the ND-  
11 ROMO group, 24 in the BP-ROMO group, 10 in the ND-DENO group, and 23 in the BP-DENO  
12 group used active vitamin D3. The number of patients who experienced fragility fractures was  
13 34, 22, 21, and 23 in the ND-ROMO, BP-ROMO, ND-DENO, and BP-DENO groups,  
14 respectively. Two-way ANOVA showed a statistical difference between pretreatments (ND vs  
15 BP) in the mean of bone metabolic markers (P1NP:  $P < 0.001$  and TRACP-5b:  $P < 0.001$ ). No  
16 interaction was detected between pretreatment and treatment values (P1NP:  $P = 0.994$  and  
17 TRACP-5b:  $P = 0.918$ ). Post hoc Bonferroni tests showed that the mean of bone metabolic  
18 markers of patients in the ND-ROMO group was significantly higher than that of those in the  
19 BP-ROMO group (P1NP:  $P < 0.001$  and TRACP-5b:  $P < 0.001$ ) and that of patients in the ND-  
20 DENO group was significantly higher than that of those in the BP-DENO group (P1NP:  $P <$   
21  $0.001$  and TRACP-5b:  $P < 0.001$ ). There were no differences in age, Ca levels, estimated  
22 glomerular filtration rate (eGFR) levels, 25(OH)D levels, intact PTH level, and percent young  
23 adult mean (% YAM) at baseline, between the groups. Notably, one patient each in the BP-

1 ROMO experienced the right calcaneus fracture at 6 months after administration. One patient in  
2 the ND-DENO group and two patients in the BP-DENO group were observed the occurrence of  
3 new vertebral body fracture at 12 months after administration.

#### 4 ***Longitudinal changes in Ca, PINP, and TRACP 5b levels***

5 For the decrease in serum Ca levels from baseline to 1 or 2 weeks, two-way ANOVA  
6 showed a statistically significant difference between pretreatments (ND vs BP) ( $P = 0.031$ ). No  
7 interaction was detected between the pretreatment and treatment values ( $P = 0.485$ ). Post hoc  
8 Bonferroni tests did not show significant differences between ND and BP in the ROMO and  
9 DENO groups (ROMO:  $P = 0.491$  and DENO:  $P = 0.093$ ). While no patients showed  
10 hypocalcaemia (Ca level  $< 8.4$ ) in the ROMO group, three patients in the ND-ROMO group  
11 showed hypocalcaemia. However, none experienced serious side effects related to it (tonic  
12 convulsions and tetany).

13 For the change of PINP levels at 3, 6, and 12 months, two-way ANOVA showed  
14 statistically significant differences between pretreatments (ND vs BP) (3 months:  $P = 0.003$ , 6  
15 months:  $P < 0.001$ , and 12 months:  $P < 0.001$ ) and treatments (ROMO vs DMAb) (3 months:  $P <$   
16  $0.001$ , 6 months:  $P < 0.001$ , and 12 months:  $P < 0.001$ ) (Fig. 2a). There were significant  
17 interactions between pretreatment and treatment values at 6 and 12 months (6 months:  $P = 0.026$   
18 and 12 months:  $P = 0.009$ ). For the change of TRACP-5b levels at 3, 6, and 12 months, two-way  
19 ANOVA showed statistically significant differences between pretreatments (ND vs BP) (3  
20 months:  $P < 0.003$ , 6 months:  $P = 0.001$ , and 12 months:  $P < 0.001$ ) and treatments (ROMO vs  
21 DENO) (3 months:  $P < 0.001$ , 6 months:  $P < 0.001$ , and 12 months:  $P < 0.001$ ) (Fig. 2b). No  
22 interaction was detected between the pretreatment and treatment values.

