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ORIGINAL ARTICLE

Long-term effect of denosumab on bone microarchitecture as assessed by tissue thickness–adjusted trabecular bone score in postmenopausal women with osteoporosis: results from FREEDOM and its open-label extension

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Abstract

Summary In postmenopausal women with osteoporosis, up to 10 years of denosumab treatment significantly and continuously improved bone microarchitecture assessed by tissue thickness–adjusted trabecular bone score, independently of bone mineral density. Long-term denosumab treatment decreased the number of high fracture-risk patients and shifted more patients to lower fracture-risk categories.

Purpose To investigate the long-term effect of denosumab on bone microarchitecture assessed by tissue thickness–adjusted trabecular bone score (TBS_{TT}) in post-hoc subgroup analysis of FREEDOM and open-label extension (OLE).

Methods Postmenopausal women with lumbar spine (LS) or total hip BMD T-score <-2.5 and ≥ -4.0 who completed the FREEDOM DXA substudy and continued in OLE were included. Patients received either denosumab 60 mg subcutaneously every 6 months for 3 years and same-dose open-label denosumab for 7 years (long-term denosumab; $n=150$) or placebo for 3 years and open-label denosumab for 7 years (crossover denosumab; $n=129$). BMD and TBS_{TT} were assessed on LS DXA scans at FREEDOM baseline, month 1, and years 1–6, 8, and 10.

Results In long-term denosumab group, continued increases from baseline to years 4, 5, 6, 8, and 10 in BMD (11.6%, 13.7%, 15.5%, 18.5%, and 22.4%) and TBS_{TT} (3.2%, 2.9%, 4.1%, 3.6%, and 4.7%) were observed (all $P < 0.0001$). Long-term denosumab treatment decreased the proportion of patients at high fracture-risk (according to TBS_{TT} and BMD T-score) from baseline up to year 10 (93.7 to 40.4%), resulting in increases in the proportions at medium-risk (6.3 to 53.9%) and low-risk (0 to 5.7%) ($P < 0.0001$). Similar responses were observed in crossover denosumab group. Changes in BMD and TBS_{TT} were poorly correlated during denosumab treatment.

Conclusion In postmenopausal women with osteoporosis, up to 10 years of denosumab significantly and continuously improved bone microarchitecture assessed by TBS_{TT}, independently of BMD, and shifted more patients to lower fracture-risk categories.

Keywords Bone mineral density (BMD) · Denosumab · Osteoporosis · Postmenopausal women · Soft tissue thickness · Trabecular bone score (TBS)

Introduction

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and a consequent increase in fracture risk [1]. Bone mass is measured by bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA). BMD is a major determinant of bone strength and the gold standard for the diagnosis of osteoporosis [2]. Decreased BMD is considered to be an important predictor of osteoporotic fractures [3].

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However, the risk of fracture also depends on factors other than BMD, since many individuals with a fragility fracture have non-osteoporotic BMD values [4, 5].

Evaluating bone microarchitecture, indirectly measured by trabecular bone score (TBS), enhances the assessment of bone strength and fracture risk, beyond BMD assessment alone [2]. TBS is a gray-level textural metric extracted from DXA scans; it uses 2-dimensional DXA images to characterize the variations in gray-level amplitude in the corresponding 3-dimensional tissue microarchitecture [6, 7]. A high TBS value correlates with a large number of low-amplitude variations that indicate more homogeneous and stronger bone microstructure, while a low TBS value correlates with a low number of high-amplitude variations that indicate more variable, separated, and deteriorated bone microstructure [6, 8]. TBS is predictive of osteoporotic fractures independently of BMD and/or clinical risk factors from the Fracture Risk Assessment Tool (FRAX®) and has been shown to complement both BMD and FRAX® to improve fracture risk prediction [2, 6, 9–14]. TBS has been included in many national and international guidelines such as the International Society for Clinical Densitometry (ISCD) Official Positions [15] and American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis [16] as a readily available, noninvasive tool beyond standard BMD measurements and clinical risk factors to improve categorization of patients at risk for fracture [2].

The TBS algorithm accounts for the presence of regional soft tissues, as the gray-level texture of the DXA image depends on both the bone and soft tissues, with the latter attenuating the X-rays, gray level variations, and eventually the TBS value [17]. The recently updated TBS algorithm directly corrects for the soft tissue thickness (tissue thickness–adjusted TBS or TBS_{TT}) in the region of the spine, replacing the previously used TBS algorithm correcting for body mass index (BMI), a proxy for soft tissue thickness. It has been shown that TBS_{TT} neutralizes the regional soft tissue noise on DXA images better than BMI-adjusted TBS (TBS_{BMI}) as it is less dependent on whole body morphotype [18].

In postmenopausal women, increased tissue exposure to RANK ligand due to estrogen deficiency accelerates bone resorption and induces bone loss, leading to osteoporosis [19]. Denosumab is a fully human monoclonal antibody against RANK ligand that reduces osteoclast number and activity and decreases bone resorption [20–23]. During the 3-year phase 3 FREEDOM study in postmenopausal women with osteoporosis, denosumab treatment significantly increased BMD and reduced the risk of vertebral, nonvertebral, and hip fracture compared with placebo [24]. A subset of women participated in a prospective FREEDOM DXA substudy, in which they underwent more extensive BMD assessments and showed significant BMD gains comparable to those in the overall FREEDOM population [25]. Because of the chronic nature of osteoporosis, the 3-year FREEDOM trial was followed by a 7-year open-label extension (OLE), during which all patients received denosumab. Up to 10 years of denosumab treatment was associated with continued increases in BMD and low incidence of new vertebral and nonvertebral fractures [26, 27].

