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Original article

# Efficacy of once-weekly and twice-weekly injections of teriparatide by patient characteristics: A post hoc analysis of the TWICE study

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ABSTRACT

*Objectives:* To assess differences in efficacy of a 28.2-μg teriparatide formulation for twice-weekly use (2/W-TPTD) by patient characteristics.
*Methods:* A *post hoc* analysis was performed using data from a multicenter, randomized, double-blind, double-dummy, non-inferiority trial (TWICE study) conducted in Japan comparing the efficacies of once-weekly and twice-weekly injections of teriparatide (TPTD). Specifically, a stratified analysis of percentage changes from baseline was performed using the final data on lumbar spine bone mineral density (BMD) after a 48-week treatment period (n = 251, 2/W-TPTD; n = 239, a 56.5-μg teriparatide formulation for once-weekly use [1/W-TPTD]).
*Results:* Across all subgroups defined by patient characteristics that included 9 or more subjects, the lumbar spine BMD increased significantly in both groups. In the 2/W-TPTD group, the percentage change was significantly higher in subjects with no non-vertebral fractures without large external force occurring at or after age 50 years versus those with such fractures. The lower the stratification in baseline lumbar spine BMD, total hip BMD, or femoral neck BMD, the greater was the percentage change.
*Conclusions:* Whereas all subgroups can expect a significant improvement in lumbar spine BMD, there were some patient characteristics that affected the percentage increase in BMD.


## 1. Introduction

Teriparatide (TPTD) formulations promote bone formation and are used in patients with a high risk of bone fractures. In Japan, a 28.2-μg teriparatide formulation for twice-weekly use (2/W-TPTD) became commercially available in December 2019, adding to the previously available once-daily 20-μg teriparatide formulation (D-TPTD) and a 56.5-μg teriparatide formulation for once-weekly use (1/W-TPTD).

1/W-TPTD has been shown to increase bone mineral density (BMD) of the lumbar spine and the proximal femur [1,2] and reduce spine fracture risk by approximately 80% compared with placebo [2]. Meanwhile, the formulation is associated with issues including nausea, vomiting, and other adverse drug reactions, as well as low rates of treatment continuation due to the requirement for once-weekly outpatient visits, among other things [3]. Thus, 2/W-TPTD was developed to overcome these issues. We previously reported that, in a comparative study against 1/W-TPTD, 2/W-TPTD was associated with lower incidences of adverse drug reactions and resulted in significantly higher percentage changes in lumbar spine BMD at weeks 24 and 48 and at the final time point [4]. The percentage change in lumbar spine BMD at the final time point was 7.3% and 5.9%, respectively, with 2/W-TPTD and 1/W-TPTD. However, differences in the efficacy of 2/W-TPTD among subgroups defined by patient characteristics have yet to be reported. In the TOWER trial, 1/W-TPTD reportedly significantly reduced the incidence of spine fractures compared with placebo and was associated with a relative risk (RR) (95% confidence interval [CI]) of 0.20 (0.09–0.45) overall, 0.06 (0.01–0.48) in the subgroup aged under 75 years, and 0.32 (0.13–0.80) in the subgroup aged 75 years or older, showing differences depending on patient characteristics [5]. When providing treatment with 2/W-TPTD, it is also clinically important to understand that the drug's efficacy differs depending on patient characteristics. Therefore, differences in the change in

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lumbar spine BMD, the primary endpoint in the TWICE study, were analyzed among various subgroups.

## 2. Methods

### 2.1. Study design

The participants in this *post hoc* study were 553 patients who took part in a 48-week, multicenter, randomized, double-blind, double-dummy, active-controlled, non-inferiority study (JapicCTI-163477) conducted in Japan [4] and were randomized to 1 of 2 groups: a twice-weekly group that received TPTD 28.2 μg twice weekly and placebo once weekly, or a once-weekly group that received TPTD 56.5 μg once weekly and placebo twice weekly in a 1:1 ratio by dynamic allocation based on the minimization method. In principle, the TPTD 28.2 μg twice-weekly and placebo injections were self-administered using an autoinjector every 3 or 4 days, with 2 or 3 days between injections, whereas the TPTD 56.5 μg once-weekly and placebo injections were administered during outpatient visits. In addition, all participants received daily oral calcium 610 mg, vitamin $D_3$ 400 IU, and magnesium 30 mg as concomitant treatment (SHIN CALCICHEW® $D_3$; Takeda Consumer Healthcare Company Ltd., Osaka, Japan). The JapicCTI-163477 study was conducted following the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice (GCP), and institutional review board approval was obtained before the commencement of the study at each study site. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. Informed consent was obtained from all individual participants included in the study. This *post hoc* study was conducted with the primary objective of comparing the effects of background factors on the effect of TPTD to increase BMD between the two groups through a stratified analysis based on the baseline background factors.