## 1 *Longitudinal changes in BMD*

2           At 6 and 12 months after the administration of ROMO or DENO, all groups showed  
3 increases in lumbar spine, femoral neck, and total hip BMDs compared to those at baseline (Fig.  
4 3). For the change in BMD of the lumbar spine at 6 and 12 months, two-way ANOVA showed a  
5 statistically significant difference between treatments (ROMO vs DENO) (6 months:  $P < 0.001$   
6 and 12 months:  $P < 0.001$ ) (Fig. 3a). No interaction was detected between the pretreatment and  
7 treatment values. For the change in BMD of the femoral neck at 6 months, two-way ANOVA  
8 showed a statistically significant difference between pretreatments (ND vs BP) ( $P = 0.031$ ) (Fig.  
9 3b). For that at 12 months, two-way ANOVA showed a statistically significant difference  
10 between treatments (ROMO vs DENO) ( $P = 0.041$ ). No interaction was detected between the  
11 pretreatment and treatment values. For the change in BMD of the total hip at 6 months, two-way  
12 ANOVA showed a statistically significant difference between pretreatments (ND vs BP) (6  
13 months:  $P = 0.027$  and 12 months:  $P = 0.006$ ) (Fig. 3c). There was a significant interaction  
14 between pretreatment and 12-month treatment values of BMDs of the total hip ( $P = 0.021$ ).

## 15 *Association between change in BMD from baseline to 12 months in the ROMO groups*

16           Spearman's correlation coefficients revealed that the significant confounders ( $P < 0.05$ )  
17 for the BMD change of the lumbar spine at 12 months were age ( $r = -0.283$ ,  $P = 0.021$ ), BMI ( $r =$   
18  $-0.273$ ,  $P = 0.035$ ), P1NP value at baseline ( $r = 0.389$ ,  $P = 0.001$ ), TRACP-5b value at baseline ( $r$   
19  $= 0.401$ ,  $P < 0.001$ ) and its percentage change at three months ( $r = -0.326$ ,  $P = 0.024$ ), and 25  
20 OHD value at baseline ( $r = 0.271$ ,  $P = 0.029$ ). The significant confounders for the BMD change  
21 of the femoral neck at 12 months were age ( $r = -0.410$ ,  $P = 0.002$ ), P1NP value at baseline ( $r =$   
22  $0.310$ ,  $P = 0.025$ ), and TRACP-5b value at baseline ( $r = 0.359$ ,  $P = 0.009$ ) and its percentage  
23 change at three months ( $r = -0.295$ ,  $P = 0.044$ ). The significant confounders for the BMD change

1 of the total hip at 12 months were P1NP value at baseline ( $r = 0.494$ ,  $P < 0.001$ ) and its  
2 percentage change at three months ( $r = -0.331$ ,  $P = 0.025$ ), and TRACP-5b value at baseline ( $r =$   
3  $0.489$ ,  $P < 0.001$ ) and its percentage change at three months ( $r = -0.329$ ,  $P = 0.025$ ).

4 In the linear regression models adjusted for age, body mass index (BMI), pretreatment  
5 with BPs and active vitamin D, history of fragility fractures, and 25(OH)D levels, the % changes  
6 of BMD of the lumbar spine from baseline to 12 months were associated with P1NP value at  
7 baseline ( $\beta = 0.439$ ,  $P = 0.003$ ), and TRACP-5b value at baseline ( $\beta = 0.576$ ,  $P < 0.001$ ) and its  
8 percentage change at three months ( $\beta = -0.528$ ,  $P = 0.003$ ) (Table 2). Percentage changes of BMD  
9 of the femoral neck from baseline to 12 months were associated with P1NP ( $\beta = 0.343$ ,  $P = 0.049$ )  
10 and TRACP-5b ( $\beta = 0.467$ ,  $P = 0.015$ ) values at baseline. Percentage changes of BMD of the total  
11 hip from baseline to 12 months were associated with P1NP value at baseline ( $\beta = 0.434$ ,  $P = 0.003$ ),  
12 and TRACP-5b value at baseline ( $\beta = 0.329$ ,  $P = 0.037$ ) and its percentage change at three months  
13 ( $\beta = -0.407$ ,  $P = 0.029$ ).