To explore the effect of long-term denosumab treatment on TBS and bone microarchitecture, this FREEDOM TBS post-hoc analysis employed the updated TBS algorithm (TBS_{TT}) [18] to evaluate lumbar spine (LS) DXA scans of women who completed the DXA substudy and enrolled in the OLE study. The initial report based on the 3-year DXA substudy demonstrated that denosumab significantly improved TBS_{TT} vs placebo independently of BMD [28]. Further, TBS_{TT} showed greater changes from baseline and larger differences from placebo than TBS_{BMI} in response to denosumab treatment [28]. Here, we present the treatment outcome of long-term denosumab on TBS_{TT} and bone microarchitecture during the OLE with denosumab administration for up to 7 or 10 years.

Methods

Study design and patients

Study designs of the FREEDOM (NCT00089791) and OLE (NCT00523341) studies and the DXA substudy have previously been described [24–26] (Fig. 1). FREEDOM was a phase 3, multicenter, randomized, double-blind, placebo-controlled study conducted at 213 centers worldwide in 7808 postmenopausal women with a BMD T-score between −4.0 and −2.5 at the lumbar spine or total hip. Patients were randomized 1:1 centrally to receive either denosumab 60 mg or placebo subcutaneously every 6 months for 3 years and were instructed to take daily supplementation of calcium (≥1000 mg) and vitamin D (≥400 IU). All patients who completed the FREEDOM study without discontinuing treatment or missing more than one dose of study drug were eligible to enter the OLE and receive open-label denosumab 60 mg subcutaneously every 6 months for 7 years. The prospective DXA substudy was conducted at 19 centers that performed more frequent BMD assessments and evaluations of additional skeletal sites for 441 women. Informed consent was obtained for all patients in the FREEDOM and OLE studies and the DXA substudy.

This FREEDOM TBS post-hoc analysis analyzed TBS_{TT} on 2409 LS DXA scans collected from 279 women who completed the DXA substudy and rolled over to the OLE study (Fig. 1). Patients with BMI >38 kg/m^2 or <15 kg/m^2 were excluded as it was out of the manufacturer-recommended

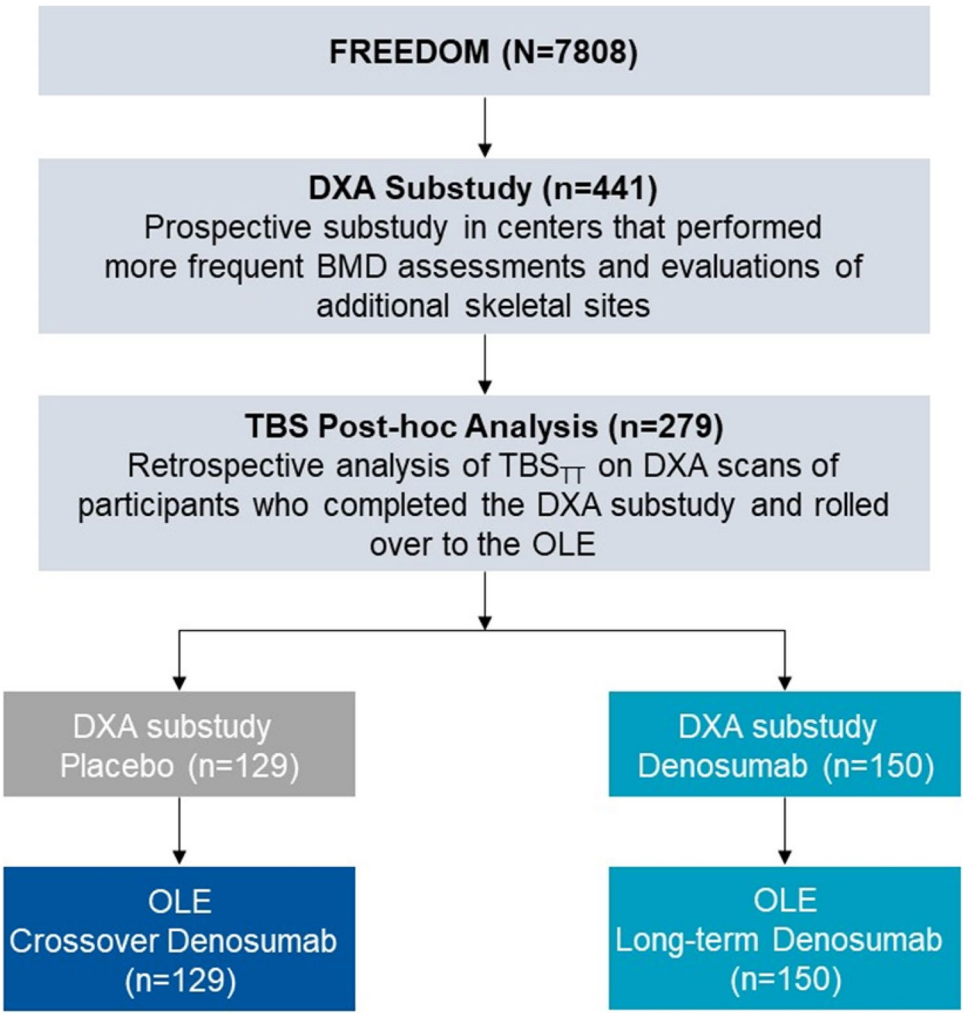


Fig. 1 Study flowchart

range for a proper assessment of TBS. Similarly, patients were excluded if the DXA scanner or the acquisition mode used for BMD assessment was not compatible with TBS algorithm. Women who received 3 years of denosumab in the DXA substudy and continued in the OLE could have up to 10 years of denosumab exposure (long-term denosumab group). Women who received 3 years of placebo in the DXA substudy and crossed over to denosumab in the OLE could have up to 7 years of denosumab exposure (crossover denosumab group).