### 2.2. Study subjects

The methods have been published previously and are only presented briefly here [4].

The inclusion criteria were as follows: age 65 years or older and capable of walking independently; diagnosed as having primary osteoporosis based on the diagnostic criteria for primary osteoporosis (FY2012 revised version) [6]; having experienced between 1 and 5 prevalent fractures between the fourth thoracic vertebra (Th4) and the fourth lumbar vertebra (L4); a mean BMD of the second through fourth lumbar vertebrae (L2–L4) of < 80% of the young adult mean (YAM) at the time of study enrollment; and capable of self-administering injections. The exclusion criteria were as follows: diagnosed as having secondary osteoporosis; any non-osteoporotic disease leading to reduced bone mass; any X-ray findings by dual energy X-ray absorptiometry (DXA) affecting the assessment of lumbar spine BMD; a serum calcium level ≥ 11.0 mg/dL; a malignant or metastatic bone tumor; undergone previous radiation therapy affecting the bone or otherwise considered to be at high risk of developing osteosarcoma; and a serum alkaline phosphatase level more than double the standard level. In addition, patients who were judged by the investigator as being unsuitable for participation, or who had previously received treatment with TPTD or an anti-receptor activator of nuclear factor-κ B ligand antibody, bisphosphonate (BP) within the previous 52 weeks, or any other osteoporosis drug within the previous 8 weeks were also excluded.

### 2.3. Efficacy endpoints

In this study, data obtained from the JapicCTI-163477 study were examined to investigate the effects of the participants' demographic characteristics and intrinsic and extrinsic factors on the percentage change in lumbar spine (L2–L4) BMD at the final time point. The intrinsic and extrinsic factors were as follows; sex, age, height, weight, body mass index (BMI), postmenopausal duration (years), history of non-vertebral fractures without large external force at or after age 50 years, history relevant to bone metabolism, smoking, alcohol consumption, parent with a femoral fracture, 25-OH vitamin D3, number of prevalent vertebral fractures at baseline, lumbar spine BMD (based on YAM) (%) at baseline, femoral neck BMD (based on YAM) (%) at baseline, total hip BMD (based on YAM) (%) at baseline, and estimated glomerular filtration rate (eGFR) at baseline.

### 2.4. Efficacy measures

DXA was used to measure the BMD of the lumbar spine and femur at screening, baseline, and weeks 24 and 48. All DXA measurements were carried out using a Discovery, Explorer, Horizon (Hologic, Marlborough, MA, USA), Lunar DPX, Lunar iDXA, or Lunar Prodigy (GE Healthcare, Chicago, IL, USA) device. All devices were calibrated for precision control before each test with an attached lumbar spine phantom. To establish external quality control (QC), specialists examined QC sheets from all study sites monthly and performed maintenance as required. All lumbar and femoral BMD measurements were analyzed centrally in a BMD analysis laboratory. In addition, whether a datum was to be included or warranted reanalysis was evaluated centrally according to criteria for BMD assessments established in advance by a data review committee.

Next, to measure bone turnover markers, samples were obtained at baseline and before the investigational drug was administered at weeks 4, 12, 24, and 48. Then, depending on the type of marker, the samples were stored in either a refrigerator or a freezer before being sent to a validated laboratory (LSI Medience Corp., Tokyo, Japan) for collective measurements. Serum osteocalcin was measured using a fluorescence enzyme immunoassay (Tosoh Corp., Tokyo, Japan), serum type I procollagen-*N*-propeptide and serum type I collagen cross-linked *C*-telopeptide by an electrochemiluminescence immunoassay (Roche Diagnostics K·K., Tokyo, Japan), and urinary type I collagen cross-linked *N*-telopeptide by an enzyme immunoassay (Alere Medical Co., Ltd., Tokyo, Japan).

