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Note	

1 **Original Article**

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3 Effects of prior osteoporosis treatment on 12-month treatment response of romosozumab in

4 patients with postmenopausal osteoporosis

5

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36

37

Abstract

Objectives:

To investigate the effects of prior treatment and determine the predictors of a 12-month treatment response of romosozumab (ROMO) in 148 patients with postmenopausal osteoporosis.

Methods:

In this prospective, observational, and multicenter study, treatment naïve patients (Naïve; n = 50) or patients previously treated with bisphosphonates (BP; n = 37) or denosumab (DMAb; n = 45) or teriparatide (TPTD; n = 16) (mean age, 75.0 years; T-scores of the lumbar spine [LS] −3.2 and total hip [TH] −2.6) were switched to ROMO due to insufficient effects of prior treatment. Bone mineral density (BMD) and serum bone turnover markers were evaluated for 12 months.

Results:

At 12 months, changes in LS BMD were Naïve (18.2%), BP (10.2%), DMAb (6.4%), and TPTD (11.2%) ($P < 0.001$ between groups) and changes in TH BMD were Naïve (5.6%), BP (3.3%), DMAb (0.6%), and TPTD (4.4%) ($P < 0.01$ between groups), respectively. In all groups, the LS BMD significantly increased from baseline at 6 and 12 months, although only the DMAb group failed to obtain a significant increase in TH BMD during 12-month treatment. Mean values of N-terminal type I procollagen propeptide (PINP; μg/L) from baseline → 1 month → 12 months were Naïve (67.9 → 134.1 → 51.0), BP (32. 2 → 81.7 → 40.9), DMAb (30.4 → 56.2 → 75.3), and TPTD (97.4 → 105.1 → 37.1), and those of isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b; mU/dL) were Naïve (500.4 → 283.8 → 267.1), BP (273.4 → 203.1 → 242.0), DMAb (220.3 → 246.1 → 304.8), and TPTD

61 (446.6 → 305.1 → 235.7), respectively. Multiple regression analysis revealed that the

62 significant predictors of BMD change at 12 months were difference of prior treatment ($r =$

63 -2.8, $P < 0.001$) and value of PINP at 1 month ($r = 0.04$, $P < 0.01$) for LS, and difference of

64 prior treatment ($r = -1.3$, $P < 0.05$) and percentage change of TRACP-5b at 1 month ($r =$

65 -0.06, $P < 0.05$) for TH.

66 *Conclusions:*

67 The early effects of ROMO on LS and TH BMD increase at 12 months were significantly

68 affected by the difference of prior treatment and are predicted by the early change in bone

69 turnover markers.

70

71 **Keywords**

72 romosozumab; prior treatment; predictor; bone turnover marker; postmenopausal

73 osteoporosis

74

75 **Abbreviations**

76 BMD; bone mineral density

77 BP; bisphosphonates

78 DMAb; denosumab

79 FN; femoral neck

80 LS; lumbar spine

81 N.S.; not significant

4

82   PINP; N-terminal type I procollagen propeptide

83   RANKL; receptor activator of nuclear factor–kappa B ligand

84   ROMO; romosozumab

85   TH; total hip

86   TPTD; teriparatide

87   TRACP-5b; isoform 5b of tartrate-resistant acid phosphatase

88

1. Introduction

90   Romosozumab (ROMO), a monoclonal anti-sclerostin antibody, is a novel osteoporosis agent

91   which promotes Wnt signaling by blocking sclerostin [1]. ROMO directly promotes bone

92   formation by osteoblasts, and also indirectly inhibits bone resorption by osteoclasts via

93   promoting production of osteoprotegerin (*in vivo* decoy of receptor activator of nuclear

94   factor–kappa B [RANK] ligand [RANKL]) from osteoblasts and osteocytes [2]. As a result of

95   this dual effect, the anabolic window (the difference between bone formation and bone

96   resorption), which determines the osteoporosis treatment effects, became larger with ROMO

97   than with other osteoporosis agents [3]. Especially, this anabolic window became largest

98   within 1 month after ROMO induction [1]. Consequently, ROMO showed superior increase

99   of bone mineral density (BMD) in postmenopausal women compared with alendronate or

100   teriparatide (TPTD) [1].

101   Previous researchers have investigated the effects of prior treatment on bone anabolic agents.

102   The prior use of denosumab (DMAb) before TPTD resulted in a transient decrease of BMD

103   associated with increase of bone resorption markers [4]. In addition, the prior use of

104 bisphosphonates (BP) diminished the increasing response of BMD to TPTD [5, 6]. In

105 contrast, only a few studies have shown the effects of subsequent treatment of ROMO after

106 alendronate [7] or DMAb [8], without direct comparison between other agents.

107 Taking these findings into consideration, we hypothesized that prior antiresorptive treatment

108 (such as BP or DMAb) might diminish the effects of sequential treatment by ROMO. In

109 addition, no studies have directly compared the effects of ROMO between prior

110 treatment-naïve cases, prior treatment by antiresorptive treatment (BP or DMAb) cases, or

111 prior treatment by TPTD cases.

112 In March 2019, Japan became the first country to approve the use of ROMO, and its clinical

113 data based on real-world settings are of great interest. We recently reported that the early

114 effects of ROMO on the increase of BMD at 6 months were significantly affected by the

115 difference of prior treatment [9]. In addition, we also reported a case which suffered multiple

116 spontaneous vertebral fractures after discontinuation of DMAb followed by delayed induction

117 of ROMO [10]. In this study, we aim to clarify the effects of prior treatment and to determine

118 the early predictors of the 12-month treatment response of ROMO in patients with

119 postmenopausal osteoporosis by adding patients' number and longer follow-up periods to our

120 previous study.