Study assessments

LS (L1-L4) DXA scans were performed using Lunar (GE Healthcare, Madison, WI, USA) or Hologic (Hologic Inc., Bedford, MA, USA) DXA bone densitometers at FREEDOM baseline, month 1, and years 1, 2, and 3 in the DXA substudy [25] and at OLE baseline and OLE years 1, 2, 3, 5, and 7. For an individual patient, the same type of machine was used for all measurements throughout the study. All DXA scans were centrally read by Clario (formerly BioClinica or Synarc; Princeton, NJ, USA) [25].

TBS_{TT} was assessed using a pre-release of TBS iNsight software version 4.0 (Medimaps group, Geneva, Switzerland) to compensate for the soft tissue thickness of the specific region of interest directly. TBS_{TT} was calculated as the mean of the individual measurements for each included vertebra. The calculation was performed blinded from clinical outcomes and treatment group allocation. Both LS BMD and TBS_{TT} were calculated from the LS DXA scans in the same region of interest (L1-L4) [28]. Fractured vertebrae (prevalent or incident), as confirmed by X-rays, or clearly abnormal and non-assessable vertebrae were excluded from the assessments of both BMD and TBS_{TT}, following the ISCD criteria [15].

Vertebral osteoporotic fractures were centrally identified by Clario based on lateral spine radiographs by a semiquantitative grading scale [29]. Clinical and nonvertebral osteoporotic fractures required confirmation by diagnostic imaging or a radiologist's report [24, 26].

Statistical analyses

This analysis included patients who completed the DXA substudy and continued to the OLE and had LS BMD and TBS_{TT} measurements at baseline and at least one post-baseline visit. Missing data were not imputed. The percent changes in LS BMD and TBS_{TT} from baseline to every year up to year 10 were analyzed using a repeated-measures mixed effects linear model, adjusting for visit, baseline value, machine type, treatment-by-visit interaction, and baseline value-by-machine type interaction. Statistical inferences on (i) differences between the denosumab and placebo groups during the 3-year DXA substudy, (ii) within-group differences from FREEDOM baseline for the placebo group and the long-term denosumab group over up to 10 years, and (iii) within-group differences from OLE baseline for the crossover denosumab group over up to 7 years (Fig. 1) were assessed at appropriate follow-up timepoints with no adjustment for multiplicity. The results were reported as least-squares means and associated two-sided 95% confidence intervals (CIs).

Bone microarchitecture based on TBS_{TT} fracture risk categories (TBS_{TT} ≤1.027, degraded microarchitecture with high fracture risk; TBS_{TT} >1.027 to ≤1.074, partially degraded microarchitecture with medium fracture risk; TBS_{TT} >1.074, normal microarchitecture with low fracture risk) was evaluated at baseline and up to year 3 for the placebo group, at OLE baseline and up to OLE year 7 for the crossover denosumab group, and at baseline and up to year 10 for the long-term denosumab group. These TBS_{TT} risk thresholds of 1.027 and 1.074 are equivalent to 1.230 and 1.310, the risk thresholds reported for the classical TBS_{BMI} algorithm, because TBS_{TT} thresholds were derived from the same analysis of the same population that generated TBS_{BMI} thresholds [12]. At the commercial release of the newest version of TBS_{TT}, the thresholds will be calibrated to historical ones for clinical continuity. Statistical inferences on the significance of the within-group change in the percentage of patients in each TBS_{TT} degradation category from baseline to the respective follow-up timepoint were evaluated using Bhapkar's test for homogeneity.

The effect of long-term denosumab treatment on the risk of osteoporotic fractures was analyzed by TBS_{TT} and BMD T-score risk categories (BMD T-score ≤−2.5, or TBS_{TT} ≤1.027 and −2.5 < BMD <−1.0, high risk; TBS_{TT} >1.027 and −2.5 < BMD <−1.0, or BMD ≥−1.0 and TBS_{TT} ≤ 1.074, medium risk; BMD ≥−1.0 and TBS_{TT} >1.074, low risk). The percentages of patients in each risk category in the crossover denosumab group at OLE baseline and up to OLE year 7 and in the long-term denosumab group at baseline and up to year 10 were summarized, and statistical inferences on the significance of the changes were evaluated using Bhapkar's test for homogeneity. To further assess the association between change in TBS_{TT} and fracture risk, the incidence of vertebral fractures, nonvertebral fractures, or clinical fractures was calculated for patients stratified into tertiles of mean TBS_{TT} percentage change from OLE baseline until up to OLE year 7 in the crossover denosumab group and from FREEDOM baseline until up to year 10 in the long-term denosumab group.

The correlation between LS BMD and TBS_{TT} was evaluated using Pearson correlation coefficients for mean percentage changes from baseline to last follow-up timepoints within the placebo group, the crossover denosumab group, and the long-term denosumab group.

Results

This analysis included a total of 279 postmenopausal women with osteoporosis: 150 women received up to 10 years of denosumab treatment during the entire study; 129 women received placebo for 3 years during the DXA substudy and then crossed over to receive up to 7 years of denosumab treatment during the OLE (Fig. 1). Baseline characteristics were mostly balanced between the placebo group and the long-term denosumab group at FREEDOM baseline. The mean LS BMD T-score was −2.8, and mean TBS_{TT} was 1.03 in all patients included in the analysis at FREEDOM baseline. About 19% and 25% of women had a vertebral fracture in the placebo and the long-term denosumab groups, respectively, at FREEDOM baseline. At OLE baseline, patients in the long-term denosumab group, who had received 3 years of denosumab before entering the OLE, had higher mean LS BMD T-score (−2.1) and TBS_{TT} (1.06) than patients in the crossover denosumab group (−2.8, and 1.02, respectively) (Table 1).