### 2.5. Statistical analysis

The analysis of efficacy was carried out on the full analysis set, which included all participants who had received the investigational drug, except for those who had deviated from the GCP, who had been confirmed to have no osteoporosis, or for whom no post-treatment efficacy data were available.

Lumbar spine BMD at the final time point was used in the stratified analysis. The lumbar spine BMD values at baseline and the final time point in each subgroup were then compared using paired *t*-tests. Percentage changes in lumbar spine BMD by subgroup were compared within the 1/W-TPTD group and the 2/W-TPTD group, respectively, by Student's *t*-test or analysis of variance (ANOVA). Percentage changes in lumbar spine BMD by subgroup were compared between the 1/W-TPTD group and the 2/W-TPTD group by Student's *t*-test. Additionally, the factors related to percentage change in BMD were subjected to multiple regression analysis. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria [https://www.R-project.org/

]). All statistical tests were performed with a significance level of 0.05.

## 3. Results

The disposition of subjects and the characteristics of the subject population, which have been reported in a previous publication, are summarized below [4].

From among 859 patients at 92 sites throughout Japan who had provided informed consent to participate in the study, 553 (aged ≥ 65 years) with primary osteoporosis and considered to be at a high risk of fracture were randomly allocated to the 2 groups: 277 to the 2/W-TPTD group and 276 to the 1/W-TPTD group. All 553 patients received treatment with the investigational drug, among whom 242 (87.4%) and 235 (85.1%) in the 2/W-TPTD and 1/W-TPTD groups, respectively, completed treatment. Two patients in the 28.2-μg 2/W-TPTD group—one with no efficacy data and the other who had taken unallocated study drugs—were excluded from the FAS. No significant differences were seen between the 2 groups in the participants' baseline characteristics (Table 1).

Table 2 shows the percentage change in lumbar spine BMD (L2–L4) at the final time point by subgroups. In the 2/W-TPTD group, significant increases in lumbar spine BMD (L2–L4) at the final time point were observed across all subgroups with 9 patients or more, and an increasing trend was observed in subgroups with fewer than 9 subjects. Except in some subgroups with very few subjects, percentage changes at the final time point generally differed little among the subgroups defined by variables; however, in some subgroups, a significant difference or such a trend was seen in the percentage change depending on the baseline value.

In the 2/W-TPTD group, the percentage change was significantly higher in the subgroup without a history of fractures. In the 1W-TPTD group, the percentage change was significantly higher in the subgroup of subjects with a height under 150 cm than in the subgroup of subjects 150 cm tall or taller, and also in the subgroup of subjects without a parent with a fractured hip versus the subgroup of subjects with such a parent.

The data further showed that the percentage increase in BMD was significantly higher in the subgroup with a low baseline lumbar spine BMD than in the subgroup with a high baseline BMD in both groups. Comparisons of percentage changes in lumbar spine BMD between subgroups defined by baseline femoral neck BMDs and total hip BMDs, respectively, showed no significant differences, but similar trends. An intergroup comparative analysis of the data from subgroups defined by each factor indicated the absence of a significant difference between the 2 groups in general, but a significant improvement in the 2/W-TPTD group relative to the 1/W-TPTD group in some populations. The stratified analysis comparing 1/W-TPTD and 2/W-TPTD also showed that the percentage increase in lumbar spine BMD tended to be greater with 2/W-TPTD across all variables.

Moreover, multiple regression analysis showed that the factors associated with a substantial percentage change in BMD were low baseline BMD, absence of non-vertebral fractures without large external force occurring at or after age 50 years in the 2/W-TPTD group, and low baseline BMD in the 1/W-TPTD group (Table 3).

## 4. Discussion

A previous report showed that 2/W-TPTD provides comparable efficacy to 1/W-TPTD [4]. In the present study, a post hoc analysis of study data was performed to assess the effects of background factors on percentage change in lumbar spine BMD. In general, lumbar spine BMD increased in every subgroup, just as the percentage change did in the overall subject population. The stratified analysis demonstrated that the subgroups that showed a difference, although small, ie, a higher trend of percentage increase in BMD, included the subgroups with an absence of non-vertebral fractures without large external force occurring at or after age 50 years, and low baseline lumbar spine and femoral proximal and neck BMDs (≤60% YAM).