14

## 15 **Discussion**

16 This study investigated the longitudinal efficacy of ROMO over 12 months, the  
17 maximum period approved for insurance practice in Japan, in a real-world setting. It showed that  
18 ROMO increased the BMDs of the lumbar spine, femoral neck, and total hip at 12 months. This  
19 finding was consistent with that of a previous clinical trial [20-22] and a 6-month-observational  
20 study in a real-world setting [11,12] on Japanese patients with postmenopausal osteoporosis.  
21 Considering that the ND-ROMO and BP-ROMO groups showed increases in BMDs of the  
22 lumbar spine, femoral neck, and total hip from 6 to 12 months regardless of the decrease in dual  
23 effect, increase in bone formation, and decrease in bone resorption [4,5], continuous

1 administration of ROMO for 12 months could potentially increase BMD.

2 Consistent with previous reports [11,23], we found that the bone metabolic markers at  
3 baseline were associated with changes in BMD over 12 months in patients treated with ROMO.  
4 Therefore, bone metabolic markers at baseline are useful predictors of BMD during ROMO  
5 treatment. This finding suggested that pretreatment with bisphosphonate decreased the increase  
6 of BMD with ROMO. Contrary to other clinical observations [12], this study did not show any  
7 association between early changes in P1NP and changes in BMD at 12 months. However, we  
8 observed that early changes in TRACP-5b were associated with changes in BMD at 12 months.  
9 This discrepancy may be attributed to the current study evaluating only the three months change  
10 and not the one month change as previously described [12]. Considering that ROMO was  
11 associated with a transient increase in bone formation markers and sustained decrease in bone-  
12 resorption markers [5], earlier changes in bone metabolic markers, such as in one month, might  
13 be more appropriate for predicting changes in BMD.

14 This study showed that ROMO significantly increased the lumbar spine and femoral  
15 neck BMD at 12 months compared to DENO. Therefore, ROMO is more effective in increasing  
16 BMD than DENO, alendronate, and teriparatide; this finding is in line with results shown in a  
17 phase 2, multicentre, international, and randomized control study [5]. On the other hand, this  
18 study also showed that the effects of ROMO switched from BP on BMD of femoral neck and  
19 total hip were almost same with DENO. Therefore, 12 months ROMO treatment may not be a  
20 more ideal and sufficient treatment for patients with low BMD of femoral neck or total hip who  
21 received BP therapy previously. To the best of our knowledge, this is the first study that  
22 compares the efficacy of ROMO and DENO in postmenopausal osteoporosis patients with a high  
23 risk of fracture. Because the characteristics of patients recruited varied with time, the comparison

1 between ROMO and DENO may not be accurate; this is the main limitation of this study.  
2 Therefore, a randomized control comparison study is warranted in the future to confirm the  
3 superiority of ROMO over DENO.

4         The FRAME trial showed that BMD continued to increase after switching from ROMO  
5 to DENO [7], and Ebina et al. showed that pretreatment for bone resorption attenuated the  
6 increase of BMD in ROMO compared to that in the control group [11]. Additionally, Kashii et  
7 al. showed that ROMO is not effective in preventing vertebral fractures or multiple spontaneous  
8 clinical vertebral fractures after DENO discontinuation [24]. Therefore, it might be better for  
9 postmenopausal patients with a high risk of fracture to be treated first with ROMO rather than  
10 with bone resorption inhibitors. Comparison studies in the future should address this speculation  
11 to establish a therapeutic strategy for osteoporosis with a high risk of fracture.

12         This study has some limitations. First, the study had a small sample size. Therefore, the  
13 statistical power of the results might be attenuated, and the fracture occurrence rate after  
14 initiation of treatment might be underestimated. Second, this study included pretreatment with  
15 various BPs, including alendronate and risedronate, and active vitamin D3, such as alfacalcidol  
16 and ELD, which might have affected the results. Because this was not a randomized study,  
17 differences in patients' backgrounds may potentially affect the physicians' treatment selection  
18 and subsequent effects. Larger randomized studies with longer follow-up periods should be  
19 conducted in the future.

20         In conclusion, in this 12-month follow-up study of postmenopausal osteoporosis patients  
21 with a high risk of fracture who were introduced to ROMO or DENO in a real-world setting,  
22 ROMO continuously increased BMD for 12 months and performed better than DENO. On the  
23 other hand, effects of ROMO switched from BP on BMD of femoral neck and total hip were

1 almost same with DENO. For patients treated by ROMO, bone metabolic markers at baseline  
2 and changes in TRACP-5b levels from the baseline to 3 months were associated with changes in  
3 BMD from baseline to 12 months. These findings suggest that these parameters could be useful  
4 in predicting the efficacy of ROMO. Although these results may contribute to establishing a  
5 therapeutic strategy for osteoporosis with a high risk of fracture, further investigations are  
6 required.