121

122 **2. Methods**

123 *2.1 Study design and subjects*

124 This prospective, observational, nonrandomized study was conducted in 6 centers in

125 accordance with the Japanese Guidelines for Prevention and Treatment of Osteoporosis 2011

126 [11]. A total of 148 postmenopausal patients with osteoporosis who were treatment naïve

127 (Naïve; n = 50) or treated previously with BP (n = 37), DMAb (n = 45), or TPTD (n = 16)

128 were switched to ROMO based on their physicians' decision due to an insufficient increase in

129 BMD by the prior treatment [9]. Patients generally received vitamin D and calcium

130 supplements (Table 1) and were followed up for 12 months. Figure 1 shows the study design,

131 schedule, and patient flow.

132

2.2 BMD assessment

134 Areal BMD was assessed in the LS (L2–L4), total hip (TH), and femoral neck (FN) using

135 dual-energy X-ray absorptiometry (Discovery, Hologic, Inc., Waltham, MA, USA) at

136 baseline, 6 months, and 12 months after ROMO induction. BMD data were standardized by

137 the correction method proposed by the Japan Osteoporosis Society in reference to the

138 International Society for Clinical Densitometry Guidance [12]. Regions of severe sclerosis,

139 vertebral fracture, and surgical sites were excluded from the BMD measurements, as

140 previously described [13].

141

2.3 Biochemical markers of bone turnover

143 Bone turnover markers were measured at baseline, 1 month, 6 months, and 12 months after

144 ROMO induction. From each patient, serum was obtained in the morning after an overnight

145 fast. Using an enzyme-linked immunosorbent assay, we measured isoform 5b of

146 tartrate-resistant acid phosphatase (TRACP-5b; Nittobo Medical Co. Ltd., Tokyo, Japan) as a

147 bone resorption marker, and N-terminal type I procollagen propeptide (PINP; Roche

148 Diagnostics, Basel, Switzerland) as a bone formation marker. (A previous report

149 demonstrated that the TRACP-5b level is a useful bone resorption marker that demonstrates

7

150 higher clinical sensitivity and signal-to-noise ratio compared with serum cross-linked

151 C-telopeptide of type I collagen [CTX] levels [14].) Serum 25-hydroxycholecalciferol

152 [25(OH)D] levels were measured by electrochemiluminescence using the Elecsys system

153 (Roche Diagnostics, Basel, Switzerland).

154

2.4 Radiographs

156 Spinal radiographs were obtained routinely at baseline, 6 months, and 12 months after

157 ROMO administration. For subjects who had symptoms of incidental clinical vertebral or

158 nonvertebral fractures, each attending investigator assessed unscheduled radiographs.

159

2.5 Statistical analysis

161 The differences between study groups were assessed using analysis of variance (between four

162 groups) and the Steel-Dwass test (between two groups) for continuous variables and using the

163 Fisher's exact test (between four groups) for categorical variables. Changes in BMD and

164 bone turnover marker levels from the baseline to the specified time points within each study

165 group were assessed using the Wilcoxon signed-rank test. Spearman's correlation coefficients

166 were calculated to identify significant indicators of change in LS or TH BMD ($P < 0.05$), and

167 then they were submitted to multiple regression analysis to identify their significance. All

168 statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical

169 University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for

170 Statistical Computing, Vienna, Austria) [15]. A *P* value of < 0.05 was considered significant.

171

2.6 Ethical statement

173 This study was conducted in accordance with the ethical standards of the Declaration of

174 Helsinki and approved by the institutional ethical review board of Osaka University Graduate

175 School of Medicine (approval No. 18258; Osaka University, Graduate School of Medicine)

176 and each institute. The board waived the requirement for patient informed consent by posting

177 the opt-out information in the hospitals' homepage.

178

3. Results

180 Table 1 shows the clinical backgrounds of the patients at ROMO induction. No significant

181 difference was observed among the groups in terms of baseline age, body mass index, prior

182 vertebral and nonvertebral fracture incidence ratio, combined vitamin D and calcium dose or

183 ratio or serum calcium, estimated glomerular filtration rate, and 25(OH)D levels. However,

184 we observed a significant difference in the duration of prior treatment ($P < 0.001$), interval

185 from final prior treatment prescription ($P < 0.001$), TH BMD (g/cm^2; $P < 0.05$), FN BMD

186 (g/cm^2; $P < 0.01$), and T-score ($P < 0.05$) and in serum levels of PINP ($P < 0.001$) and

187 TRACP-5b ($P < 0.001$).

188

3.1 Bone turnover markers

190 Figure 2 displays the serum PINP value (Fig. 2a) and its percentage change (Fig. 2b) as well

191 as the TRACP-5b value (Fig. 2c) and its percentage change (Fig. 2d).

192 Regarding PINP value, the Naïve group reached its highest value compared with other groups

193 at 1 month after ROMO induction, although only the DMAb group remained within the

194 reference range (14.9–68.8 µg/L) at 1 month. The tendency in the BP group was similar to

195 that of the Naïve group, although the PINP value in the BP group remained in a smaller

196 range. The TPTD group maintained its value at 1 month, which then markedly decreased

197 from 6 to 12 months. The tendency of the percentage change of PINP was similar between

198 the Naïve, BP, and TPTD groups, although only the DMAb group showed a continuous

199 increase until 6 months, which then decreased at 12 months.