For patients with a high BMD, the larger denominator used in calculating the percentage increase in BMD may have contributed to a lesser degree of percentage increase.

Furthermore, the multiple regression analysis showed that a low baseline BMD was factor for a greater percentage change in BMD in both the 2/W-TPTD group and the 1/W-TPTD group. Additionally, absence of non-vertebral fractures without large external force occurring at or after age 50 years was also one such factor in the 2/W-TPTD group; it is unknown why it was a significant factor in the 2/W-TPTD group alone. The baseline 25-hydroxyvitamin D (25(OH)D) level, thought to have an effect on bone turnover, had no effect on the percentage increase in lumbar spine BMD either. This can be explained by the plain vitamin D and Ca supplementation given to

**Table 1**
Subjects' baseline characteristics.

| Variable | 2/W-TPTD (n = 275) | 1/W-TPTD (n = 276) |
|---|---|---|
| Age, yr | 74.1 ± 5.9 | 74.5 ± 6.0 |
| Sex (female), n (%) | 252 (91.6) | 251 (90.9) |
| Height, cm | 151.12 ± 6.64 | 150.78 ± 6.42 |
| Weight, kg | 50.18 ± 7.72 | 51.23 ± 7.51 |
| Prevalent vertebral fractures, n (%) | | |
| 0 | 48 (17.5) | 40 (14.5) |
| 1 | 131 (47.6) | 144 (52.2) |
| 2–3 | 80 (29.1) | 76 (27.5) |
| 4–5 | 14 (5.1) | 9 (3.3) |
| No bone assessment | 2 (0.7) | 7 (2.5) |
| Lumbar spine BMD T-score | −2.9 ± 0.7 (n = 267) | −2.9 ± 0.7 (n = 263) |
| Total hip BMD T-score | −2.3 ± 0.9 (n = 272) | −2.2 ± 0.8 (n = 271) |
| Femoral neck BMD T-score | −3.1 ± 0.9 (n = 272) | −2.9 ± 0.8 (n = 271) |
| 25-OH vitamin D3, ng/mL | 25.58 ± 6.62 | 26.90 ± 7.15 |
| Serum osteocalcin, ng/mL | 19.67 ± 9.99 (n = 268) | 19.48 ± 9.39 (n = 267) |
| Serum P1NP, μg/L | 52.93 ± 27.24 (n = 268) | 51.13 ± 24.27 (n = 267) |
| Urine NTX, nmol BCE/mmol Cr | 53.37 ± 31.86 (n = 268) | 51.02 ± 25.60 (n = 267) |
| Serum CTX, ng/mL | 0.367 ± 0.192 (n = 268) | 0.366 ± 0.173 (n = 267) |

Values are presented as mean ± SD or number (%).
2/W, twice-weekly; 1/W, once-weekly; TPTD, teriparatide; BMD, bone mineral density; P1NP, procollagen type 1 *N*-terminal propeptide; NTX, *N*-terminal telopeptide; BCE, bone collagen equivalents; Cr, creatinine; CTX, *C*-terminal telopeptide.