Long-term treatment with denosumab was associated with continued increases in LS BMD and TBS_{TT} during the OLE study (Fig. 2). Mean percentage changes from FREEDOM baseline to years 4, 5, 6, 8, and 10 in LS BMD (least-squares mean increases of 11.6%, 13.7%, 15.5%, 18.5%, and 22.4%, respectively) and TBS_{TT} (3.2%, 2.9%, 4.1%, 3.6%, and 4.7%, respectively) in the long-term denosumab group were all statistically significant (all $P < 0.0001$). Mean percentage changes from OLE baseline to OLE years 1, 2, 3, 5, and 7 in LS BMD (least-squares mean increases of 5.3%, 7.7%, 9.6%, 13.0%, and 17.2%, respectively; all $P < 0.0001$) and TBS_{TT} (0.3%, 0.9%, 1.1% [$P < 0.05$], 2.2%, and 3.2% [$P < 0.0001$], respectively) were also increasing in the crossover denosumab group. The overall trend of improvement in LS BMD and TBS_{TT} observed in the crossover denosumab group from OLE baseline to OLE year 7 largely replicated that observed in the long-term denosumab group during the first 7 years of denosumab treatment (Fig. 2).

Table 1 Baseline characteristics

	Placebo (*n*=129)	Crossover denosumab (*n*=129)	Long-term denosumab (*n*=150)	
	FREEDOM baseline	OLE baseline	FREEDOM baseline	OLE baseline
Age (years), mean ± SD	72.1 ± 5.3	75.2 ± 5.3	72.8 ± 4.9	75.9 ± 4.9
Body mass index (kg/m^2), mean ± SD	24.9 ± 4.2[a]	25.1 ± 4.3	25.2 ± 4.2	25.0 ± 4.5
Race, *n* (%)				
White or Caucasian	111 (86.0)	111 (86.0)	132 (88.0)	132 (88.0)
Hispanic or Latino	16 (12.4)	16 (12.4)	18 (12.0)	18 (12.0)
Other	2 (1.6)	2 (1.6)	0	0
Prevalent vertebral fracture, *n* (%)	24 (18.6)	28 (21.7)	38 (25.3)	40 (26.7)
LS BMD T-score, mean ± SD	−2.81 ± 0.60	−2.81 ± 0.65	−2.75 ± 0.81[b]	−2.10 ± 0.82[c]
TBS_{TT}, mean ± SD	1.033 ± 0.076[a]	1.018 ± 0.073[d]	1.029 ± 0.080[e]	1.060 ± 0.080[e]

BMD, bone mineral density; *LS*, lumbar spine; *SD*, standard deviation; *TBS*, trabecular bone score; *TBS_{TT}*, tissue thickness–adjusted TBS
[a]*n*=125; [b]*n*=149; [c]*n*=148; [d]*n*=124; [e]*n*=142; *n* = number of patients with observed data

Long-term denosumab therapy led to more patients having normal microarchitecture, as defined by TBS_{TT}, and fewer patients with degraded or partially degraded microarchitecture (Fig. 3). In the long-term denosumab group, the number of patients with normal microarchitecture increased from 26.1% at baseline to 53.2% up to year 10, and the number of patients with degraded or partially degraded microarchitecture decreased from 48.6 to 29.1% and from 25.4 to 17.7%, respectively ($P < 0.0001$). A similar improvement in bone microstructure was observed in the crossover denosumab group from OLE baseline over up to 7 years of denosumab treatment ($P < 0.0001$). In comparison, bone microstructure remained unchanged or slightly deteriorated in the placebo group from FREEDOM baseline to year 3 ($P = 0.0480$).

When the risk of osteoporotic fracture was assessed based on both TBS_{TT} and BMD T-score, long-term denosumab therapy was found to result in more patients exiting the high-risk category and entering the medium- and low-risk categories (Fig. 4a). In the long-term denosumab group, the number of patients in the high-risk category decreased from 93.7% at baseline to 40.4% at up to year 10, and in the medium-risk and low-risk categories increased from 6.3 to 53.9% and from 0 to 5.7%, respectively ($P < 0.0001$). A similar effect of treatment shifting patients into lower risk categories was observed in the crossover denosumab group from OLE baseline to up to OLE year 7 (high risk, 89.6 to 48.7%; medium risk, 10.4 to 49.6%; and low risk, 0 to 1.7%; $P < 0.0001$).

Consistent with TBS as a predictor of osteoporotic fractures [2, 6, 9–14], patients who achieved TBS_{TT} improvement in the highest tertile (i.e., the largest TBS_{TT} improvement) during long-term denosumab treatment tended to have reduced fracture risk (Fig. 4b). Only a small group of patients who had TBS_{TT} data at both baseline and year 10 (i.e., OLE year 7) were analyzed for fracture incidences by tertiles. In the long-term denosumab group (*n*=66), incidences of new or worsening vertebral fractures, nonvertebral fractures, and clinical fractures occurring up to year 10 were 4.8%, 0%, and 0%, respectively, in patients with the largest TBS_{TT} percentage change from baseline to up to year 10, compared to 13.6%, 4.5%, and 9.1%, respectively, in patients with smallest TBS_{TT} changes, and 17.4%, 8.7%, and 13.0%, respectively, in patients with medium TBS_{TT} changes. This trend was also observed in the crossover denosumab group (*n*=56) when comparing patients with the largest TBS_{TT} percentage change from OLE baseline to up to OLE year 7 (vertebral, nonvertebral, and clinical fractures occurring up to OLE year 7, 0%, 0%, and 0%, respectively) versus patients with smallest TBS_{TT} changes (10.5%, 10.5%, and 10.5%, respectively) and medium TBS_{TT} changes (5.3%, 21.1%, and 26.3%, respectively).