200 Regarding the TRACP-5b value and percentage change, the Naïve and TPTD groups showed

201 marked decreases from 1 to 12 months. This tendency was similar in the BP group, although

202 the decreasing rate of this group from 1 to 12 months was smaller than that of the Naïve and

203 TPTD groups. On the other hand, the DMAb group showed a continuous increase from 1 to

204 12 months in both value and percentage change.

205

206 *3.2 Changes in BMD*

207 Regarding the change in LS BMD (Fig. 3a), the Naïve group had the highest increase (mean

208 ± standard errors; P value compared with baseline) (12.9% ± 0.8%; $P < 0.001$), followed by

209 TPTD (8.4% ± 0.9%; $P < 0.001$), BP (7.6% ± 1.0%; $P < 0.001$), and DMAb (3.6% ± 0.6%; P

210 < 0.001) at 6 months ($P < 0.001$ between groups). At 12 months, the Naïve group still

211 demonstrated the highest increase (18.2% ± 1.1%; $P < 0.001$), followed by the TPTD (11.2%

212 ± 1.4%; $P < 0.001$), BP (10.2% ± 0.9%; $P < 0.001$), and DMAb (6.4% ± 0.6%; $P < 0.001$)

213 groups ($P < 0.001$ between groups).

214 Regarding the change in TH BMD (Fig. 3b), the Naïve group showed the highest increase

215 (4.1% ± 0.7%; $P < 0.001$), followed by the TPTD (3.5% ± 1.0%; $P < 0.01$), BP (2.0% ±

216 0.6%; $P < 0.01$), and DMAb (1.0% ± 0.7%; $P =$ not significant; N.S.) groups at 6 months (P

10

217 < 0.05 between groups). At 12 months, the Naïve group still had the highest increase (5.6% ±

218 0.8%; *P* < 0.001), followed by the TPTD (4.4% ± 1.2%; *P* < 0.01), BP (3.3% ± 1.2%; *P* <

219 0.01), and DMAb (0.6% ± 0.9%; *P* = N.S.) groups (*P* < 0.01 between groups).

220 Regarding the change in FN BMD (Fig. 3c), the Naïve group demonstrated the highest

221 increase (4.2% ± 1.2%; *P* < 0.01), followed by the TPTD (2.2% ± 1.1%; *P* = N.S.), DMAb

222 (1.5% ± 1.0%; *P* = N.S.), and BP (0.5% ± 1.0%; *P* = N.S.) groups at months (*P* = N.S.

223 between groups). At 12 months, the Naïve group still showed the highest increase (4.9% ±

224 1.1%; *P* < 0.001), followed by the TPTD (3.5% ± 1.2%; *P* < 0.05), BP (3.1% ± 0.9%; *P* <

225 0.01), and DMAb (0.7% ± 0.8%; *P* = N.S.) groups (*P* < 0.05 between groups).

226 Of note, only the DMAb group failed to obtain a significant increase in both TH and FN

227 BMD during 12 months of ROMO treatment.

228

3.3 Significant predictor variables of the change in LS and TH BMD

230 To investigate the early predictor of BMD response at 12 months, confounders that showed a

231 significant correlation with LS or TH BMD change at 12 months (including prior therapy

232 before ROMO [categorized as Naïve (1), TPTD (2), BP (3), and DMAb (4)]; PINP [value of

233 baseline and 1 month], TRACP-5b [value of baseline and percentage change at 1 month and 6

234 months], and baseline BMD [LS or TH T-score]) were subjected to stepwise multiple

235 regression analysis.

236 Regarding the change in LS BMD at 12 months, significant predictors were the difference of

237 prior therapy before ROMO (partial regression coefficient = −2.8, *P* < 0.001), the value of

238 PINP at 1 month (partial regression coefficient = 0.04, *P* < 0.01), and the baseline LS BMD

239 T-score (partial regression coefficient = −1.5, *P* < 0.05).

11

240 Regarding the change in TH BMD, the significant predictors were the baseline TH BMD

241 T-score (partial regression coefficient = −3.3, $P < 0.001$), the baseline value of PINP (partial

242 regression coefficient = 0.04, $P < 0.01$), percentage change in TRACP-5b at 1 month (partial

243 regression coefficient = −0.06, $P < 0.05$) and 6 months (partial regression coefficient = −0.02,

244 $P < 0.05$), and difference of prior therapy before ROMO (partial regression coefficient =

245 −1.3, $P < 0.05$).

246

3.4 Incidence of fragility fracture

248 Nine patients (6.1%) suffered major fragility fractures during the observation period. In the

249 Naïve group, one patient suffered a distal humerus fracture. In the BP group, we observed

250 one each for proximal humerus fracture, distal radius fracture, proximal tibia fracture, patella

251 fracture, and vertebral fracture. In the DMAb group, we noted one each for rib fracture,

252 proximal humerus fracture, and multiple vertebral fracture [10]. In the TPTD group, no

253 fracture incidence was observed.

254

3.5 Incidence of treatment discontinuation

256 During the observation period, 14 patients (9.5%) discontinued the treatment. Two patients

257 discontinued because of injection pain, dizziness, blood pressure elevation, and lost

258 follow-up. One patient discontinued due to subarachnoid hemorrhage attributed to aneurysm

259 rupture, decreased blood pressure, facial flush, herpes zoster, oral lichen planus, and surgery

260 for valvular disease.

261

4. Discussion

This study demonstrated that BMD increase by 12-month administration of ROMO were significantly affected by the difference of prior treatment, and are predicted by the early change in bone turnover markers.