**Table 2**
Percent change from baseline in lumbar spine BMD (L2-L4) at the final time point.

| Variable | 2/W-TPTD | | | 1/W-TPTD | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | P-value (paired *t*-test) | N | Mean (SD) | P-value (paired *t*-test) | P-value (Student's *t*-test) |
| Sex | | | | | | | |
| Male | 23 | 8.0 (5.9) | < 0.001 | 22 | 5.8 (5.2) | < 0.001 | 0.182 |
| Female | 228 | 7.2 (5.3) | < 0.001 | 217 | 6.0 (5.3) | < 0.001 | 0.013 |
| P-value (Student's *t*-test) | 0.476 | | | 0.884 | | | |
| Age, yr | | | | | | | |
| 65 - < 70 | 61 | 7.7 (5.2) | < 0.001 | 64 | 6.4 (5.0) | < 0.001 | 0.138 |
| 70 - < 80 | 144 | 7.6 (4.9) | < 0.001 | 125 | 6.3 (5.4) | < 0.001 | 0.038 |
| ≥ 80 | 46 | 5.7 (6.5) | < 0.001 | 50 | 4.5 (5.2) | < 0.001 | 0.330 |
| P-value (ANOVA) | 0.079 | | | 0.104 | | | |
| Height, cm | | | | | | | |
| < 150 | 113 | 7.4 (5.6) | < 0.001 | 112 | 6.7 (6.0) | < 0.001 | 0.333 |
| ≥ 150 | 138 | 7.2 (5.1) | < 0.001 | 127 | 5.3 (4.5) | < 0.001 | 0.002 |
| P-value (Student's *t*-test) | 0.744 | | | 0.049 | | | |
| Body mass index, kg/m$^2$ | | | | | | | |
| < 18.5 | 27 | 8.5 (5.6) | < 0.001 | 24 | 5.4 (4.1) | < 0.001 | 0.028 |
| 18.5 - < 25.0 | 190 | 6.9 (5.0) | < 0.001 | 165 | 5.9 (5.4) | < 0.001 | 0.072 |
| ≥ 25.0 | 34 | 8.3 (6.7) | < 0.001 | 50 | 6.2 (5.4) | < 0.001 | 0.124 |
| P-value (ANOVA) | 0.189 | | | 0.796 | | | |
| Postmenopausal duration, yr | | | | | | | |
| < 10 | 1 | 9.3 (–) | | 0 | -(–) | – | – |
| 10 - < 20 | 58 | 7.9 (5.1) | < 0.001 | 58 | 6.5 (5.2) | < 0.001 | 0.149 |
| ≥ 20 | 169 | 7.0 (5.3) | < 0.001 | 159 | 5.8 (5.4) | < 0.001 | 0.043 |
| Male | 23 | 8.0 (5.9) | < 0.001 | 22 | 5.8 (5.2) | < 0.001 | 0.182 |
| P-value (ANOVA) | 0.609 | | | 0.691 | | | |
| Non-vertebral fractures without large external force occurring at or after age 50 years | | | | | | | |
| Yes | 77 | 6.1 (4.2) | < 0.001 | 47 | 5.5 (4.7) | < 0.001 | 0.441 |
| No | 174 | 7.8 (5.7) | < 0.001 | 192 | 6.1 (5.4) | < 0.001 | 0.003 |
| P-value (Student's *t*-test) | 0.020 | | | 0.506 | | | |
| Medical history relevant to bone metabolism | | | | | | | |
| Yes | 20 | 7.4 (5.0) | < 0.001 | 23 | 6.6 (4.9) | < 0.001 | 0.574 |
| No | 231 | 7.3 (5.3) | < 0.001 | 216 | 5.9 (5.3) | < 0.001 | 0.006 |
| P-value (Student's *t*-test) | 0.895 | | | 0.541 | | | |
| Current smoking | | | | | | | |
| Yes | 11 | 7.3 (4.1) | < 0.001 | 9 | 7.0 (3.3) | < 0.001 | 0.857 |
| No | 240 | 7.3 (5.4) | < 0.001 | 230 | 5.9 (5.4) | < 0.001 | 0.005 |