Over the course of long-term denosumab treatment, changes in TBS_{TT} were largely unrelated to changes in LS BMD (Fig. 5). Pearson correlation coefficient between the mean percentage changes of TBS_{TT} and LS BMD was 0.05 from baseline to year 10 in the long-term denosumab group and 0.28 from OLE baseline to OLE year 7 in the crossover denosumab group, both of which were below the threshold commonly interpreted as poor correlation (<0.3) [30, 31].

Discussion

Results from this FREEDOM TBS post-hoc analysis showed that up to 10 years of denosumab treatment significantly and continuously improved TBS_{TT} and bone microarchitecture in postmenopausal women with osteoporosis. The correlation between changes in TBS_{TT} and LS BMD remained poor over 10 years, confirming that the two measures provide

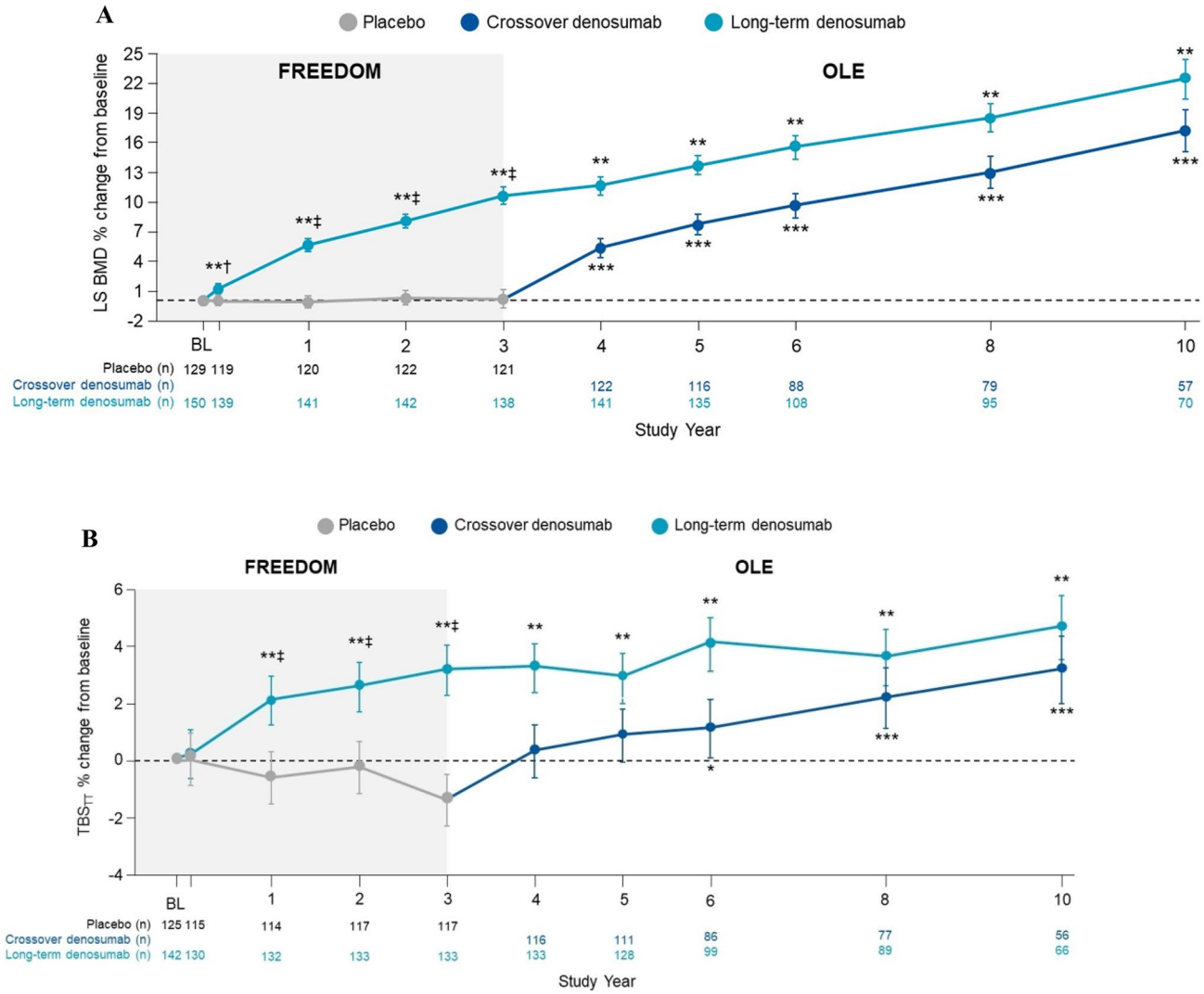


Fig. 2 Percentage change from baseline by visit and treatment group for (**A**) LS BMD and (**B**) TBS_{TT}. Data are presented as least-squares mean and 95% confidence interval. n = number of patients with observed data. *$P < 0.05$ compared with OLE baseline; **$P < 0.0001$ compared with baseline; ***$P < 0.0001$ compared with OLE baseline; $^{\dagger}P < 0.001$ compared with placebo; $^{\ddagger}P < 0.0001$ compared with placebo. BL, baseline; BMD, bone mineral density; LS, lumbar spine; TBS, trabecular bone score; TBS_{TT}, tissue thickness–adjusted TBS

independent information on bone strength. Long-term denosumab shifted more patients to lower-risk categories assessed by both TBS_{TT} and BMD T-score. Patients with the largest TBS_{TT} improvement during long-term denosumab treatment tended to experience a reduced incidence of fractures, supporting the importance of improving TBS in patients receiving anti-osteoporotic therapies.