Regarding BP, BMD gain after switching alendronate to ROMO was smaller than initial treatment by ROMO [16], which was similar to our results. A previous animal study showed that BP is absorbed not only by osteoclasts but also by osteoblasts, which leads to the suppression of bone modeling by lining osteoblasts [17]. In the present study, the BP group showed a smaller absolute value of PINP compared with the Naïve group at every time point, suggesting suppressed bone modeling by BP. On the other hand, the baseline value and percentage decrease of TRACP-5b were lower in the BP group compared with the Naïve group at every time point. This result suggests that the inhibited bone resorption by BP may diminish further suppression of bone resorption by ROMO, due to enhanced production of osteoprotegerin. Consequently, the narrowed anabolic window by BP may lead to a smaller increase in BMD compared with the Naïve group.

Regarding DMAb, a previous report showed that patients who received ROMO after DMAb demonstrated a continuous increase in bone turnover markers at 6 months, and BMD gain was smaller than initial treatment by ROMO [8], which was similar to our results. In addition, we recently reported that patients switched from DMAb to ROMO showed increased bone turnover and diminished BMD increase compared with the Naïve group at 6 months [9]. In the present study which was extended to 12 months, only the DMAb group showed a continuous increase in bone turnover and failed to obtain a significant increase in TH and FN BMD from baseline. Taking these findings together, it seems that increased bone turnover

13

285 from DMAb discontinuation (due to increased production of RANKL from osteocytes and

286 osteoblasts) cannot be fully compensated by osteoprotegerin induced by ROMO.

287 Regarding TPTD, a previous animal study showed that TPTD stimulates not only bone

288 remodeling (accounting for 70% of bone formation) but also bone modeling (accounting for

289 20%–30% of bone formation), which was particularly dominant within the first 2 months of

290 treatment [18]. In human, TPTD strongly induced both bone remodeling and modeling at 3

291 months confirmed by iliac bone biopsies [19]. In the present study, the transition from TPTD

292 to ROMO resulted in a maintained PINP level and a rapidly decreased TRACP-5b level at 1

293 month. Collectively, preceding treatment with TPTD may promote bone modeling in the

294 early phase, and may leave little place for further bone modeling by ROMO. On the other

295 hand, enhanced bone resorption by TPTD (due to enhanced production of RANKL by

296 osteoblasts) may be suppressed by enhanced production of osteoprotegerin by ROMO. These

297 findings resulted in both widening of anabolic window and increase in BMD second to the

298 Naïve group.

299 Next, we investigated the early predictors of the BMD increase by ROMO. The anabolic

300 window (increase in bone formation markers and decrease in bone resorption markers)

301 became largest within 1 month after ROMO induction [1], which suggests that this early

302 response may contribute to the BMD increase. Indeed, most of the patients who showed PINP

303 increase more than 10 µg/L at 1 month from baseline showed good LS BMD increase (more

304 than 3%) at 12 months [7]. However, they did not evaluate the correlation with bone

305 resorption markers. Multiple regression analysis in the present study revealed that the

306 12-month treatment response of ROMO in BMD increase was associated with 1-month

307 response of both bone formation marker (absolute value) for LS, and bone resorption marker

14

308 (percent change) for TH. Collectively, inhibition of bone resorption at early phase may also

309 contribute to BMD increase by ROMO, which is a novel finding of the present study.

310 Regarding the order of the treatments, switching ROMO to DMAb led to a continuous

311 increase in BMD [20]. However, our present study demonstrated that only the DMAb group

312 failed to obtain a significant increase in TH and FN BMD during the 12-month of treatment.

313 Taken together, preceding ROMO with DMAb may be more hopeful treatment strategy

314 compared with preceding DMAb with ROMO.

315 This study has several limitations. The statistical power of the results might be attenuated

316 because of the small number of included patients. Due to the purpose of the study, this was

317 not a randomized study. Minor differences in the patients' backgrounds including diversity of

318 prior treatment within the same group (both oral and intravenous agents, or different

319 frequency regimens) and lack of fixed inclusion criteria might have potentially affected the

320 physicians' treatment selection and subsequent effects. Difference of the production process

321 between TRACP-5b (enzyme produced by bone resorbing osteoclasts) and CTX (C-terminal

322 telopeptide of fibrillar collagens) [14] may lead to the difference between other studies using

323 serum CTX. However, the strength of this study is that this is the first study which

324 investigated the effects of prior treatment and the early predictors of the effects of 12-month

325 treatment by ROMO in real-world settings.

326 In conclusion, in this 12-month follow-up study of postmenopausal patients with osteoporosis

327 introduced to ROMO, the Naïve group demonstrated the highest treatment response

328 compared with the other groups, as shown by the increase in BMD. Previous DMAb

329 treatment may attenuate the treatment response, especially regarding the increase in TH and

330 FN BMD. These results may contribute to the decision of adequate subsequent treatment

331 strategy by ROMO.

15

332

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336

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340

Authors' roles

342 Study design: KE, MH, HT, and MK. Study conduct: KE, MH, and MK. Data collection: KE,

343 MH, HT, YN, MK, SK, AM, HN, YK. Data analysis: KE, MH, and MK. Data interpretation:

344 KE, MH, MK, GO, YE, KT, AG, and TM. Drafting the manuscript: KE and MK. Supervise:

345 KN and SO. Approving final version of the manuscript: KE, MH, HT, YN, MK, SK, AM,

346 HN, YK, GO, YE, KT, AG, TM, KN, and SO. KE takes responsibility for the integrity of the

347 data analysis.

348

Declaration of conflicting interests

16

363

Figure legends

365

Figure 1. Study design, schedule, and patient flow.

367 ROMO, romosozumab; BP, bisphosphonate; ALN, alendronate; RIS, risedronate; IBN,

368 ibandronate; MIN, minodronate; ZOL, zoledronate; DMAb, denosumab; TPTD, teriparatide;

369 25(OH)D, 25-hydroxycholecalciferol; LS, lumbar spine; TH, total hip; FN, femoral neck;

370 TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; PINP, type I collagen N-terminal

371 propeptide.