| P-value (Student's *t*-test) | 0.992 | | | 0.546 | | | |
| Alcohol consumption (3 or more units/day) | | | | | | | |
| Yes | 9 | 9.4 (5.4) | < 0.001 | 5 | 4.8 (4.0) | 0.052 | 0.118 |
| No | 242 | 7.2 (5.3) | < 0.001 | 234 | 6.0 (5.3) | < 0.001 | 0.011 |
| P-value (Student's *t*-test) | 0.219 | | | 0.615 | | | |
| Parent fractured hip | | | | | | | |
| Yes | 36 | 7.4 (5.3) | < 0.001 | 22 | 3.0 (4.8) | 0.007 | 0.003 |
| No | 215 | 7.3 (5.3) | < 0.001 | 217 | 6.2 (5.3) | < 0.001 | 0.045 |
| P-value (Student's *t*-test) | 0.873 | | | 0.006 | | | |
| 25-OH vitamin D3 (ng/mL) | | | | | | | |
| < 20 | 50 | 8.4 (5.6) | < 0.001 | 36 | 6.6 (5.2) | < 0.001 | 0.127 |
| 20 - < 30 | 142 | 7.1 (5.2) | < 0.001 | 129 | 6.1 (5.6) | < 0.001 | 0.125 |
| ≥ 30 | 59 | 6.9 (5.4) | < 0.001 | 74 | 5.4 (4.8) | < 0.001 | 0.107 |
| P-value (ANOVA) | 0.239 | | | 0.530 | | | |
| Number of vertebral fractures at baseline | | | | | | | |
| 0 | 45 | 8.9 (4.7) | < 0.001 | 35 | 3.9 (3.7) | < 0.001 | < 0.001 |
| 1 | 118 | 7.0 (5.2) | < 0.001 | 129 | 6.3 (5.3) | < 0.001 | 0.310 |
| 2–3 | 72 | 6.8 (5.6) | < 0.001 | 63 | 6.3 (5.6) | < 0.001 | 0.655 |
| 4–5 | 14 | 6.7 (5.8) | 0.001 | 6 | 2.3 (5.3) | 0.333 | 0.124 |
| Missing or not reported | 2 | 13.9 (8.6) | 0.271 | 6 | 10.1 (5.6) | 0.005 | 0.483 |
| P-value (ANOVA) | 0.081 | | | 0.012 | | | |
| Lumbar spine BMD (based on YAM) (L2-L4) (%) | | | | | | | |
| <60 | 74 | 9.4 (5.5) | < 0.001 | 61 | 8.2 (6.1) | < 0.001 | 0.228 |
| 60 - < 70 | 93 | 7.0 (5.1) | < 0.001 | 89 | 5.4 (5.4) | < 0.001 | 0.053 |
| 70 - < 80 | 79 | 5.9 (4.8) | < 0.001 | 87 | 5.0 (4.0) | < 0.001 | 0.199 |
| ≥ 80 | 5 | 4.3 (4.4) | 0.098 | 2 | 1.4 (1.0) | 0.284 | 0.424 |
| P-value (ANOVA) | <0.001 | | | < 0.001 | | | |
| Lumbar spine BMD (based on YAM) (L1-L4) (%) | | | | | | | |
| < 60 | 54 | 9.4 (5.8) | < 0.001 | 45 | 7.4 (5.1) | < 0.001 | 0.083 |
| 60 - < 70 | 86 | 7.6 (5.3) | < 0.001 | 82 | 5.4 (5.3) | < 0.001 | 0.008 |
| 70 - < 80 | 74 | 5.8 (4.3) | < 0.001 | 76 | 4.6 (3.8) | < 0.001 | 0.075 |
| ≥ 80 | 3 | 3.0 (5.5) | 0.448 | 4 | 6.7 (4.1) | 0.047 | 0.357 |
| Missing or not reported | 34 | 6.8 (5.3) | < 0.001 | 32 | 8.4 (7.2) | < 0.001 | 0.314 |
| P-value (ANOVA) | 0.001 | | | 0.002 | | | |
| Femoral neck BMD (based on YAM) (%) | | | | | | | |
| < 60 | 82 | 8.5 (5.6) | < 0.001 | 52 | 7.1 (6.6) | < 0.001 | 0.180 |
| 60 - < 70 | 107 | 6.4 (5.2) | < 0.001 | 97 | 6.3 (5.2) | < 0.001 | 0.903 |
| 70 - < 80 | 46 | 7.6 (4.7) | < 0.001 | 68 | 5.0 (4.5) | < 0.001 | 0.004 |