TBS, a noninvasive measurement of bone microarchitecture based upon DXA images, is sensitive to changes over time from either natural disease progression or osteoporosis treatment. Different therapies have been shown to impact TBS to different degrees [7, 13, 14], likely due to their differential effects on the two components of bone remodeling: resorption and formation. For antiresorptive agents, the magnitude of changes in TBS was greater with denosumab treatment compared with bisphosphonates (e.g., alendronate, risedronate, ibandronate, zoledronic acid) [13, 32, 33]. For the bone-building agents, teriparatide and romosozumab, TBS changes were faster and of greater amplitude than antiresorptive agents [34]. However, previous studies assessing the effect of bone-affecting therapies on TBS were conducted for no more than 3 years.

The current analysis is the first report to evaluate the long-term impact of denosumab treatment for up to 10 years on bone microstructure as assessed by the updated TBS_{TT} computation algorithm, which directly corrects for the effect of regional soft tissue thickness on the DXA image and has been clinically validated to evaluate TBS and maintain its

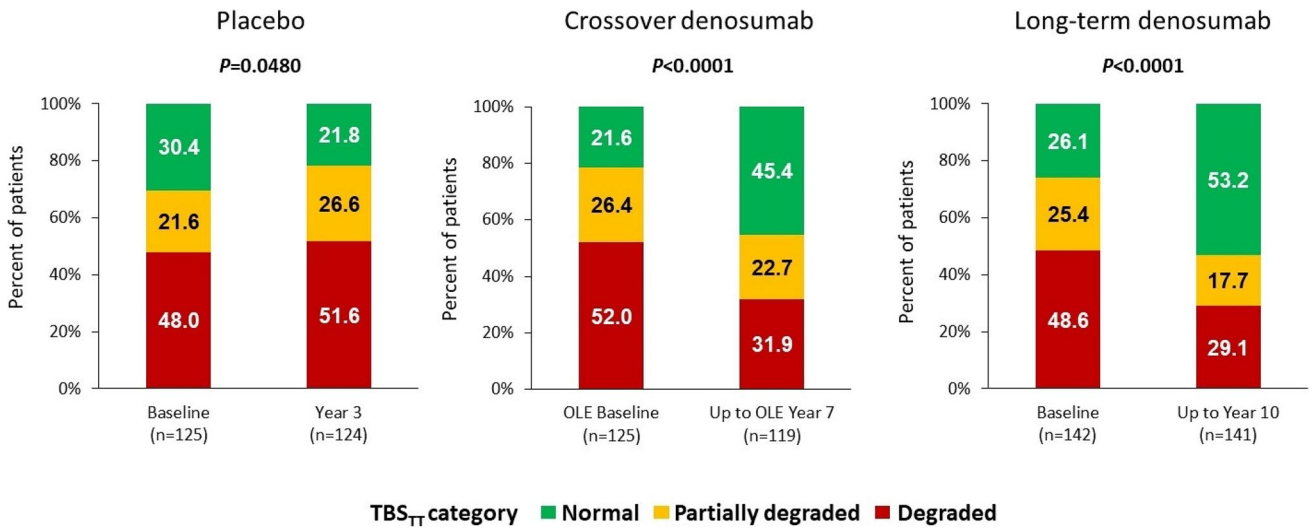


Fig. 3 Percentage of patients by TBS_{TT} risk category in the placebo group at baseline and year 3, in the crossover denosumab group at OLE baseline and up to OLE year 7, and in the long-term denosumab group at baseline and up to year 10. n = number of patients with observed data. P value based on Bhapkar's test for homogeneity. TBS, trabecular bone score; TBS_{TT}, tissue thickness–adjusted TBS. Degraded, TBS_{TT} ≤1.027; partially degraded, TBS_{TT} >1.027 to ≤1.074; normal, TBS_{TT} >1.074

clinical performance [18]. Our results show that the initial increase in TBS_{TT} observed during the 3-year FREEDOM DXA substudy [28] persisted with long-term denosumab treatment in the OLE, with bone microstructure showing consistent improvement over time. Denosumab has been shown previously to prevent plate perforation and preserve axially aligned trabeculae [35], and modeling-based bone formation could occur despite the potent inhibitory effect of denosumab on bone resorption [36], all of which may have contributed to the observed long-term improvement in trabecular bone microstructure. This first observation of continued improvements in TBS_{TT} and bone microstructure for up to 10 years with an osteoporosis therapy, denosumab, is important as it may lead to a better understanding of the role of TBS in monitoring therapeutic responses and guiding management of patients undergoing long-term treatment.

Previous studies have shown that TBS provides a measure of bone strength not captured by BMD [7]. Our results confirmed that even with up to 10 years of treatment, changes in TBS_{TT} and changes in LS BMD were largely unrelated, supporting the independent and complementary nature of the two measurements. TBS can predict osteoporotic fractures as well as BMD in postmenopausal women [7] and improve fracture risk prediction when used in conjunction with BMD [2, 9–13]. Our results provide further support and show that patients who achieved the largest TBS_{TT} changes during long-term denosumab treatment tended to have reduced incidences of new or worsening vertebral fractures, nonvertebral fractures, and clinical fractures, compared to patients with smaller TBS_{TT} changes. It is worth noting that this analysis was descriptive in nature, and the small sample size within each tertile might be associated with high variance of fracture incidences, which may explain why patients with medium TBS_{TT} changes, unexpectedly, had slightly higher incidences of fractures than patients with the smallest TBS_{TT} changes. However, the overall trend of reduced fracture incidences in patients with the largest TBS_{TT} changes supports a role for TBS as a predictor of osteoporotic fractures [7]. When fracture risk was evaluated by both TBS_{TT} and BMD T-score in all patients who completed the DXA substudy and rolled over into the OLE study, we found that long-term denosumab reduced the number of patients at high risk, shifting a majority into lower risk categories. This result is consistent with the maintenance of low fracture incidence over 10 years of therapy with denosumab in the overall population of FREEDOM and OLE [26].