7

### 8 **Acknowledgements**

9 This study was funded by Grant-in-Aid for Young Scientists from the Ministry of Education,  
10 Culture, Sports, Science, and Technology of Japan 20K17948 (T. Shimizu).

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1 Table 1 Clinical characteristics at baseline

Variable	Romosozumab		Denosumab	
	ND	BPs	ND	BPs
Number	43	38	38	35
Age, years	75.3 (1.2)	73.7 (1.7)	71.8 (1.4)	74.4 (1.5)
BMI <sup>*,†</sup> , kg/m <sup>2</sup>	22.1 (0.6)	20.0 (0.6)	22.7 (0.5)	22.2 (0.6)
Duration of pretreatment <sup>*</sup> , months	NA	26.2 (3.9)	NA	43.8 (5.9)
Prior active vitamin D3 use	21 patients	24 patients	10 patients	23 patients
History of fragility fractures	34 patients	22 patients	21 patients	23 patients
Ca, mg/dL	9.51 (0.08)	9.56 (0.09)	9.47 (0.06)	9.58 (0.07)
eGFR, mL/min/1.73m <sup>2</sup>	65.8 (2.4)	68.4 (2.7)	73.4 (2.3)	69.2 (3.2)
P1NP <sup>†</sup> , ng/mL	62.7 (5.9)	30.2 (4.6)	56.3 (5.4)	21.6 (2.0)
TRACP-5b <sup>†</sup> , mU/dL	497.6 (37.2)	285.5 (28.5)	451.0 (27.2)	279.5 (20.2)
25(OH)D, ng/mL	15.3 (0.8)	17.5 (0.9)	17.7 (1.0)	17.0 (1.2)
Intact PTH, pg/mL	42.2 (3.4)	32.8 (4.1)	37.1 (1.1)	36.8 (2.4)
% YAM Lumbar, %	71.5 (1.9)	68.2 (2.7)	68.5 (2.1)	71.7 (2.1)
% YAM FN, %	62.5 (2.0)	62.1 (1.6)	61.8 (1.6)	62.2 (1.6)
% YAM TH, %	69.6 (2.2)	67.5 (1.8)	68.0 (1.7)	65.9 (1.9)

2 Mean (standard error of the mean). \*: P < 0.05 romosozumab vs. denosumab, †: P < 0.05 ND vs.

3 BP group.

4 ND: naïve or vitamin D, BPs: bisphosphonates, BMI: body mass index, Ca: calcium, Cr:

5 creatinine, eGFR: estimated glomerular filtration rate, P1NP: total type 1 procollagen-N-

6 propeptide, TRACP-5b: tartrate-resistant acid phosphatase 5b, 25(OH)D: 25-hydroxy vitamin D,

7 PTH: parathyroid hormone, YAM: young adult mean, FN: femoral neck, TH: total hip

8

9

10

1 Table 2 Linear regression models of association of changes in bone mineral density among patients  
 2 treated by Romosozumab

Factor	$\beta$	95 % confidence interval		P-value
% change of BMD of the lumbar spine				
P1NP at BL	0.439	0.029	0.134	0.003
TRACP-5b at BL	0.576	0.010	0.029	<0.001
% change of P1NP at 3M	-0.136	-0.033	0.014	0.422
% change of TRACP-5b at 3M	-0.528	-0.213	-0.047	0.003
% change of BMD of the femoral neck				
P1NP at BL	0.343	0.001	0.209	0.049
TRACP-5b at BL	0.467	0.006	0.048	0.015
% change of P1NP at 3M	0.090	-0.030	0.050	0.621
% change of TRACP-5b at 3M	-0.160	-0.216	0.093	0.424
% change of BMD of the total hip				
P1NP at BL	0.434	0.029	0.139	0.003
TRACP-5b at BL	0.329	0.008	0.024	0.037
% change of P1NP at 3M	-0.079	-0.030	0.019	0.659
% change of TRACP-5b at 3M	-0.407	-0.190	-0.011	0.029

3 #Adjusted by age, body mass index, pretreatment with BPs and active vitamin D, history of  
 4 fragility fractures, and 25(OH)D levels. P1NP: total type 1 procollagen-N-propeptide, TRACP-  
 5 5b: tartrate-resistant acid phosphatase 5b, 25(OH)D: 25-hydroxy vitamin D, BL: baseline, and  
 6 3M: 3 months.