**Table 2** (*continued*)

| Variable | 2/W-TPTD | | | 1/W-TPTD | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | P-value (paired *t*-test) | N | Mean (SD) | P-value (paired *t*-test) | P-value (Student's *t*-test) |
| ≥ 80 | 14 | 6.2 (4.6) | < 0.001 | 17 | 4.5 (4.4) | < 0.001 | 0.292 |
| Missing or not reported | 2 | 3.8 (8.4) | 0 .659 | 5 | 4.4 (3.6) | 0.036 | 0.884 |
| P-value (ANOVA) | 0.059 | | | 0.160 | | | |
| Total hip BMD (based on YAM) (%) | | | | | | | |
| < 60 | 30 | 8.7 (6.6) | < 0.001 | 16 | 8.7 (8.8) | < 0.001 | 0.998 |
| 60 - < 70 | 77 | 7.8 (5.2) | < 0.001 | 63 | 6.4 (5.6) | < 0.001 | 0.119 |
| 70 - < 80 | 82 | 6.7 (5.0) | < 0.001 | 83 | 5.4 (4.8) | < 0.001 | 0.112 |
| ≥ 80 | 60 | 6.9 (5.0) | < 0.001 | 72 | 5.6 (4.5) | < 0.001 | 0.143 |
| Missing or not reported | 2 | 3.8 (8.4) | 0.659 | 5 | 4.4 (3.6) | 0.036 | 0.884 |
| P-value (ANOVA) | 0.244 | | | 0.175 | | | |
| eGFR, mL/min/1.73m$^2$ | | | | | | | |
| < 70 | 126 | 7.2 (5.9) | < 0.001 | 138 | 6.1 (5.6) | < 0.001 | 0.123 |
| ≥ 70 | 125 | 7.4 (4.7) | < 0.001 | 101 | 5.8 (4.9) | < 0.001 | 0.011 |
| P-value (Student's *t*-test) | 0.697 | | | 0.683 | | | |

BMD, bone mineral density; 2/W, twice-weekly; 1/W, once-weekly; TPTD, teriparatide; ANOVA, analysis of variance; YAM, young adult mean; eGFR, estimated glomerular filtration rate.

**Table 3**
Factors related to percent change from baseline in lumbar spine BMD (L2-L4) at the final time point.

a: 2/W-TPTD group (n=249)

| Variable | Partial regression coefficient | Standard error | Standard partial regression coefficient | Lower limit | Upper limit | P-value |
|---|---|---|---|---|---|---|
| Baseline BMD (g/cm$^2$) | -14.862 | 3.319 | -0.275 | -21.400 | -8.323 | <0.001 |
| Age (years) | -0.072 | 0.064 | -0.079 | -0.198 | 0.055 | 0.266 |
| Sex (male: 1, female: 0) | -1.055 | 1.333 | 0.058 | -3.681 | 1.570 | 0.429 |
| Height (cm) | 0.002 | 0.062 | 0.003 | -0.120 | 0.125 | 0.968 |
| Body mass index (kg/m$^2$) | 0.123 | 0.114 | 0.068 | -0.101 | 0.348 | 0.280 |
| 25-OH vitamin D3 (ng/mL) | -0.064 | 0.051 | -0.080 | -0.165 | 0.036 | 0.206 |
| Number of vertebral fractures at baseline | -0.530 | 0.298 | -0.108 | -1.117 | 0.057 | 0.076 |
| Non-vertebral fractures without large external force occurring at or after age 50 years | 1.594 | 0.689 | -0.140 | 0.236 | 2.952 | 0.022 |
| eGFR (mL/min/1.73m$^2$) | 0.030 | 0.023 | 0.087 | -0.015 | 0.074 | 0.187 |

b: 1/W-TPTD group (n = 233)

| Variable | Partial regression coefficient | Standard error | Standard partial regression coefficient | Lower limit | Upper limit | P-value |
|---|---|---|---|---|---|---|
| Baseline BMD, g/cm$^2$ | −19.125 | 3.411 | −0.356 | −25.847 | −12.403 | < 0.001 |
| Age, yr | −0.111 | 0.063 | −0.127 | −0.235 | 0.013 | 0.078 |
| Sex (male: 1, female: 0) | 2.329 | 1.413 | 0.130 | −0.456 | 5.114 | 0.101 |
| Height, cm | −0.104 | 0.067 | −0.129 | −0.237 | 0.028 | 0.121 |
| Body mass index, kg/m$^2$ | 0.126 | 0.109 | 0.074 | −0.090 | 0.341 | 0.251 |
| 25-OH vitamin D3, ng/mL | −0.053 | 0.046 | −0.074 | −0.143 | 0.038 | 0.251 |
| Number of vertebral fractures at baseline | 0.139 | 0.373 | 0.023 | −0.597 | 0.875 | 0.711 |
| Non-vertebral fractures at or after age 50 | −0.219 | 0.820 | −0.017 | −1.835 | 1.397 | 0.789 |
| eGFR, mL/minute/1.73m$^2$ | −0.040 | 0.028 | −0.101 | −0.095 | 0.014 | 0.148 |