372

17

373 **Figure 2. Serum PINP value (a) and its percentage change (b); serum TRACP-5b value**

374 **(c) and its percentage change (d).**

375 PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of tartrate-resistant

376 acid phosphatase; BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide. Bars indicate

377 mean ± standard errors. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$; change from baseline within

378 each treatment group.

379

380 **Figure 3. Percentage change in BMD in the lumbar spine (a), total hip (b), and femoral**

381 **neck (c).**

382 BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; BMD, bone mineral density.

383 Bars indicate mean ± standard errors. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$; difference between

384 the two indicated groups. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$; change from baseline within

385 each treatment group.

386

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Table 1

1 **Table 1. Patients' clinical characteristics at baseline**

Variable	Naïve group (n = 50)	BP group (n = 37)	DMAb group (n = 45)	TPTD group (n = 16)	P value
Age (years)	73.9 ± 6.7	74.7 ± 7.1	76.1 ± 7.7	75.9 ± 6.0	N.S.
Body mass index (kg/m^2)	20.5 ± 2.9	20.5 ± 3.7	19.7 ± 1.8	19.6 ± 2.4	N.S.
Prior vertebral fracture (%)	40.0	43.2	53.3	56.2	N.S.
Prior nonvertebral fracture (%)	26.0	18.9	15.6	25.0	N.S.
Prior osteoporosis treatment	None	ALN (weekly p.o. n = 10/monthly i.v. n = 1) RIS (weekly and monthly p.o. n = 17) IBN (monthly p.o. n = 2/ monthly i.v. n = 2) MIN (monthly p.o. n = 3) ZOL (yearly i.v. n = 2)	DMAb 60 mg (every 6 months s.c. n = 45)	Daily TPTD 20μg (s.c. n = 12) Weekly TPTD 56.5 μg (s.c. n = 4)	N.A.
Duration of prior treatment (months)	0	28.1 ± 23.3	24.1 ± 15.8	11.6 ± 8.0	<0.001
Interval from final prior treatment prescription (months)	0	3.6 ± 5.3	6.2 ± 1.3	1.6 ± 1.0	<0.001
Combined VD, % (n/N)	94.0 (47/50) ALF (n = 16) ELD (n = 31)	94.6 (35/37) ALF (n = 13) ELD (n = 22)	100.0 (45/45) ALF (n = 18) ELD (n = 27)	93.8 (15/16) ALF (n = 2) ELD (n = 13)	N.S.
Combined VD, μg/day	0.6 ± 0.3	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	N.S.

Combined Ca, % (n/N)	76.0 (38/50)	62.2 (23/37)	77.8 (35/45)	87.5 (14/16)	N.S.
Combined Ca, mg/day	336.0 ± 289.8	383.8 ± 430.4	613.3 ± 594.5	356.9 ± 312.7	N.S.
Lumbar spine BMD (g/cm^2)	0.654 ± 0.133	0.732 ± 0.116	0.705 ± 0.138	0.698 ± 0.109	N.S.
Lumbar spine BMD (T-score)	−3.4 ± 1.0	−2.9 ± 0.9	−2.9 ± 1.2	−3.3 ± 0.9	N.S.
Total hip BMD (g/cm^2)	0.607 ± 0.079	0.635 ± 0.082	0.573 ± 0.087	0.614 ± 0.096	<0.05
Total hip BMD (T-score)	−2.7 ± 0.7	−2.4 ± 0.7	−2.7 ± 0.9	−2.6 ± 0.8	N.S.
Femoral neck BMD (g/cm^2)	0.519 ± 0.087	0.572 ± 0.109	0.484 ± 0.087	0.547 ± 0.096	<0.01
Femoral neck BMD (T-score)	−3.2 ± 0.7	−2.7 ± 0.8	−3.1 ± 0.8	−2.9 ± 0.8	<0.05
Corrected serum Ca (mg/dl)	9.3 ± 0.4	9.5 ± 0.4	9.6 ± 0.6	9.5 ± 0.3	N.S.
eGFR (ml/min/1.73 m^2)	71.0 ± 15.0	71.7 ± 17.9	65.1 ± 20.4	73.9 ± 17.1	N.S.
PINP (μg/l)	67.9 ± 32.0	32.2 ± 28.8	30.4 ± 30.9	97.4 ± 73.2	<0.001
TRACP-5b (mU/dl)	500.4 ± 246.1	273.4 ± 133.6	220.3 ± 142.9	446.6 ± 196.2	<0.001
25(OH)D (ng/ml)	15.0 ± 4.7	16.3 ± 5.3	15.3 ± 7.0	14.0 ± 4.9	N.S.