7

1 **Figure legends**

2 **Fig. 1** Study design. SERM: selective estrogen receptor modulator.

3 **Fig. 2** Comparison of longitudinal changes in (a) serum P1NP and (b) serum TRACP-5b levels at

4 3-, 6-, and 12-months post-administration. Data show mean  $\pm$  standard error of the mean, \*P <

5 0.05: Romosozumab vs. Denosumab, †P<0.05: non-bisphosphonate vs. bisphosphonate.

6 #P<0.05, interaction. BP: bisphosphonates, P1NP: total type 1 procollagen-N-propeptide,

7 TRACP-5b: tartrate-resistant acid phosphatase 5b.

8 **Fig. 3** Longitudinal % changes in bone mineral densities of the (a) lumbar, (b) femoral neck, and

9 (c) total hip. Data show mean  $\pm$  standard error of the mean. \*P < 0.05: Romosozumab vs.

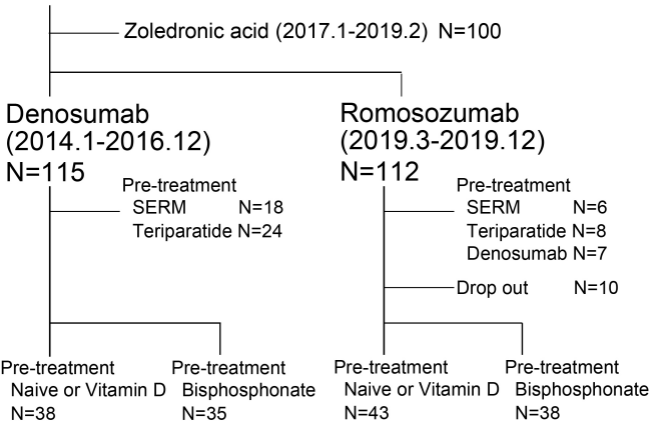
10 Denosumab, †P<0.05: non-bisphosphonate vs. bisphosphonate. BP: bisphosphonate. BMD: bone

11 mineral density.

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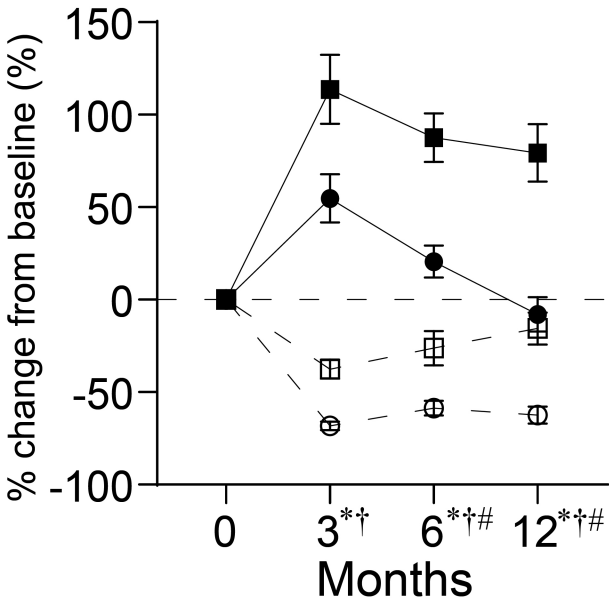
# Postmenopausal osteoporosis with high risk of fracture