*P-value < 0.05 by multiple regression analysis.
BMD, bone mineral density; 2/W, twice-weekly; TPTD, teriparatide; eGFR, estimated glomerular filtration rate.
* P-value < 0.05 by multiple regression analysis.
BMD, bone mineral density; 1/W, twice-weekly; TPTD, teriparatide; eGFR, estimated glomerular filtration rate.

all subjects, which may have masked the effect of a low baseline 25(OH)D level. Additionally, the number of existing vertebral fractures, which is strongly associated with the risk of vertebral fractures, also had no effect. As shown above, though there are factors contributing to a greater percentage change in BMD, as shown in Table 2, BMD improved significantly in every subgroup. Keep in mind that these data do not suggest that patients with characteristics different from those described above would respond less well, and that the data merely identify the patient characteristics that facilitate a greater percentage change. As previously reported from the present study, the percentage increase in lumbar spine BMD after 12 months was significantly higher with 2/W-TPTD than with 1/W-TPTD. Similarly, the stratified analysis comparing 2/W-TPTD and 1/W-TPTD also showed that the percentage increase tended to be greater with 2/W-TPTD across all variables.

The present report omits the finding from a detailed safety analysis that 2/W-TPTD was associated with lower incidences of adverse drug reactions than 1/W-TPTD, which has been reported previously [4,7].

Since this stratified analysis was performed using data from patients in a clinical study that excluded patients with secondary osteoporosis or with a non-osteoporotic disease that causes decreased bone mass and those who had received treatment with BP within 1 year, the subject population assessed differed somewhat from the patient population seen in clinical practice, preventing an analysis stratified by the clinically important indicators of renal impairment, hepatic impairment, and an assessment of the effect of treatment subsequent to BP therapy. Furthermore, the fact that sample sizes were not calculated in a strict manner in the intragroup stratified analysis and the lack of a stratified analysis of safety are limiting factors of the present stratified analysis. In the future, it will be necessary to collect more data on the efficacy and

safety of 2/W-TPTD from patients with broader background characteristics in clinical practice.

## 5. Conclusions

Intergroup comparisons of data from subgroups (defined by different variables) of patients in a clinical study were performed, and there was no substantial difference in the percentage change at the final time point between the 2 groups or a trend for a greater change in the 2/W-TPTD group than in the 1/W-TPTD group. Moreover, across all subgroups that included 9 or more subjects, the lumbar spine BMD increased significantly in both groups. Factors contributing to a greater percentage change in BMD by 2/W-TPTD included absence of non-vertebral fractures occurring at or after age 50 years, and a low baseline BMD.

## CRediT author statement

**Toshitsugu Sugimoto:** Original Study Design, Formal analysis, Writing – original draft. **Takeshi Yoshimura:** Formal analysis, Writing - original draft. **Toyonobu Uzawa:** Formal analysis, Writing - original draft, Writing – review & editing.

## Conflicts of interest

Toshitsugu Sugimoto has received research grants from Astellas Pharma, Eisai, Daiichi-Sankyo, Chugai Pharmaceutical, and Eli Lilly Japan, as well as consulting and/or lecture fees from Asahi Kasei Pharma, Teijin Pharma and Daiichi-Sankyo. Takeshi Yoshimura and Toyonobu Uzawa are the employee of the Asahi Kasei Pharma Corporation. The study was sponsored and funded by Asahi Kasei Pharma Corporation, Tokyo, Japan. The sponsor had responsibility for quality control. The corresponding author had full access to all of the data in the study and had responsibility for the decision to submit for publication. The study was jointly designed by the authors and the sponsor, Asahi Kasei Pharma Corporation. The authors discussed the interpretation of the data and the conclusions of the manuscript with the sponsor. Data analyses for publication were the responsibilities of the sponsor.

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