Limitations of the present analysis include the absence of a placebo control over the long-term denosumab treatment period and the lack of direct measures of trabecular architecture. However, placebo could not be continued beyond 3 years in the OLE in consideration of the well-being of the patients. In addition, the crossover denosumab group showed very similar results compared with the long-term denosumab group, confirming the treatment effect of long-term denosumab therapy. Although TBS is an indirect measure of trabecular microarchitecture, it has been correlated with bone microarchitecture measures such as connectivity density, trabecular number, trabecular separation, trabecular bone volume over tissue volume, and structure model index in several studies, and is a US Food and Drug Administration–approved application to DXA images [2, 6, 37]. DXA scanners involved in the study were not TBS calibrated using

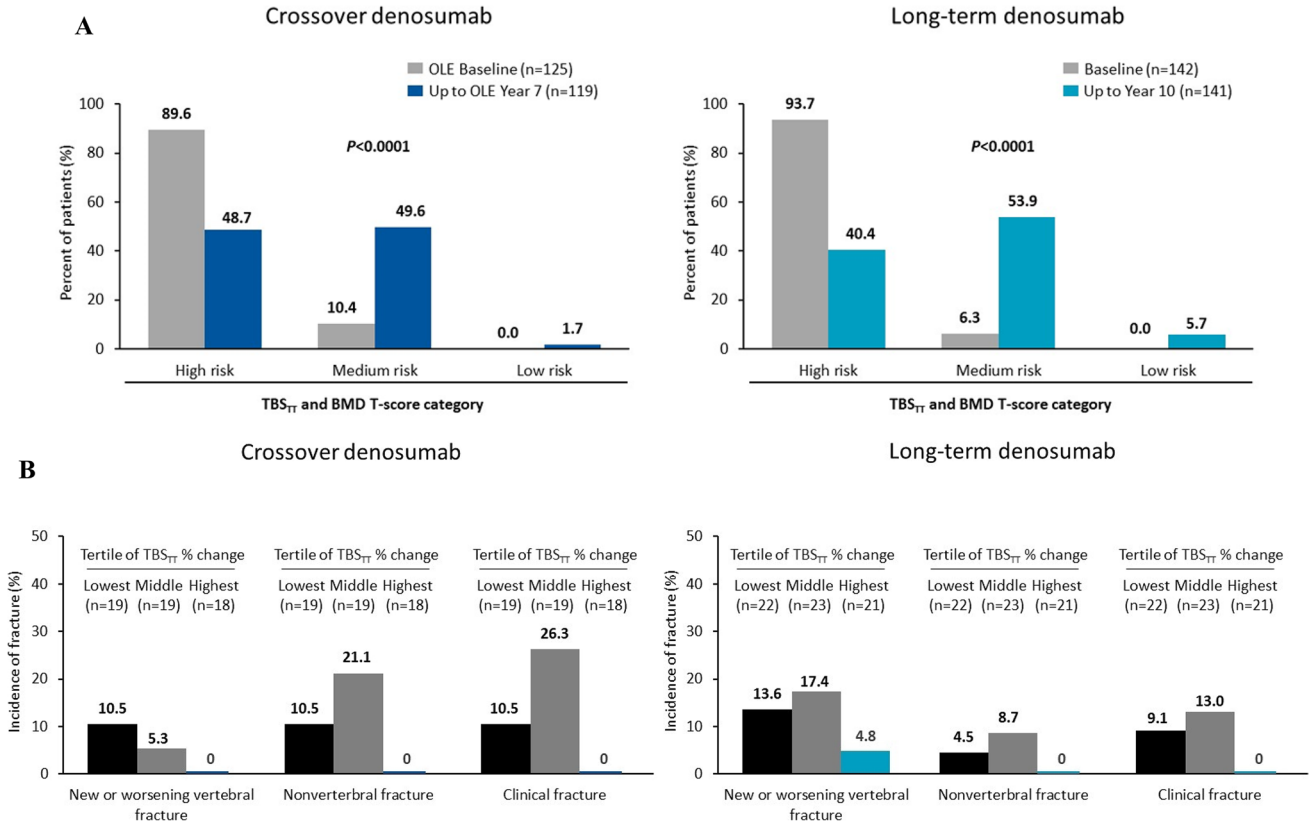


Fig. 4 Fracture risk by TBS_{TT} and BMD T-score (**A**) or tertiles of mean TBS_{TT} percent change (**B**). BMD, bone mineral density. TBS, trabecular bone score; TBS_{TT}, tissue thickness–adjusted TBS. **A** Percentage of patients within each TBS_{TT} and BMD T-score risk category in the crossover denosumab group at OLE baseline and up to OLE year 7 and in the long-term denosumab group at baseline and up to year 10. *n* = number of patients with observed data. *P* value based on Bhapkar's test for homogeneity. High risk, BMD T-score ≤−2.5, or TBS_{TT} ≤1.027 and −2.5 < BMD <−1.0; medium risk, TBS_{TT} >1.027 and −2.5 < BMD < −1.0, or BMD ≥−1.0 and TBS_{TT} ≤ 1.074; low risk, BMD ≥−1.0 and TBS_{TT} >1.074. **B** Incidence of new or worsening vertebral fractures, nonvertebral fractures, and clinical fractures by tertiles of mean TBS_{TT} percentage change in the crossover denosumab group from OLE baseline until up to OLE year 7 and in the long-term denosumab group from baseline until up to year 10. *n* = number of patients with observed TBS_{TT} data at baseline and the specified timepoint within each tertile. Patients within the lowest tertile had the smallest mean TBS_{TT} percentage change, and patients within the highest tertile had the largest mean TBS_{TT} percentage change