N=327

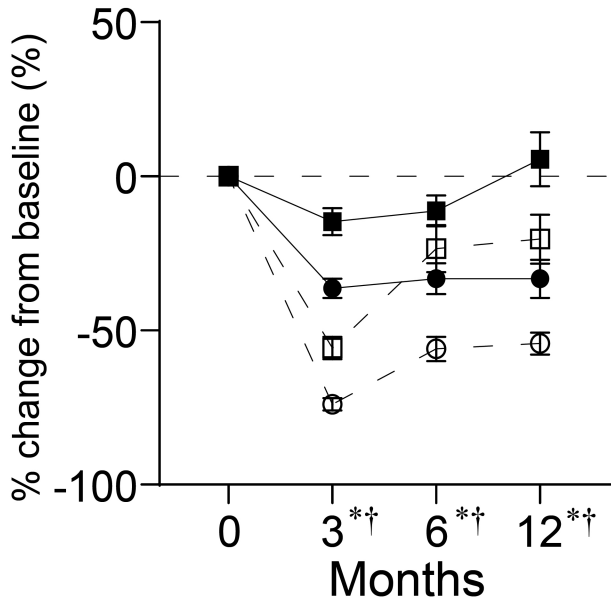


**a****Change of P1NP, %**

- Romosozumab switched from naïve or vitamin D (N=43)
- Romosozumab switched from BP (N=38)
- Denosumab switched from naïve or vitamin D (N=38)
- Denosumab switched from BP (N=35)

**b****Change of TRACP-5b, %**

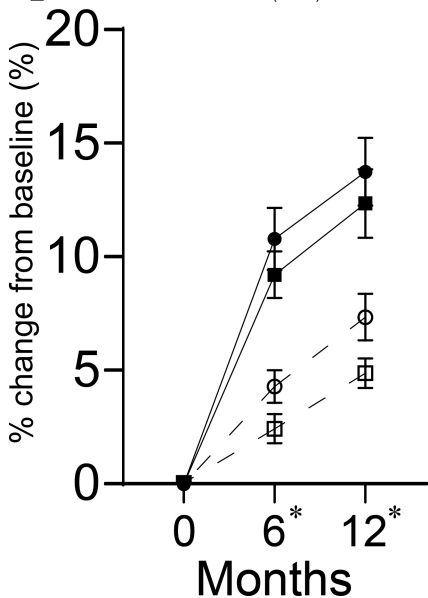
- Romosozumab switched from naïve or vitamin D (N=43)
- Romosozumab switched from BP (N=38)
- Denosumab switched from naïve or vitamin D (N=38)
- Denosumab switched from BP (N=35)



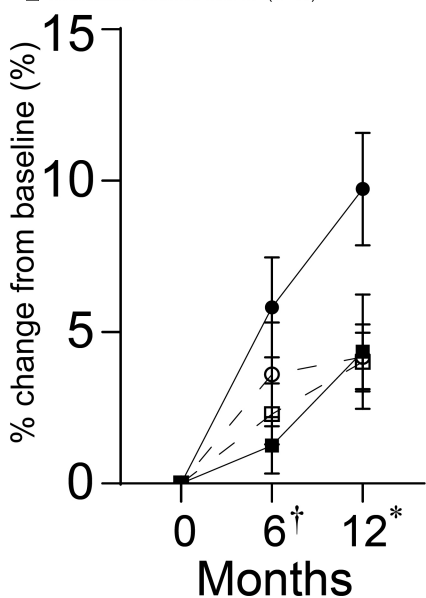


**a**Change of BMD<sub>lumbar spine</sub> %

- Romosozumab switched from naïve or vitamin D (N=43)
- Romosozumab switched from BP (N=38)
- Denosumab switched from naïve or vitamin D (N=38)
- Denosumab switched from BP (N=35)

**b**Change of BMD<sub>femoral neck</sub> %

- Romosozumab switched from naïve or vitamin D (N=43)
- Romosozumab switched from BP (N=38)
- Denosumab switched from naïve or vitamin D (N=38)
- Denosumab switched from BP (N=35)

**c**Change of BMD<sub>total hip</sub> %

- Romosozumab switched from naïve or vitamin D (N=43)
- Romosozumab switched from BP (N=38)
- Denosumab switched from naïve or vitamin D (N=38)
- Denosumab switched from BP (N=35)