2   Mean ± standard deviation. % = number of patients with measurements/total number of patients.

3   Differences between the groups were determined by ANOVA or Fisher's exact test. N.S.= not significant.

4   ANOVA, analysis of variance; BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; p.o., oral

5   administration; i.v., intravenous; s.c., subcutaneous injection; ALN, alendronate; RIS, risedronate; MIN,

6   minodronate; ZOL, zoledronate; VD, vitamin D; ALF, alfacalcidol; ELD, eldecalcitol; Ca, calcium; BMD, bone

7   mineral density; eGFR, estimated glomerular filtration rate; PINP, type I collagen N-terminal propeptide;

8   TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; 25(OH)D, 25-hydroxycholecalciferol.
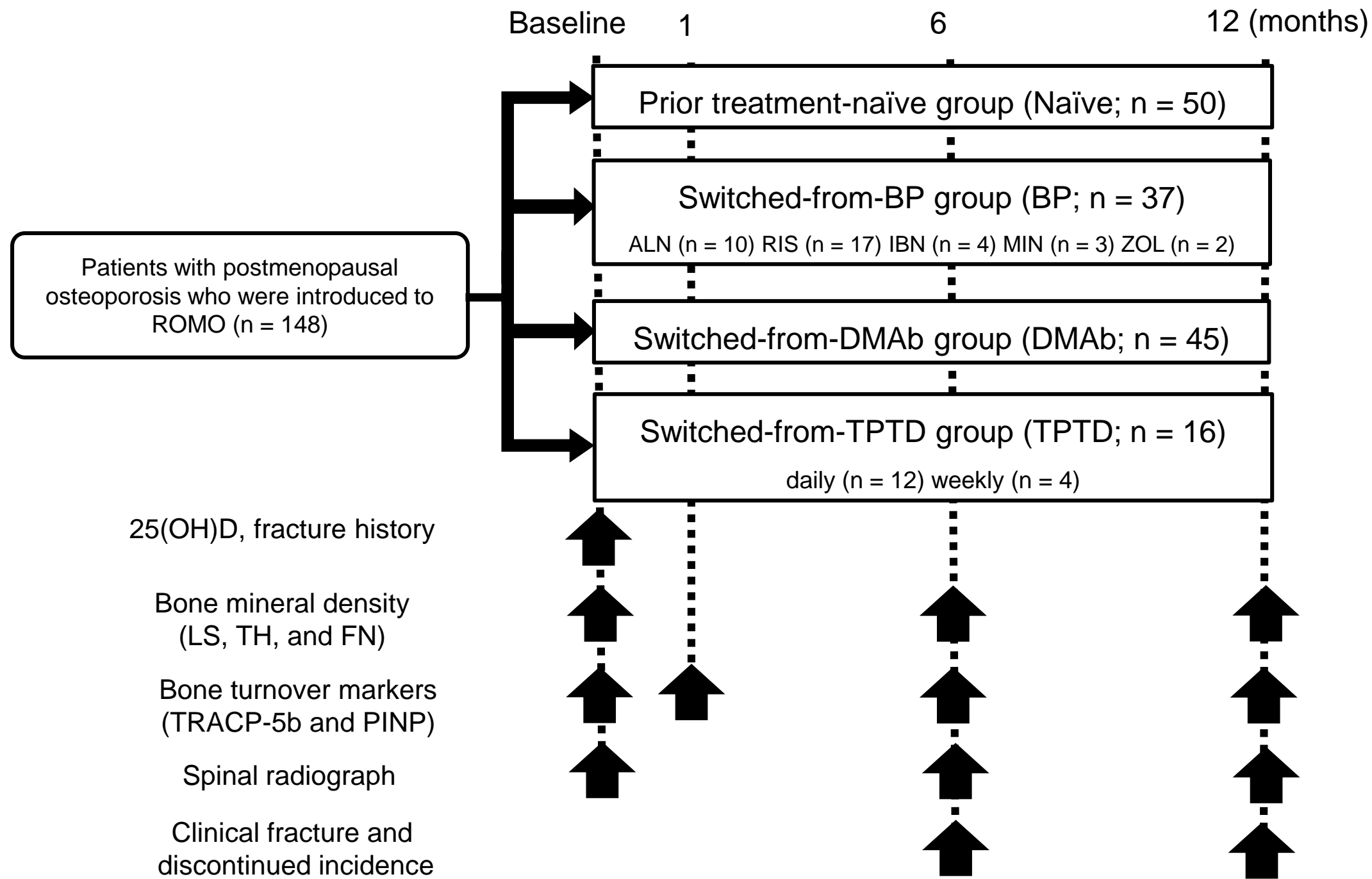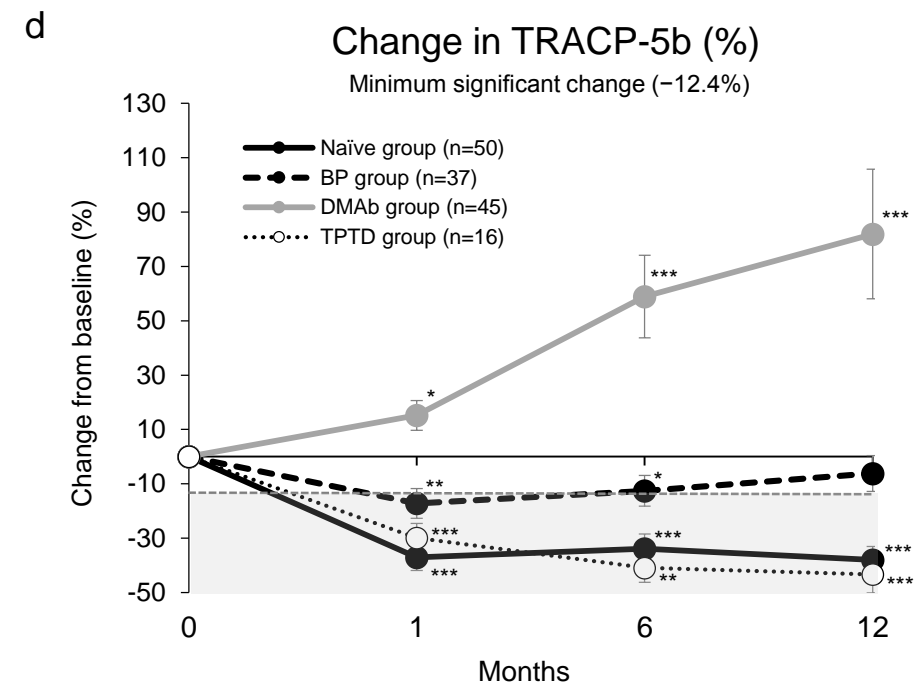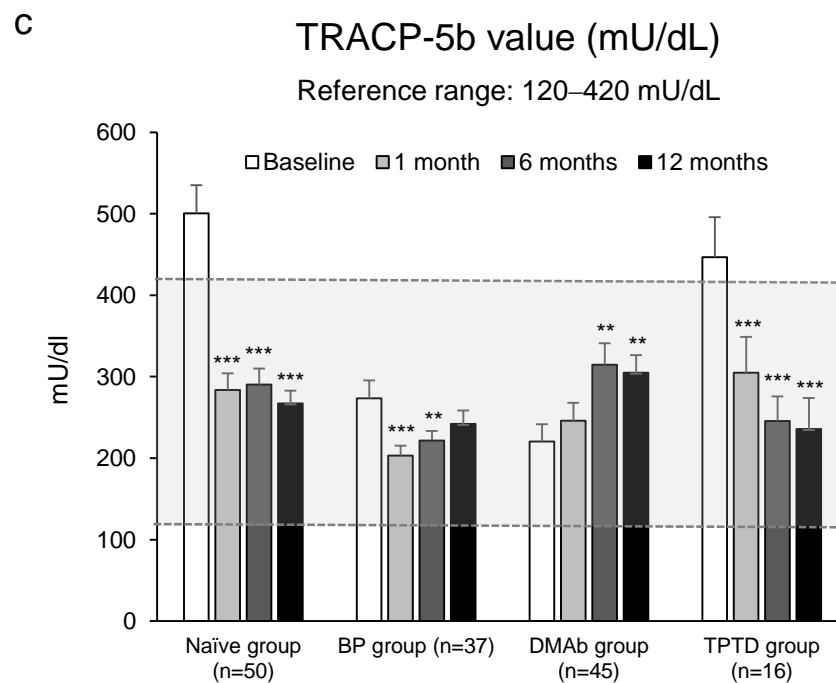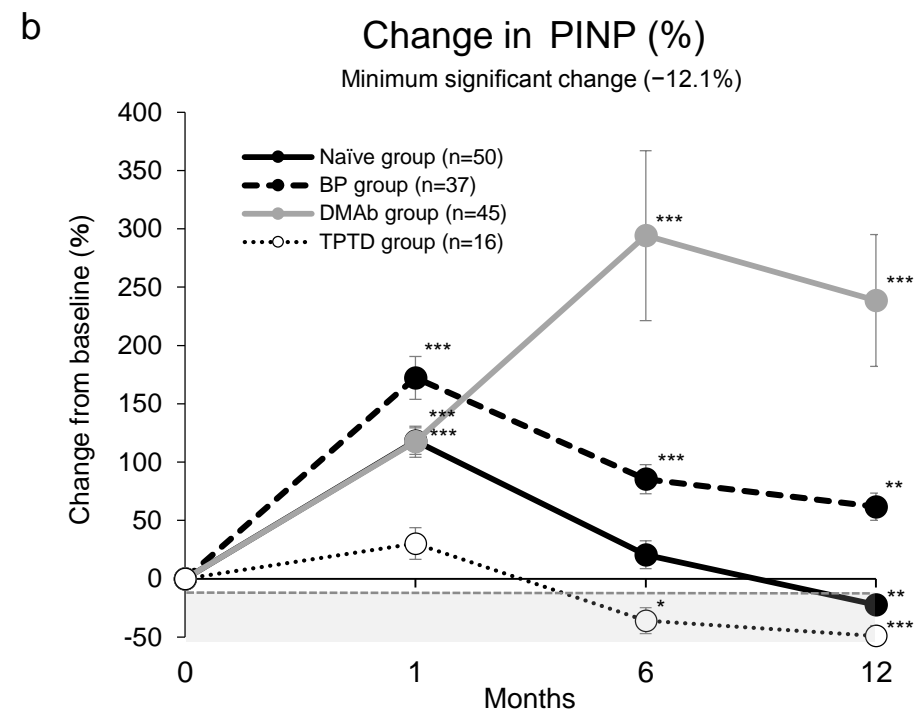
Figure 1