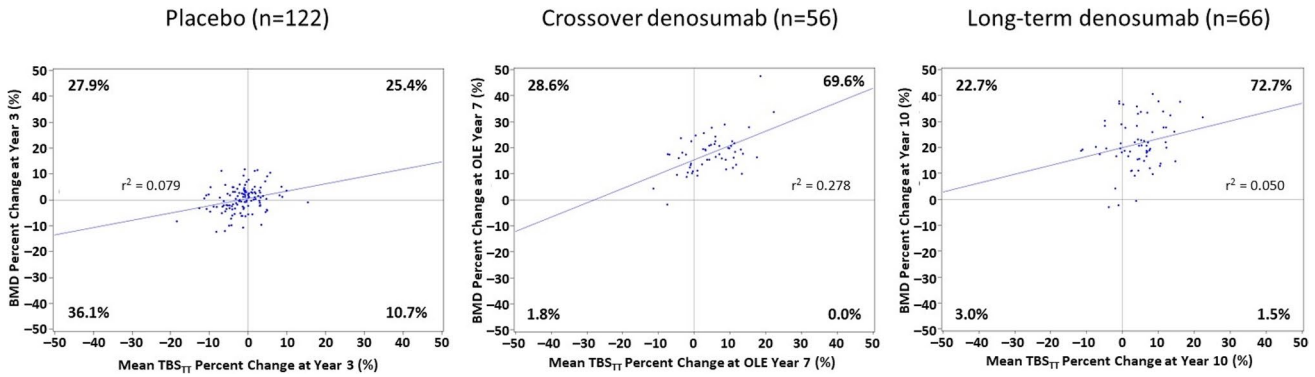


Fig. 5 Relationship between LS BMD percentage change and TBS_{TT} percentage change in the placebo group from baseline to year 3, in the crossover denosumab group from OLE baseline to OLE year 7, and in the long-term denosumab group from baseline to year 10. *n* = number of patients with observed BMD and TBS_{TT} data at the specified timepoint. Pearson correlation between the mean percentage changes of BMD and TBS_{TT}: $r^2 = 0.079$ in the placebo group from baseline to year 3; $r^2 = 0.278$ in the crossover denosumab group from OLE baseline to OLE year 7; $r^2 = 0.050$ in the long-term denosumab group from baseline to year 10. BMD, bone mineral density; LS, lumbar spine; TBS, trabecular bone score; TBS_{TT}, tissue thickness–adjusted TBS

a fractal dedicated phantom. TBS_{TT} categories may have smaller within group variability if calibration phantom was applied. Although long-term treatment with denosumab led to significant increases in TBS_{TT}, 4.7% on average in a group of 66 patients at year 10 (Fig. 2b), one should be cautious in interpreting TBS_{TT} changes from baseline at the individual level without considering the least significant change of both BMD and TBS at your site. This study is a retrospective analysis in a small subset of the total FREEDOM population, which may limit the generalizability of the study results. Nevertheless, the effect of long-term denosumab on TBS_{TT} likely reflects the effect in the originally randomized patients in FREEDOM because the baseline characteristics and LS BMD changes over up to 10 years of denosumab treatment in this FREEDOM TBS post-hoc analysis were similar to those reported in the overall population [24, 26].

In conclusion, long-term denosumab resulted in continued increases in TBS_{TT} and improved bone microarchitecture in postmenopausal women with osteoporosis. This treatment effect was observed over a longer duration of treatment (up to 10 years) than in previous osteoporosis trials [13, 33] and detected using the updated TBS_{TT} algorithm that better adjusts for regional soft tissue thickness [18]. Changes in TBS_{TT} were poorly correlated with changes in LS BMD over up to 10 years of denosumab treatment, supporting the independent and complementary role of TBS_{TT} to BMD. Long-term denosumab treatment shifted more patients to lower fracture-risk categories based on both TBS_{TT} and BMD T-score, and patients with the largest TBS_{TT} improvement trended toward having a reduced incidence of fracture. Different osteoporosis therapies have differential effects on resorption and formation of bone remodeling and may vary in their efficacies and time frames to impact bone structure and/or density. TBS, a convenient tool for evaluating bone microarchitecture and predicting fracture risk, should be incorporated into clinical practice, along with BMD and other risk factors, for monitoring treatment responses and managing patients undergoing long-term osteoporosis therapy.

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Data availability Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/.

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Declarations

Ethics approval The study complied with the principles of the Declaration of Helsinki. Institutional review boards and ethics committees approved the protocol and consent process. All procedures performed in studies involving humans were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual patients included in the study.

Conflicts of interest Didier Hans is the co-owner of the TBS patent and has corresponding ownership shares and position at Medimaps group. Enisa Shevroja has no conflict of interest. Michael McClung received honorarium and consulting fees from Amgen. Michele McDermott is an employee and stockholder of Amgen. Shuang Huang is an employee and stockholder of Amgen. Min Kim is an employee and stockholder of Amgen.

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