Baseline 1 6 12 (months)

Patients with postmenopausal osteoporosis who were introduced to ROMO (n = 148)

Prior treatment-naïve group (Naïve; n = 50)

Switched-from-BP group (BP; n = 37)
ALN (n = 10) RIS (n = 17) IBN (n = 4) MIN (n = 3) ZOL (n = 2)

Switched-from-DMAb group (DMAb; n = 45)

Switched-from-TPTD group (TPTD; n = 16)
daily (n = 12) weekly (n = 4)

25(OH)D, fracture history

Bone mineral density (LS, TH, and FN)

Bone turnover markers (TRACP-5b and PINP)

Spinal radiograph

Clinical fracture and discontinued incidence

Figure 2

a. PINP value (µg/L)
Reference range: 14.9–68.8 µg/L

b. Change in PINP (%)
Minimum significant change (−12.1%)

c. TRACP-5b value (mU/dL)
Reference range: 120–420 mU/dL

d. Change in TRACP-5b (%)
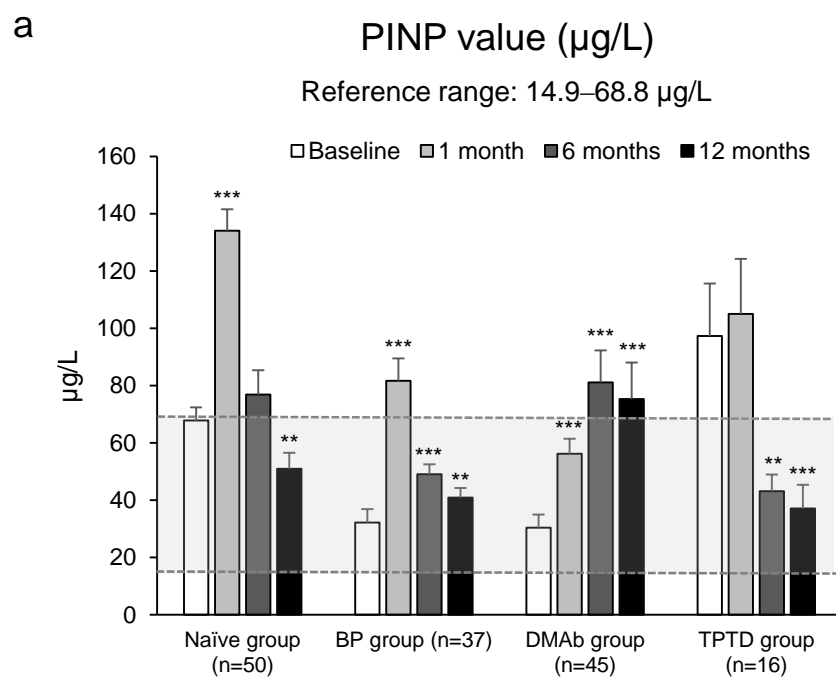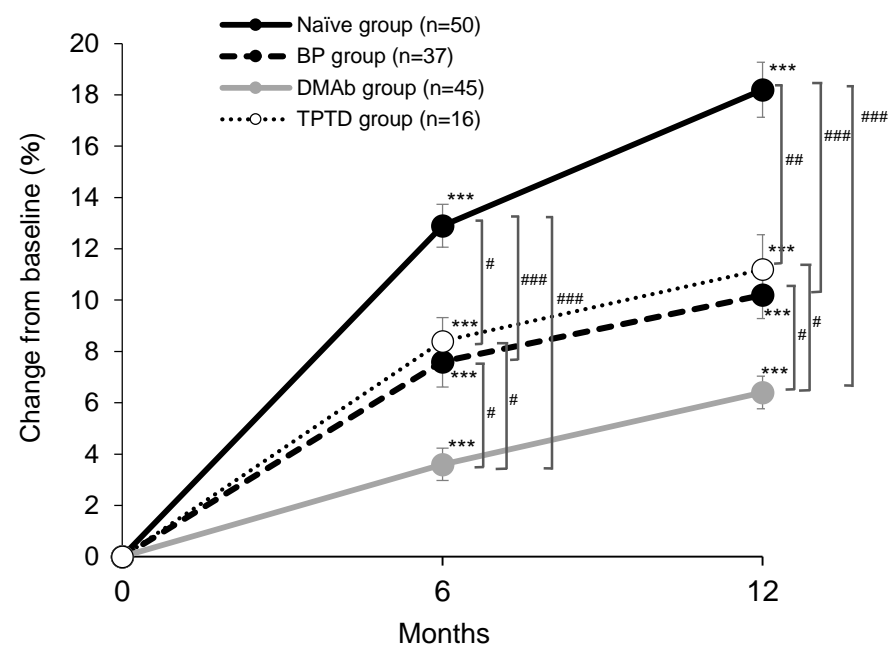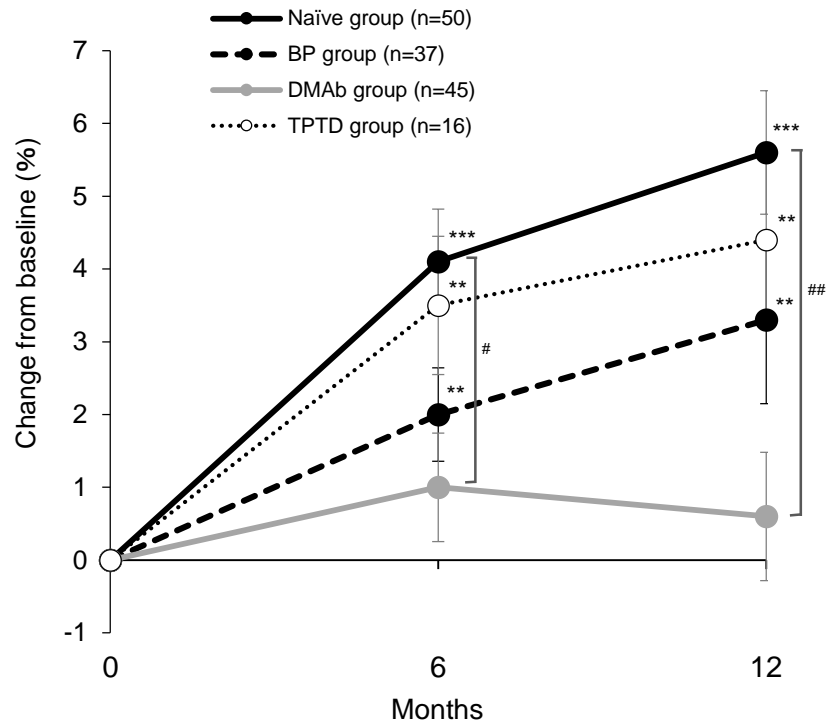Minimum significant change (−12.4%)

Figure 3

a Change in lumbar spine BMD (%)

b Change in total hip BMD (%)

c Change in femoral neck BMD (%)